02-01

Childhood Cancer Survivors Study
Analysis Concept Proposal
February 2002

Title: Hormonal and Neurological Late Effects of Treatment in CCSS Cases Diagnosed with First Primary Rhabdomyosarcoma (RMS)

(A) Working Group and Investigators

This proposal will be set within the Chronic Disease Working Group.
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(B) Background and Rationale

Advances in the diagnosis and treatment of rhabdomyosarcoma (RMS) over the past 30 years have increased overall long-term survival from less than 33% in the 1960s to 70% in the1990s.[1] During this time, researchers have also found that late effects are an undeniable and unfortunate consequence of the treatments needed to cure patients of their disease. As early as 1976, Tefft, et al., described late effects occurring in RMS patients treated with combined chemo- and radiotherapy.[2] More recent studies have documented problems associated with radiotherapy (e.g., cataracts, dental abnormalities, orbital and other bony hypoplasia, decreased statural growth, and neuroendocrine disorders); surgery (e.g., bowel obstruction, loss of ejaculatory function); chemotherapy (e.g., infertility, hearing loss); and combinations of these therapies (e.g., learning and cognitive deficits).[3-11]

Despite these findings, the picture of the late effects occurring in RMS patients is incomplete. Most investigations have documented frequencies of late sequelae and are based on relatively small case series. Little is known regarding the rates of late effects in RMS cases relative to a population of untreated (unexposed) individuals. Although the risk of late effects varies by treatment, the magnitude of risk is unknown. In addition, it is difficult to compare results from studies because of differences in the definition of outcomes and treatments. Other difficulties arise in comparing results from studies that were not specifically designed to investigate late effects in patients.

The Childhood Cancer Survivors Study (CCSS) is a large, retrospective cohort study with extensive medical and treatment data on cancer survivors as well as outcome data for random sample of sibling (unexposed) controls. It was specifically designed to investigate the long-term late effects of cancer therapies. An analysis of CCSS data will broaden our understanding of late

effects in RMS survivors. The purpose of this investigation is to characterize the hormonal and neurological late effects of therapies in RMS survivors. To facilitate comparisons with other studies, we will also provide a detailed description of the RMS survivor population, including a summary of variables such as demographics, socioeconomic status (e.g., educational level, income, etc.), and possibly selected health habits (i.e., exercise, smoking).

(C) Specific Aims/Objectives/Research Hypotheses

We propose to characterize the hormonal and neurological adverse effects of cancer treatments in RMS cases in two separate analyses. The first analysis will provide a description of adverse hormonal and height/body mass index (BMI) outcomes occurring among survivors relative to sibling controls. Preliminary analyses (graphs attached) of height and BMI data for survivors show, relative to 1995 National Heath Interview Survey (NHIS) data, an excess of cases with very short stature and very low BMIs. Thus, as a part of our analyses, we will investigate the patient characteristics and treatment-related factors that are associated with severe growth retardation (height < 5th percentile[‡]) and very low BMI (BMI < 5th percentile or another appropriate cutoff point as indicated by the study group investigators or publications committee). The second analysis will provide a description of the rates of adverse neurological outcomes in survivors, including hearing, speech, and vision, and taste deficits, as well as potential neurological deficits related to the sensation in and movement of arms, legs, etc. Objectives and hypotheses for each of the two proposed analyses are listed separately below. (Also see attachment AA for selected survivor demographics based on preliminary data.)

(1) Hormonal Outcomes and Height/BMI:
The objective of this analysis is to describe the rates of growth hormone deficiency, hypothyroidism, and other indicators of hormonal dysfunction in survivors relative to sibling controls. Further, we will investigate the patient characteristics and treatment-related factors among cases, at least 18 years of age at survey completion, that are associated with severe growth retardation and very low BMI. If there are adequate numbers, we will assess whether the rates of adverse hormonal sequelae vary by Intergroup Rhabdomyosarcoma Study (IRS) protocol number and/or treatment era. The trend analyses by protocol number will be restricted to CCSS survivors who were treated on IRS protocols (approximately 40% of RMS survivors, or roughly 244 cases). To address the question of trends in the rates of hormonal late effects using all CCSS survivors with treatment data (approximate N=611), we will investigate whether the rates of these adverse outcomes vary by treatment era.

