04-13

Childhood Cancer Survivor Study
Analysis Concept Proposal

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Title: The Long-term Complications of Treatment in Ewing's sarcoma: a Report from the Childhood Cancer Survivor Study

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1.0 Overall Background and Rationale:

Ewing's sarcoma (ES) is the second most common bone tumor of childhood. With multimodality therapy, the overall five-year survival rate of localized Ewing's sarcoma is 60-70%. Although most of these patients are likely to be cured with a combination of chemotherapy and surgery or radiation, a substantial proportion will face significant morbidities.
Our objectives are to determine the prevalence of medical late effects including cardiac disease, infertility, premature ovarian failure and second malignancy utilizing the Childhood Cancer Survivor Study (CCSS) cohort of ES cancer survivors.

2.0 Sections of the Proposal

This proposal will be presented in two different sections with specific aims and hypotheses. The analyses are as follows:

Analysis 1: Major outcomes in ES survivors. The cardiac and gonadal late effects, second malignant neoplasms (SMN) and late mortality in Ewing's sarcoma survivors

Analysis 2: The functional limitations in ES survivors.

3.0 Analysis 1: The cardiac and gonadal late effects and second malignant neoplasms (SMN) in Ewing's sarcoma survivors

3.1 Specific Background and Rationale

As mentioned in the previous section, a limited number of studies have shown that ES survivors are at risk for gonadal toxicity following their treatment. These problems include premature ovarian failure, and fertility.

Cardiac complications have also been described in ES. Risk factors include anthracycline administration and chest radiation therapy.

A risk of SMN has been found in ES survivors. The cumulative incidence of SMN at 20 years after ES treatment is around 3% and the risk increases with time. The most common SMN reported after ES are myelodysplasia/leukemia, soft tissue sarcomas and osteosarcomas.

3.2 Specific Aims

In this population of survivors of ES:

3.2.1 Determine the prevalence of these categories of medical conditions **(outcome)**: gonadal, cardiac and SMN.

3.2.2 Compare the hazard ratio, reported as the relative risk (RR), of each medical outcome between ES survivors and the sibling comparison group (case-sibling comparisons)

3.2.3 Compare the hazard ratio, reported as the relative risk (RR) of late outcomes (first occurrence more than 5 years after diagnosis) among the survivors as a function of treatment (case-case comparison)

Alkylators
Anthracyclines
Topo II inhibitors
Radiation

3.3 Hypotheses

3.3.1 Survivors of ES will have an increased risk of cardiac and gonadal complications and SMN compared to sibling controls.

3.3.2 There is an increased prevalence of medical outcomes, which is, dose related – increased alkylators- increased risk of gonadal toxicity and SMN, increased anthracycline-increased risk of cardiac toxicity.

3.4. Analysis Framework

3.4.1 Outcomes of interest (baseline questionnaire items)

3.4.1.1 **Cardiac outcomes**: self reported diagnosis of:

- Coronary artery disease (F.2) (F.5) (F.6) (F.10)
- Irregular heartbeat or palpitations (F.3)
- Congestive heart failure or cardiomyopathy (F.4)
- A stroke or a cerebrovascular accident (F.9)
- Exercise induced chest pain, shortness of breath, or irregular heartbeat (F.17)
- Medications for high blood pressure or for heart (B8.12)

3.4.1.2 **Gonadal toxicity**: self reported diagnosis

- Low sperm count (E.15)
- Have you ever had a menstrual period (E.16)
- Are you currently having menstrual periods (E.17)

- Have you and a partner ever become pregnant (M.9)
- Did you need medication to go into puberty (E.11)
- Have you ever taken hormones to have your period (E.18)
- Medications (B8.2-OCP use), (B8.3-HRT), (B8.4-testosterone)

3.4.1.3 **Second malignant neoplasms** (SMN): Externally validated second malignant neoplasms only

- New malignancy
- Recurrence
- Breast lump removal/biopsy
- Non-melanoma skin cancer

3.4.2 Subject Population (Table1)

- Cases: ES survivors
- Controls: All CCSS siblings

3.4.3 Exploratory Variables

- **Outcome Variables**: see above

- Exposure variables:
- Exposure to Cyclophosphamide and Cyclophosphamide cumulative dose
- Exposure to Ifosfamide and Ifosfamide cumulative dose
- Exposure to Anthracycline and Anthracycline cumulative dose
- Exposure to any radiation therapy
- Radiation therapy field(s)
- Era of treatment (1970-1974, 1975-1979, 1980-1986)

- Potential confounders and effect modifiers:
- Gender
- Ethnicity
- Age at diagnosis
- Year of diagnosis
- Current age
- Time interval between ES diagnosis and current age

3.5 <u>Analyses</u>

The analyses will be conducted at the Statistical Center at Fred Hutchison Cancer Research Center with Dr. John Whitton supervising the analyses.

