CHILDHOOD CANCER SURVIVOR STUDY
Analysis Concept Proposal

1. **TITLE:** Follow-Up of Long Term Survivors of Hodgkin's Disease Diagnosed in Childhood and Adolescence – A Report from the Childhood Cancer Survivors Study

2. **WORKING GROUP AND INVESTIGATORS:** This proposed study will be within the Cancer Control, Chronic Disease and Neuropsychological Working Groups. Collaborating investigators will include:

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3. BACKGROUND AND RATIONALE:

Hodgkin's disease (HD) is a radiation and chemotherapy responsive lymphoma that may present in children, adolescents/young adults, or the elderly. Prior to the 1970s, treatment approaches were similar for adults and children and involved high-dose (35-44 Gy), extended-field radiation with or without combination chemotherapy. With increased disease-free survival, pediatric investigators recognized that irradiation of large volumes of tissue/organs to high doses produced unacceptable long-term effects in the physically immature patient (1, 2). These concerns motivated the development of combined-modality therapy regimens in which cycles of chemotherapy replaced a portion of the radiation therapy in laparotomy-staged children (3). As with adults, early combination chemotherapy in children largely utilized mechlorethamine, vincristine, procarbazine, and prednisone (MOPP) and/or Adriamycin, bleomycin, vincristine, dacarbazine (ABVD) or similar derivative regimens in combination with low-dose (15-25.5 Gy), involved-field radiation. By the 1980s, this evolution of therapy resulted in achievement of 5-year disease-free survival rates in children and adolescents in the range of 75% to 90%(3). After demonstrating efficacy of the combined modality treatment approach using systemic therapy with reduced radiation doses and treatment fields, increasing recognition of late sequelae after high dose radiation like second malignancies and cardiovascular disease, as well as subsequent advances in diagnostic imaging technology provided the impetus for investigators to abandon surgical staging and the use of radiation as a single treatment modality in the 1990s.

As survival potential for patients with HD improved, appreciation of cancer-related late sequelae has become increasingly apparent with aging of this group. Second malignant neoplasms (SMN) (4-7), anthracycline- and radiation-mediated cardiovascular toxicity (8, 9), pulmonary insufficiency (10, 11), impaired fertility (12-15), thyroid dysfunction (16, 17), musculoskeletal abnormalities (18) and late psychological sequelae (19, 20) are among the most common sequelae documented in numerous studies of survivors of HD. In the CCSS study evaluating chronic health conditions in adults surviving childhood cancer, HD survivors were among the 3 diagnostic groups at highest risk to report having severe or life-threatening medical conditions or multiple conditions (21-23). The majority of studies to date have focused on specific late sequelae, and hence been limited in their ability to comprehensively evaluate long-term overall health, including the physical and psychosocial cancer-related morbidity in a large survivor population with well-characterized socio-demographic, diagnostic and treatment information.

The 2383 survivors of HD participating in the CCSS provide a unique opportunity to identify host- and treatment-related factors predisposing to mortality and morbidity in aging HD survivors. Previous CCSS investigations have provided insight regarding the impact of cancer and its therapy on various aspects of HD survivor health:

Mortality: Five year survivors of HD comprise 13% of the CCSS cohort. At the initial evaluation for mortality in the CCSS, 328 of the 2383 five-year survivors of Hodgkin's disease in the cohort had died, which accounted for 16% of late mortality and represented an age- and sex-adjusted SMR of 8.3 (95% CI 7.4-9.2) (25). Late mortality was due to recurrence of HD in 41.5% (n=136) of the deceased. Second malignancy accounted for 69 late deaths (21%), and cardiac, pulmonary, and other causes accounted for the rest.
Chronic health conditions: In the analysis of chronic health conditions in adult survivors in the CCSS, Oeffinger *et al*. (22) demonstrated that HD survivors had a 10-fold (RR 10.2; 95%CI: 9.3-12.5) and an almost 9-fold (RR 8.7; 95% CI: 7.4-10.2) excess risk of reporting a serious or life-threatening health condition and 2 or more chronic health conditions, respectively, in comparison to the age matched sibling cohort. Of greater concern is the demonstration that the incidence of conditions increases over time, without evidence of plateau.
Health status: Hudson *et al*. demonstrated that adult survivors in the CCSS are at substantial risk for adverse health status, a reflection of morbidity (20). The most frequent impacted health domains included mental health (impaired in almost 18% of HD survivors) and cancer-related anxiety (reported in almost 16%). HD survivors had higher odds of adverse health staus in general health (RR 2.7; 95% CI: 2.2-3.4), functional status (RR 2.4; 95%CI: 1.8-3.3), activity limitations (RR 2.1; 95% CI: 1.7-2.7) and mental health (RR 2.0; 95% CI: 1.6-2.4) domains when compared to their siblings. Overall, 40% of HD survivors of the CCSS reported adverse status in at least one domain.
Psychosocial: Zebrack et al (19) found that HD survivors did have an elevated risk of depression and somatization, but this did not attain statistical significance when corrected for gender and SES. The role of other medical morbidities contributing to their adverse psychological health remains unclear.

SMN: HD disease survivors were one of the first survivor groups to bring the recognition of SMNs to the forefront of survivorship concerns. In the initial evaluation of the CCSS, Neglia et al demonstrated that 37.2% of SMNs (n=111 of 298) occurred in HD survivors, with a cumulative risk of 7.63% at 20 yrs and absolute risk of 5.13 per 1000 person-years (4). In fact, in that analysis HD survivors had the highest relative risk (RR 2.34; 95%CI, 1.44-3.81) for a SMN compared to patients with any other primary cancer diagnosis. This risk was largely accounted for by the high incidence of breast cancer. In a subsequent study examining breast cancer in the CCSS, 68% of all cases occurred in HD survivors (5). Secondary leukemias, sarcomas and thyroid cancers represent the second and third most common histologic subtypes of SMNs in HD survivors.
Gonadal dysfunction: HD survivors comprised 30% of female participants in the CCSS reporting acute ovarian failure (AOF). HD was a significant risk factor for AOF in the univariate analysis, but did not retain significance in the multivariable model after inclusion of age at diagnosis and exposure to pelvic radiotherapy and specific aklylating agents (15). However, in a study of premature menopause in the CCSS, survivors of HD had a 9-fold higher rate of non-surgical premature menopause compared to other survivors. This evaluation, which included 404 female survivors of HD, indicated an excess risk for this group after controlling for age at diagnosis, attained age and exposure to ovarian irradiation and alkylating agents (14). The assessment of male gonadal function is more challenging, and true fertility rates are difficult to determine in male cancer survivors. However, in a study of partners of male survivors in the CCSS, Green et al reported the rate of miscarriage was higher for partners of male survivors who received > 5 gm/m2 of procarbazine, a chemotherapeutic agent commonly used in regimens for HD (13).

Although there are established risks for other late morbidities in HD survivors, the incident risk period for specific late complications and the pattern of less severe co-morbidities has not been examined in pediatric HD survivors. For example, it is known that CCSS survivors who received chest irradiation have an increased relative risk of pulmonary fibrosis and respiratory symptoms (11). However, the extent to which HD patients account for this population has not been assessed. With regard to endocrine late effects, thyroid dysfunction following gland irradiation has been well described. In the CCSS, HD survivors exhibited a 17-fold excess risk of hypothyroidism and a 27-fold excess risk of thyroid nodules compared to sibling controls (17). Furthermore, this group has a risk of thyroid cancer which was 18 times that of the general population. Although it is likely that the risk of thyroid dysfunction is correlated to the risks of other radiation mediated late morbidities, this has not been previously demonstrated in HD survivors.