Hypotheses:

i. Survivors will have higher rates of hypothyroidism than siblings. Risk will be highest among females and among cases who have received radiation to the thyroid. Cases treated at an early age (<5 years) may also be at increased risk.[12]

ii. Survivors will have higher rates of growth hormone deficiency than siblings. Risk will be highest among cases, particularly those diagnosed with orbital and nasopharyngeal RMS, who have received radiation to the hypothalamus-pituitary axis (preferred exposure variable) or cranial radiation (default exposure variable).[12]

iii. The risk of severe growth retardation (reported height < 5th NHIS height percentile) will be greater among cases who received cranial radiation (CRT), received radiation

[‡] Note: Because our data are cross-sectional, we cannot conduct analyses of the more familiar measurement, decrement from initial height. However, using initial heights of survivors treated on IRS protocols, we would be able to analyze changes from initial height to final height in a subset of survivors, in addition to the logistic regression modeling approach described herein.

therapy at an early age (<5 years), and who received high cumulative doses of CRT (>3000 cGY).

iv. The risk of very low BMI (observed BMI < 5th NHIS BMI percentile) will be greater among cases who received CRT, who received CRT at an early age (<5 years), and who received high cumulative doses of CRT (>3000 cGY).

v. The risk for hypothyroidism, growth hormone deficiency and other adverse hormonal outcomes will be higher in cases treated on earlier IRS protocols/treatment eras than those treated on later IRS protocols/treatment eras.

vi. If the numbers are adequate, we will investigate other associations between these adverse outcomes and treatments. Two relationships suggested from the literature are that the risk of linear growth deficits increases with increasing drug intensity[13] and with simultaneous administration of radiotherapy and radiosensitizing drugs (doxorubicin and/or actinomycin D).[14]

(2) Neurological/Sensory Deficits:*

The objective of this analysis is to describe the occurrence of neurological and sensory deficits in RMS survivors relative to sibling controls. We will describe the occurrence of neurological and sensory outcomes by tumor site, and type and extent of surgical intervention as indicated by International Classification of Diseases, 9th Revision, Clinical Modification[15] (ICD-9-CM) codes. The effects of cancer stage and tumor size are also of interest; however, these variables were not collected in the CCSS. To describe the effect of these factors on the occurrence of neurological/sensory deficits, we will use IRS stage and tumor size data in analyses restricted to survivors treated on IRS protocols (approximate N=244). We will also investigate the patient characteristics and treatment-related factors that explain or modify the risk of adverse neurological and sensory outcomes among survivors. Peripheral neuropathy and other long-term neurological deficits have been associated with vincristine, VP16, VM26, and methotrexate.[16] If the numbers are adequate, we will investigate the dose-response relationships between neurological outcomes and increasing doses of these chemotherapeutic agents. Finally, as described previously, we will investigate whether there are trends in the risk of neurological/sensory deficits by IRS protocol number and/or treatment era.

Hypotheses:

i. Visual, hearing, and speech deficits will occur more frequently among cases than sibling controls. The risk of these outcomes will be highest among cases with RMS of the head and neck (orbit, parameninges, other head and neck sites) and among cases who have received the highest doses of CRT.

ii. Survivors who received platinum containing drugs (cis-platinum, carboplatin) will have an increased risk of hearing deficits compared to survivors who have not received such agents.

iii. The risk of neurological/sensory deficits will increase with increasing dose and intensity levels of the vincristine, VP16, VM26, and methotrexate. The highest risk of these outcomes will occur among cases who received both the highest intensity level of chemotherapy and the highest cumulative doses of radiotherapy.

iv. The risk of adverse neurological and sensory sequelae will be higher in cases treated on earlier IRS protocols/treatment eras than those treated on later IRS protocols/treatment eras.

