05-05

CHILDHOOD CANCER SURVIVOR STUDY

Analysis Concept Proposal

1. **TITLE:** Health related quality of life in adult survivors of childhood Wilms' tumor or neuroblastoma

2. WORKING GROUP INVESTIGATORS:

This proposed study will be within the Neuropsychological working group. Proposed investigators include:

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3. BACKGROUND AND RATIONALE:

Neuroblastoma and Wilms' tumor are the two most common extracranial solid tumors of childhood, accounting for approximately 15% of malignancies in the pediatric population [1]. Similarities between these tumors include their peak incidence in children younger than 5 years and their predominantly abdominal presentation (65% of neuroblastomas and all Wilms' tumors). However, Wilms' tumor is associated with a high rate of cure[2], while children with high-risk neuroblastoma fair poorly despite intensive therapy[3]. In Wilms' tumor, the evolution of therapy has focused on achieving higher cure rates with a minimization of long-term effects. Although there has been a similar focus in children with low or intermediate risk neuroblastoma,

treatment of patients with high-risk disease has become increasingly intensified[3]. In prior treatment eras, children with Wilms' tumor and low/intermediate risk neuroblastoma were exposed to more aggressive multimodal therapies, including radical surgery, orthovoltage radiation and chemotherapy. Consequently, even survivors of low or intermediate risk neuroblastoma as well as Wilms' tumor experience significant late effects – amongst the most frequent of these is scoliosis secondary to asymmetric radiation of the spine[4,5]. Although there have been several publications describing the long term medical complications of neuroblastoma [6-13] and Wilms' tumor[14-19], there is a paucity of literature describing health-related quality of life (HRQL) in these survivors. In the only publication comparing HRQL in these groups, Barr and colleagues used the Health Utilities Index (HUI) [20] to compare 52 survivors of Wilms' tumor (stages 2-5) with 26 survivors of neuroblastoma (inoperable stage 3 and stage 4). Although there was not a statistically significant difference in overall HUI scores between the two groups, a greater proportion of neuroblastoma survivors had a HUI utility score less than 0.8, and more children who had survived Wilms' tumor were reported by their parents to have no disabilities. This study was limited by the use of proxy respondents and the fact that the majority of participants had not reached adulthood. A limited assessment of the health status in these two diagnostic groups was included in a publication assessing health status in adult survivors of childhood cancer[21]. In this analysis, 41% of neuroblastoma survivors and 38% of Wilms' tumor survivors reported an adverse outcome in at lease one health status domain. Compared to healthy siblings, survivors of both neuroblastoma and Wilms' tumor were more likely to have moderate to extreme adverse health status outcomes in the domains of general health, functional impairment, activity limitations and mental health. Furthermore, survivors of Wilms tumor (but not neuroblastoma) had an increased likelihood of an adverse outcome on the global, somatization and anxiety domains of the Brief Symptom Index (BSI-18). However, this study did not compare these two groups directly, nor did it focus on specific disease or treatment related predictors of poor outcome in these patients.

An analysis of HRQL in survivors of Neuroblastoma or Wilms' tumor treated between 1970 and 1986 would be a unique contribution to the literature. This cohort is likely to differ from a more contemporary group of patients because of the increased intensity of therapy used in low/intermediate risk neuroblastoma patients and the majority of Wilms' tumor patients, as well

as the likelihood that few patients with advanced stage neuroblastoma are likely to be long-term survivors.

In this study, HRQL will be assessed with two instruments, the SF-36 and the Ladder of Life. The SF-36 is a 36-item survey which is a widely used and well-validated instrument that assesses several aspects of quality of life including physical, social and psychological functioning. This self-report measure contains 8 individual subscales that represent three general areas of health-related QOL: physical, emotional, and social well-being[22]. The subscales include physical functioning, role function-physical (assessing role limitations caused by physical factors), bodily pain, social functioning, mental health, role function-emotional (assessing role limitations caused by emotional factors), vitality, and general health. General population norms are available for the SF-36[23]. The SF-36 can also be scored as two summary scales—one for physical health and a second for mental health. The data for these summary scales are presented as t-scores, with a normal healthy population mean score set at 50 and a score of 60 or 40 representing 1 standard deviation (SD) above or below the mean, respectively. These scales are called the SF-36 Physical (PCS) and Mental (MCS) Component Summary scales. The Ladder of Life assesses respondents' QOL with three self-report items that provide a subjective rating of QOL in the past, at the present time, and anticipated for the future.[6] Ratings are made on a 10-point scale ranging from "Best Possible Life" to "Worst Possible Life." This scale provides a global rating of life satisfaction and is widely used in epidemiologic and population studies as well as in clinical samples of cancer survivors[24,25].

4. SPECIFIC AIMS/OBJECTIVES/RESEARCH HYPOTHESES:

The purpose of this manuscript will be to look at both the similarities and differences between adult survivors of childhood neuroblastoma and Wilms' tumor, and to explore the factors within each group that impact on HRQL. To accomplish this, we will examine the relationship between sociodemographic, disease and treatment variables and outcomes in HRQL.