Anthracycline chemotherapy and thoracic radiation are well-established contributing variables to cardiovascular morbidity (8, 9) among survivors of HD. However, cardiovascular outcomes have not been well studied in HD survivors in the CCSS in the context of other co-morbidities. Bowers et al report a RR of 5.62 (in comparison to sibling cohort) of late occurring stroke in HD survivors within the CCSS, all of whom received mantle irradiation, and many of whom had associated arrhythmia, valvular disease and/or congestive heart failure. It is therefore likely that the risk of heart disease will be similarly increased in the HD survivor population.

While CCSS reports to date have characterized the morbidity in HD survivors, the specific cancer treatment, potential treatment and host interactions and associated late sequelae remain to be characterized. The goal of the current proposal is to characterize cause-specific morbidity and mortality in HD survivors in the CCSS, in a way that will be comprehensive of currently understood treatment and host risk factors. This focus will provide useful information to clinicians and survivors by more specifically characterizing groups at risk for treatment morbidity. The scope of this proposal is deliberately broad in order to encompass the late medical and psychosocial effects on the survivor of childhood HD.

4. SPECIFIC AIMS/OBJECTIVES/RESEARCH HYPOTHESES:

1. To estimate the cumulative incidence of overall mortality, late relapse, SMN, and selected serious health conditions occurring since cancer diagnosis among long-term survivors of HD who are ≥ 5 yrs. from diagnosis. The medical conditions to be evaluated will be limited to severe (grade 3-5) cardiac and pulmonary toxicity.

Hypothesis 1a: The incidence of late relapse increases for a defined period of time beyond 5 yrs and then plateaus.
Hypothesis 1b: The incidence of SMN, selected health conditions and of death in this cohort continues to rise with increasing time since initial diagnosis.

2. To determine the impact of host factors and treatment factors on non-relapse mortality in survivors of HD.

Hypothesis 2:

- Hypothesis 2a: Non-relapse mortality will be associated with treatment intensity (more than 1 regimen) and treatment pattern (supra-diaphragmatic irradiation).
- Hypothesis 2b: Non- relapse mortality will be associated with younger age at diagnosis

3. To determine the incidence of self-reported chronic medical conditions by severity (grade) in HD survivors, and to assess the impact of treatment factors on these outcomes. The chronic conditions (Table 1) will be limited to: thyroid, cardiac, pulmonary, esophageal/gastrointestinal, renal, gonadal dysfunction, musculoskeletal, or neurological (including chronic pain) and SMN as defined by Oeffinger et al.

Hypothesis 3: The risk of chronic health conditions will be related to treatment pattern.

- Hypothesis 3a: The risk of SMN of breast, thyroid or esophagus will be associated with survivors who received supra-diaphragmatic radiation therapy.

- Hypothesis 3b: Thyroid dysfunction (grade 1-4) is a surrogate marker for host radio-sensitivity, and hence survivors with thyroid dysfunction will be more likely to be at risk for SMNs of breast, thyroid, and esophagus, and for grade 3-5 cardiac and pulmonary disease
- Hypothesis 3c: Grade 3-5 musculoskeletal, cardiac and pulmonary disease and neurological conditions will be associated with neck and mantle field irradiation.
- Hypothesis 3d: Gonadal dysfunction is associated with infra-diaphragmatic irradiation, and is associated with a lower risk of breast SMN in HD survivors.

4. To determine if social outcomes (including insurance coverage, employment and education level, and marital status) of HD survivors are associated with, or independent of report of grade 3-5 chronic pain , or with mental health status (depression, anxiety, somatization), as indicated on the BSI-18.

Hypothesis: Lower rates of employment and educational achievement will be associated with chronic pain and with indicators of impaired mental health status.

5. ANALYSIS FRAMEWORK:

Subjects

The proposed analysis will encompass all respondents with HD disease in the CCSS, including patients deceased at study entry but who survived ≥5 yrs from initial diagnosis. This analysis will include those who were both children and adults at time of enrollment in CCSS.

Measures

Variables of interest for this analysis are delineated in Table 1.