* Note: Quality of life and psychosocial functioning will not be considered in these analyses.

(D) Analysis Framework

Outcomes of Interest

1. Hormonal Outcomes/Height/BMI: outcomes in sections E, plus the height and weight variables of the baseline survey
2. Neurological/Sensory Deficits: outcomes in sections C and J of the baseline survey

Population of Cases/Siblings

- Cases: CCSS participants of the first baseline survey, diagnosed with a first primary RMS (ICD-O-2[†] morphology codes 8900.3,8901.3,8902.3,8910.3,8920.3) for whom medical record release has been obtained
- Siblings: CCSS participants of the first baseline survey

Methods

(1) Rates and Relative Risks:

Statistical analyses will be consistent with the approach outlined at the April 2001 CCSS Investigator's Meeting. Accordingly, multivariate Cox Proportional Hazard models with time dependent covariates will be used to obtain hazard rate ratios (relative risks) for late effects occurring in four time intervals: prior to diagnosis; within diagnosis and end of treatment; within the end of treatment date to just under five years after diagnosis; and five or more years since diagnosis to the date of last follow-up. Events occurring in this latter category will be defined as "late effects." Individuals who have not had an event prior to the date of last follow-up will be censored.

For each analysis, we will conduct: (a) case-sibling comparisons adjusted for intra-family correlations, to investigate differences in the relative risks of late effects in cases versus sibling controls; and (b) case-case comparisons to investigate whether the rates of late effects in cases vary by treatment differences and patient characteristics.

- Modeling: For case-sibling comparisons, sex will be included in these models as a covariate. For case-case comparisons, analyses of treatment and patient characteristics will be restricted to outcomes defined as "late effects" (above). Predictor variables for the case-case analyses will include: radiation yes/no (and/or radiation maximum dose and/or fractionation, if available); chemotherapy (and/or drug dose); age at diagnosis; sex; IRS protocol number or treatment era (below); and primary anatomic site, grouped using IRS definitions (below). Standard methods for evaluating confounding and effect modification (interaction) in will be performed.[17, 18]
- IRS Sites/Groups (See attachment BB for codes): The IRS assigns a numeric code ranging from 1 to 106 to cancer sites. These cancer site codes are grouped into broad cancer categories: orbit, head and neck, parameningeal, genitourinary non-bladder /prostate, bladder/prostate, extremity, retroperineum, trunk, intrathoracic sites, perineum-anus, and other. We will map CCSS cancer site codes (ICD-O-2[†] site codes) to IRS site codes and cancer groups, with slight modification. We will refer to cancers sites and their groupings classified using the IRS coding scheme as IRS cancer sites and IRS cancer groups, respectively.
- IRS Protocol Numbers/Treatment Era: Dr. Scott Baker and Ms. Pauline Mitby will be consulted regarding the development of these variables, which can be defined using CCSS treatment dates and IRS protocol numbers.

[†] International Classification of Diseases for Oncology, 2nd Edition[19]

- Missing Data: Multiple imputation methodology will be used to deal with missing age data (i.e., the time interval of outcome occurrence is unknown because age at first event was not recorded on the baseline questionnaire). To implement this methodology, the statistical unit in Seattle will run logistic regression models to impute the value of the missing time interval. Ten separate data files of imputed data will be generated. Judy Punyko will process the imputed data sets using software provided by the statistical unit.
- Final reports will include rates and relative hazard rates with associated 95% confidence intervals. Two-tailed tests of statistical significance will be conducted and a p-value of 0.05 or less will be considered statistically significant. (See CC attached for sample tables of the results section).

(2) Additional Height//BMI Analyses:
Descriptive statistics and graphs will summarize differences between the race, age, and sex-adjusted height and BMI percentile distributions of RMS cases and 1995 NHIS population data. (See graphs attached). Height and BMI data for siblings may be used as a second comparison population. Note: To be included in height/BMI analyses, individuals of the case and comparison populations must be 18 years of age or older at the time of data collection.

Multivariate methods for these analyses are described below.