Hypothesis 1: Overall, the prevalence of adverse outcomes in HRQL is higher in survivors of neuroblastoma than in survivors of Wilms' tumor

Hypothesis 2: Disease variables related to adverse outcomes include younger age at treatment and location of the primary tumor (in neuroblastoma)

Hypothesis 3: Treatment variables related to adverse outcomes include the use of radiation therapy (particularly higher dose, field involving the spine), surgery (laminectomy nephrectomy) and the use of anthracyclines and alkylating agents (particularly in Wilms' tumor)

Hypothesis 4: Sociodemographic variables related to adverse outcomes include female gender, failure to complete high school and lower household annual income

ANALYSIS FRAMEWORK:

A. Sample: adults (≥ 18 years at time of response to 2nd follow-up questionnaire) who are survivors of either neuroblastoma or Wilms' tumor. There are 955 survivors of neuroblastoma and 1259 survivors of Wilms' tumor included in the CCSS cohort. Their distribution by age at diagnosis is:

Age at diagnosis (years)	Neuroblastoma	Wilms' tumor
<1	525	185
1-1.99	194	203
2-2.99	72	209
3-3.99	37	203
4-4.99	38	154
≥5	89	305
Total	**955**	**1259**

B. Outcomes of interest:

a. Health-related Quality of life

i. SF-36 – total score; summary measures (physical health, mental health); scales (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, mental health) (E and F questions on 2nd follow up questionnaire).

ii. Ladder of life (I questions on 2nd follow up questionnaire)

C. Independent (exploratory) variables

a. Sociodemographic variables:

iii. Age at interview

iv. Gender

v. Race/ethnicity

vi. Household income

vii. Health insurance

viii. Education

ix. Marital status

x. Employment status

b. Disease variables:

i. Age at diagnosis (categorical)

- Neuroblastoma (≤1, >1)
- Wilms' tumor (<2, 2-5, >5)

ii. Time from diagnosis to interview

iii. Diagnosis: neuroblastoma vs. Wilms' tumor

iv. For neuroblastoma → location of tumor (abdominal vs. thoracic vs head/neck vs spinal/paraspinal)

ICD-0 codes collected by institutional data managers classified the location of 912 neuroblastomas as follows:

Location	Number
Abdomen/pelvis	486
Thorax	255
Head/neck	53
Spine/vertebral column	14
Unknown/other	104

c. Treatment variables:

i. Chemotherapy vs. surgery vs. radiation vs. BMT vs. combination

ii. If radiation → field, dose

iii. If surgery → specific surgical procedure abstracted from ICD-9 procedure codes:

- laminectomy (3 Wilms' tumor cases, 191 neuroblastoma cases)
- nephrectomy (1031 Wilms' tumor cases, 60 neuroblastoma cases)

iv. If chemotherapy → use of anthracyclines, alkylating agents

v. Era of treatment

d. Major medical conditions (MMC):

Defined as a positive response (on baseline questionnaire) to any one of the following medications (B.8): anticonvulsants (B.8 #11), cardiovascular medications (B.8 #12), chemotherapy/immune suppressants (B.8 #14), OR a positive response to the presence of any of the following medical conditions: complete deafness (C3), dialysis (D4), congestive heart failure (F4), myocardial infarction (F5), stroke or cerebrovascular accident (F9), current use of oxygen (G9), cirrhosis (H3), coronary artery bypass surgery (I7), angioplasty (I9), heart transplant (I23), lung transplant (I24), kidney transplant (I25), repeated seizures, convulsions or blackouts (J5), diagnosis of 2nd cancer (confirmed 2nd malignant neoplasm excluding basal cell carcinoma or recurrence/relapse) (K1), amputation (I1) or joint replacement (I5).

e. Self assessment of general health (E1 on 2nd follow-up questionnaire)

The analysis will involve a comparison of HRQL between diagnoses (i.e. Wilms' tumor vs neuroblastoma) and within diagnoses (i.e. each disease by therapy received, age at diagnosis etc.). The primary HRQL outcomes for both the between and within diagnoses comparisons will be the overall SF-36 score (along with the physical and mental health summary scores) and the overall Ladder of Life score. For the between diagnoses analysis, the diagnosis (neuroblastoma vs. Wilms' tumor), sociodemographic modifiers (age, gender, income, education) and presence of major medical conditions will be used as potential independent variables. For the within survivor analysis, we will add the disease and treatment variables into the model. We will also do secondary analyses looking at the specific scale scores on the SF-36.

Univariate analyses will be performed to assess the association between each independent variable and the outcome measures. Multivariate models will be constructed using logistic regression to estimate the relative risk for reduced HRQL where dichotomized outcomes are available or using multiple linear regression to evaluate impact of independent variables on the mean value of continuously valued outcome measures (such as SF-36 and Ladder of Life)

5. TABLES

6. REFERENCES

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