Table 1. Outcome and explanatory variable of interest for Hodgkin's analysis

Outcome variables	**Source**	**CCSS Questionnaire**
Age at Recurrence/ relapse of HD	Self-report	Baseline, FU1, FU2
Age at onset of selected health conditions : Grade 3-5 cardiac Grade 3-5 pulmonary	Self report	Baseline
Date of SMN (to include basal cell and squamous cell carcinomas of skin)	Self report Validated central pathology review (4)	Baseline, FU1, FU2
Date of Death	National Death Index	
Report of Following Grade 3-5 Health conditions (for Spec Aim 3) *: Thyroid Cardiac Pulmonary Hearing loss Cataracts Female Gonadal failure		 Baseline (E1-4), I-15, I23 Baseline (F2-21, I7, I9-10) Baseline G5-G13, I24 Baseline (C1-3;C7) Baseline (C9, I28) Baseline (E13,E16-E18)

Male gonadal failure Digestive disorder Renal Musculoskeletal Bone Health Chronic pain Neurological		Baseline (E13-E15) BaselineH7-H11, J14 Baseline (D1-5) Baseline I2 Baseline I5; Baseline J36; Baseline J2, J8-13
Social outcomes: Employment Insurance Education level		Baseline, FU1 and FU2
Disease and Treatment explanatory variables		
HD histology at diagnosis	Medical abstraction by Treating institution	Baseline
Number of treatment regimens (initial regimen/salvage regimen)		
Splenectomy (yes/no)		
Radiation (yes/no) Radiation dose >/= 30 Gy < 30 Gy Radiation site (supra-diaphragmatic) Neck Mantle Mediastinum alone Radiation site (infradiaphragmatic) Total Pelvis Peri-aortic		
Chemotherapy exposure (categorical variable) COPP MOPP ABVD		
Alkylating agent score		
Autologous or allogeneic transplant		
Overall health Status		
Covariates of Interest		
Age at diagnosis	Self report	Baseline
Time since diagnosis		
Treatment era		
Gender		
Race/ethnicity		
Age at survey response		
Family history of malignancy		
BMI		
Smoking Status		

*Chronic Health outcomes will be graded according to criteria described by Oeffinger et al (2006).

Statistical approach:

Descriptive statistics will be used to report the baseline characteristics and potential covariates of the HD population within CCSS (Appendix Table I). This will include means, standard deviations and distributions of age at diagnosis, age at survey response. Categorical variables such as the following, will be tabulated: race; gender; HD histology

at diagnosis; HD stage at diagnosis; splenectomy status; exposure to radiation; radiation site; selected chemotherapy agents; occurrence of SMN; recurrence of HD; presence or toxicity grade of selected health condition; grade 3-4 health condition (for each condition listed above).

Analysis of Specific Aim 1: Median survival and median time to key outcomes of interest will be estimated by the method of Kaplan-Meier (for overall survival) and cumulative incidence (for other outcomes) using 5 yrs. after date of diagnosis of HD as the baseline.

- Overall survival will be defined as 5 yrs. from the time from diagnosis of HD until death from any cause. Survival analysis will be stratified for HD histology and for treatment era. The survival function will be censored for the following events: last survey completion (baseline, FU1, FU2).
- Cumulative incidence for recurrence/relapse will be estimated using 5 yrs. following diagnosis as the baseline time for survival analysis. The following events will be considered competing risk events for recurrence/relapse: any SMN; non relapse death; date of last survey completion (baseline, FU1, FU2).
- Cumulative incidence for any SMN will be estimated using 5 yrs. following diagnosis as the baseline time for survival analysis. The following events will be considered competing risk events: death from any cause other than SMN; date of last survey completion (baseline, FU1, FU2).
- Cumulative incidence rate for grade 3-5 cardiac or pulmonary conditions (as defined by Oeffinger et al) will be generated from 5 yrs. after the date of HD diagnosis to the reported onset of condition. The following events will be considered competing risk events: death; date of last survey completion (baseline, FU1, FU2).