- Classification of outcomes: Cases will be classified as having severe growth retardation if their reported height is less than the 5th NHIS percentile for height. Similarly, cases will be classified as having very low BMI if their observed BMI (reported weight in kilograms divided by the square of reported height in meters) is less than the 5th NHIS percentile for BMI.
- Modeling: Logistic regression will be used to model the risk of severe growth retardation and very low BMI. Predictor variables in these models will include: cranial radiation (yes/no) and/or cumulative brain radiation dose; chemotherapy and/or chemotherapy dose; age at diagnosis; sex; and IRS cancer group as defined above. If possible, other predictor variables will be created for inclusion in the models. A drug intensity variable (or variables) will be constructed by developing a rule that takes into account the number of drugs received, their cumulative doses, and the duration of treatment. Simultaneous administration of radiotherapy and doxorubicin and/or actinomycin D can be constructed as a dummy (yes/no) variable by using the start and end dates that are associated with each treatment. Variable definitions will be worked out prior to data analysis. Standard methods for evaluating confounding and effect modification (interaction) will be performed.
- Final reports will include odds ratios with associated 95% confidence intervals. Two-tailed tests of statistical significance will be conducted and a p-value of 0.05 or less will be considered statistically significant (See CC attached for sample tables of the results section).

Dr. Yasui Yutaka and colleagues of the statistical coordinating center in Seattle will provide oversight for all analyses and results for this investigation.

(E) Special Considerations

It is likely that the hormonal and neurological analyses will be presented in separate manuscripts. Analyses will be conducted by Judy Punyko, in partial fulfillment of the requirements for the doctoral degree program in epidemiology at the University of Minnesota, Division of Epidemiology.

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(AA) Selected Survivor Demographics – Based on Preliminary Data

Total Number of RMS Cases: 682
Total Number of RMS Case with Treatment Data: 611

RMS Cases with Treatment Data by Diagnosis Age

Diagnosis Age	Number (%)
< 1	43 (7)
1 - 4	249 (41)
5 - 9	148 (24)
10-14	100 (16)
15+	71 (12)
Total	611 (100)

RMS Cases by Age at Interview/Survey Completion

Interview Age	Number (%)
< 18	169 (28)
18-24	197 (32)
25-34	202 (33)
35+	43 (7)
Total	611 (100)

RMS Cases by Treatment Modality

Treatment	Number (%)
S	4 (<1)
S+R	4 (<1)
S+C	127 (21)
C+R	5 (<1)
S+R+C	469 (77)
Missing	2 (< 1)
Total	611 (100)

S – Surgery
R – Radiation
C – Chemotherapy

RMS Cases by Histology

Histology	Number (%)
Alveolar	65 (11)
Embryonal	324 (53)
Mixed Type	4 (< 1)
Pleomorphic	7 (1)
Rhabdomyosarcoma, NOS	211 (35)
Total	611 (100)

RMS Cases by IRS Cancer Groups

IRS Cancer Group	Number (%)
Orbit	78 (13)
Head & Neck	58 (9)
Parameningeal	93 (15)
Genitourinary (Non-Bladder/Prostate)	84 (14)
Bladder/Prostate	63 (10)
Extremity	74 (12)
Retroperineum	74 (12)
Trunk	12 (2)
Other	40 (7)
Unknown	35 (6)
Total	611 (100)

(BB) IRS Cancer Site and Group Codes

IRS site codes are the numeric values and IRS group codes are the character codes found within parentheses.