Regression analyses for Specific Aims 2 and 3: To estimate the impact of demographic and cancer-related and treatment factors on the risk of specified outcomes listed under Aims 2 and 3, Cox proportional hazards regression will be used estimate the hazard ratios (HR) and associated 95% confidence intervals (95% CI). Initial regression models will be constructed to examine impact of each demographic, disease and treatment explanatory variables of interest with adjustment for some pre-specified covariates. Candidate explanatory variables of interest are shown in Table 1 above and in Table II in the Appendix. All explanatory variables significant at the $p< 0.2$ level will then be entered into the full model. Appropriate regression diagnostics will be utilized to check the proportional hazards assumption.

Cumulative incidence analysis for Specific Aim 3:

- Cumulative incidence for each grade of each specified chronic condition will be generated from 5 yrs. after the date of HD diagnosis to the reported onset of condition. Analyses of gonadal dysfunction will be limited to subjects who were between ages 15 and 44 at the time of questionnaire response. The following events will be considered competing risk events: death; date of last survey completion (baseline, FU1, FU2)

Regression analysis for Specific Aim 4: Logistic regression models will be used to examine the association between reports of grade3-5 conditions or BSI indicators and the

social outcomes (insurance coverage, employment, education level and marital status of survivors).

Statistical analysis will be performed using SAS version 9.0 software (SAS, Cary, NC).

6. SPECIAL CONSIDERATIONS:

This concept proposal is deliberately broad in order to be comprehensive of the breath of late sequelae in Hodgkin's disease survivors. It is recognized that in fact the analyses proposed above may result in more than one manuscript.

Resources are available through this working group to handle the dataset and data analysis. The analysis for Specific Aims 1 and 2 will be done by Sharon Castellino under the guidance of her Master's thesis committee (Geiger, Tooze) at Wake Forest University, and in conjunction with the CCSS Biostatistics group. Analysis of Aim 3 and 4 will be carried out at the Statistical Center in Seattle.

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APPENDIX : Proposed tables for analysis of Survivors of HD in the CCSS

Table I. Characteristics of 2383 Survivors of Hodgkin Lymphoma in the CCSS

Demographic Characteristics	**Age at entry into CCSS**	
	5-18 years	**>18 years**
Gender Male Female		
Race White Black Hispanic Asian Other		
Age at diagnosis 0-9 10-14 15-20		
Age at survey response 5-10 11-18 15-19 20-29 30+		
Treatment era 1970-1979 1980-1986		
Age – median (range)		
Histology Nodular sclerosing Mixed cellularity Lymphocyte depletion Lymphocyte predominance		
Time since completion of therapy 5-10 yrs 10-20 yrs 20+ yrs		
Treatment Chemo only Chemo +RT		
Anthracycline exposure None $\geq$250 >400		
Radiation exposure Supra-diaphragmatic Infra-diaphragmatic		
Splenectomy Yes No		
Vital status at last f/u		

Table II. Risk of specified Medical Outcomes by Initial Disease and Treatment factors

Disease and Treatment Characteristics	**Risk of Outcome HR (95% CI)**				
	Late Relapse	**SMN**	**Grade 3-5 Cardiac Disease**	**Grade 3-5 Pulmonary disease**	**Thyroid Disease**
Age at diagnosis (yrs.) 0-9 10-14 15-20 (referent)					
Histology Nodular sclerosing(referent) Mixed cellularity Lymphocyte depletion Lymphocyte predominance					
Number of treatment regimens 1 regimen ≥ 2 regimens					
Splenectomy Yes No (referent)					
Radiation (yes/no) *Radiation dose* >/= 30 Gy < 30 Gy *Radiation site* *Supra-diaphragmatic* Neck Mantle Mediastinum alone *Infra-diaphragmatic* Total Pelvis Peri-aortic					
Chemotherapy exposure Anthracycline <250 mg/m^2 ≥250 mg/m^2 Mechlorethamine Prednisone or Dex Vincristine/Vinblastine Procarbazine Bleomycin Dacarbazine COPP MOPP ABVD					
Transplantation Autologous Allogeneic					