Orbit (ORB)
1 = Eye
2 = Orbit

Head & Neck (HN)
3 = Cheek
4 = Hypopharynx
5 = Larynx
6 = Neck
7 = Oral cavity
8 = Oropharynx
9 = Parotid
10 = Scalp
11 = Thyroid/Parathyroid
12 = Other

Parameningeal (PM)
13 = Infratemporal fossa
14 = Middle ear
15 = Nasal cavity/sinus
16 = Nasopharynx
17 = Paranasal sinus
18 = Parapharyngeal area
19 = Pterygopalatine
20 = Cheek with PM extension
21 = Larynx with PM extension
22 = Orbit with PM extension
23 = Oropharynx with PM extension
24 = Other HN with PM extension
25 = Parotid with PM extension
26 = Scalp with PM extension

GU Non-Bladder/Prostate (GU)
27 = Cervix
28 = Epididymis
29 = Kidney
30 = Ovary
31 = Penis
32 = Spermatic cord
33 = Testis/Paratesticular
34 = Urachus
35 = Ureter
36 = Urethra
37 = Uterus
38 = Vagina
39 = Vulva

GU Bladder/Prostate (BP)
40 = Bladder
41 = Prostate
401 = Bladder/Prostate (Use code 401 for D9802, D9803 only)

Extremity (EXT)
42 = Arm
43 = Buttock
44 = Elbow, region of
45 = Foot
46 = Forearm
47 = Hand
48 = Knee, region of
49 = Leg
50 = Shoulder Girdle
51 = Thigh

Other (OTH)
52 = Esophagus
53 = Gall bladder/Biliary tree, including Ampula of Vater
54 = Intestine, colon/cecum/rectum
55 = Intestine, small & duodenum
56 = Liver
57 = Omentum
58 = Pancreas
59 = Peritoneal nodules
60 = Peritoneum
61 = Stomach

Intrathoracic (IT)
62 = Bronchi/bronchioles
63 = Diaphragm
64 = Heart
65 = Hilum
66 = Lung & local sites
67 = Lung & other sites
68 = Lung
69 = Mediastinum
70 = Pericardium
71 = Pleura
72 = Pleural effusion
73 = Thymus
74 = Trachea

Perineum-Anus (PA)
75 = Anus
76 = Perineum

Retroperineum (RP)
77 = Pelvis, site indeterminate
78 = Retroperitoneum

Trunk (TRK)
79 = Abdominal wall
80 = Breast
81 = Chest wall
82 = Paraspinal

Other (OTH)
83 = Adrenal glands
84 = Ascites
85 = Bone
86 = Brain, ventricles & central canal
87 = Brain, general
88 = CSF
89 = Lymph nodes, distant
90 = Lymph nodes, regional
91 = Marrow only
92 = Marrow + nodes
93 = Marrow + skin
94 = Marrow + other
95 = Meninges
96 = Multiple sites, excluding lung
97 = Muscle
98 = Peripheral nerves
99 = Pineal
100 = Pituitary
101 = Skin
102 = Spinal cord
103 = Spleen
104 = Subcutaneous
105 = Unknown
106 = Other

Note: Because of small numbers, intrathoracic (IT) and Perineum-Anus (PA) cancers will be put in the IRS cancer group "Other."

(CC) Analysis Tables – Samples & Sketches

Demographics
Sex (%)
Diagnosis Age (% Distribution)
Age at Baseline (% Distribution)
Vital Status (% Distribution)
Median Follow-up Time

Cancer
IRS Cancer Group (% Distribution)
Histology (% Distribution)
Year of Diagnosis (% Distribution)

Treatment
Treatment Protocol (% Distribution)
Drugs (% Distributions, Dose)
Surgery (% Distribution)
Radiation (% Distribution by Doses, Fractionation if available)

Number and Rate of Reported Conditions by Time Period (Cases Only)

Reported Condition	Pre_diagnosis	Diagnosis to End of Tx	End of Tx Dx+5 Years	Dx+5 Years to End Follow-up	Event Reported Unknown Age
Condition 1	$N_{11}(Rate_{11})$	$N_{12}(Rate_{12})$	$N_{13}(Rate_{13})$	$N_{14}(Rate_{14})$	$N_{15}(Rate_{15})$
Condition 2	$N_{21}(Rate_{21})$	$N_{22}(Rate_{22})$	$N_{23}(Rate_{23})$	$N_{24}(Rate_{24})$	$N_{25}(Rate_{25})$
etc.					

Case-Sibling Comparisons

Table CS1: Relative Risks and 95% CI of Reported Events by Time Period

Reported Condition	Diagnosis to End of Tx	End Tx to Diagnosis + 5 Yrs.	Diagnosis + 5 Yrs. to End Follow-up
Condition 1	RR_{11} (95%CI_{11})	RR_{12} (95% CI_{12})	RR_{13} (95%CI_{13})
Condition 2	RR_{21} (95%CI_{21})	RR_{12} (95% CI_{22})	RR_{23} (95%CI_{23})
etc.			

Case-Case Comparisons

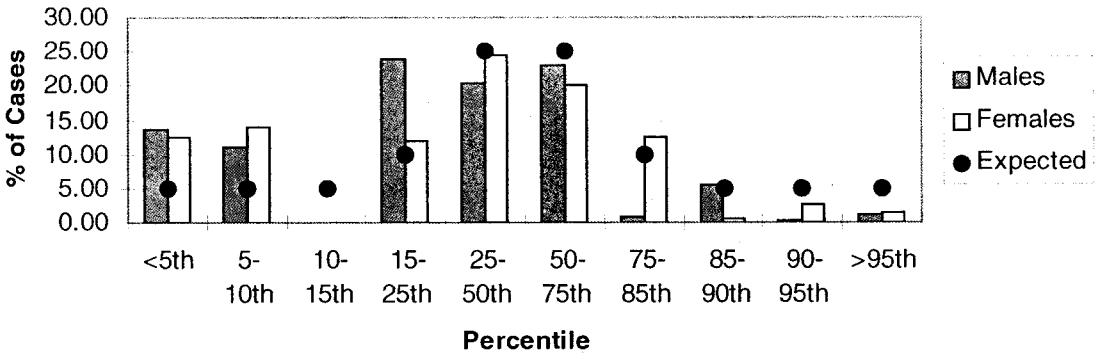
Relative Hazard Ratios

Reported Condition	TRT1	TRT2	TRT3
Condition 1	RR_{11} (95%CI_{11})	RR_{12} (95% CI_{12})	RR_{13} (95%CI_{13})
Condition 2	RR_{21} (95%CI_{21})	RR_{12} (95% CI_{22})	RR_{23} (95%CI_{23})
etc.			

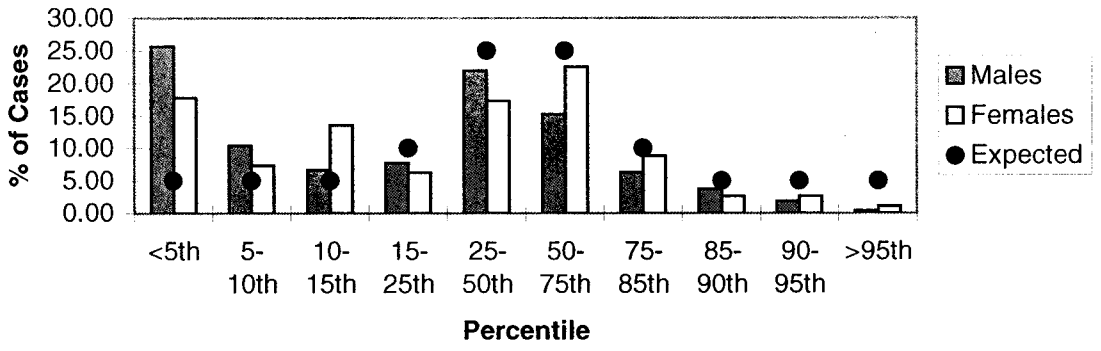
TRT1, TRT2, TRT3 = Different treatment groups

NOTE: Other tables, specific to each analysis, will be constructed to summarize multivariate analyses of treatment-related effects (chemotherapy, radiotherapy) and patient characteristics (diagnosis age, IRS cancer group, etc.)

Age and sex specific height percentiles by sex for cases 18 years and older



Age and sex specific weight percentiles by sex for cases 18 years and older



Age and sex specific BMI percentiles by sex for cases 18 years and older