3.5.1 Compare the hazard ratio, reported as the relative risk (RR), of each medical condition **(outcome)** between ES survivors and the sibling comparison group **(case-sibling comparisons).**

3.5.2 Specific analyses:

- Determine the relative risk (RR) of developing **ovarian failure** (medication needed to initiate puberty) following the exposure to **Cyclophosphamide** and **Ifosfamide** and evaluate if there is a **dose relationship.**

- Determine the relative risk (RR) of developing **ovarian failure** following the exposure to **abdominal, pelvic and spinal radiation therapy.**

- Determine the relative risk (RR) of developing **premature menopause** following the exposure to **Cyclophosphamide** and **Ifosfamide** and evaluate if there is a **dose relationship.**

- Determine the relative risk (RR) of developing **premature menopause** following the exposure to **abdominal, pelvic and spinal radiation therapy.**

- Determine the relative risk (RR) of developing **infertility** following the exposure to **Cyclophosphamide** and **Ifosfamide** and evaluate if there is a **dose relationship.**

-Determine the relative risk (RR) of developing any of **cardiovascular outcome (arrhythmia, congestive heart failure, hypertension** and **exercise induced chest pain or shortness of breath)** following the exposure to **Anthracyclines** and **chest radiation.**

-Determine the relative risk of developing any **SMN** following the exposure to **alkylators, topoisomerase II inhibitors or radiation.**

-Analyses will be adjusted for age at diagnosis, gender and other variables as appropriate.

4.0 Analysis 2: Functional limitations in ES survivors

4.1 Specific Background and Rationale:

It is important to describe the long-term complications of treatment for ES to develop and implement appropriate surveillance and treatment interventions.

4.2 Specific Aims:

In this population of survivors of ES:

4.2.1 Determine the prevalence of functional limitations among ES survivors and compare the prevalence of functional limitations in ES survivors to sibling controls.

4.3 Hypotheses

4.3.1 The group of ES survivors will have a higher prevalence of self-reported functional limitations than their sibling controls.

4.4. Analysis Framework

4.4.1 Outcomes of interest (baseline questionnaire items)

4.4.1.1 **Physical Activity:**

- Exercise or sports (N.9)

4.4.1.2 **Marriage : self reported ;**

- Have you ever been married (L.1.)

4.4.1.3 **Employment**

- Have you ever had a job (O.5)

4.4.1.4 **Insurance**

- Have you ever had difficulty in obtaining health insurace because of your health hisotry (Q.1)
- Do you currently have health insurace coverage (Q.2)
- Have you ever had difficulty in obtaining life insurace because of your health history (Q.4)
- Do you currently have life insurance coverage (Q.5)

4.4.1.5 **Domains of Health Status**

General Health N.15
Mental Health J.16-J35
Functional Impairment N.10, N.11. N.12
Activity limitations N.14 a-e
Pain J.36
Anxiety J.37

4.4.2 Subject Population (Table 1)

- Cases: ES survivors (all ages at time of baseline questionnaire)
- Controls: All CCSS siblings –not for pain, anxiety

4.4.3 Exploratory Variables

- Outcome Variables: see above

-Potential confounders and effect modifiers:

-Gender
-Ethnicity
-Age at diagnosis
-Year of diagnosis
-Current age
-Time interval between ES diagnosis and current age

4.5 Analyses

The analyses will be conducted at the University of Minnesota under Dr Gurney's supervision and with the consultation of the Statistical Center at Fred Hutchison Cancer Research Center.

4.5.1 Compare the prevalence of functional limitations among ES survivors to sibling controls, reported as Odds ratios (OR).

4.5.2SPECIFIC ANALYSES

- Determine the prevalence of limitations in physical function among ES survivors and compare them to sibling controls.

Analyses will be adjusted for age at diagnosis, gender and other variables as appropriate

Table 1: Characteristics of ES survivors and sibling cohorts

Characteristic	Survivors (n =)	Siblings (n=)
Gender		
Male		
Female		
Race		
Caucasian		
Black		
Hispanic		
Other		
Age at diagnosis (years)		
0-4 years		
5-9		
10-14		
15-20		
Age at entry into CCSS (years)		
<20 years		
20 – 29		
30 – 39		
40 – 49		
Year of diagnosis		
1970 – 1974		
1975 – 1979		
1980 – 1986		
Survival time (years)		
5 – 9		
10 – 14		
15 – 19		
20 – 24		
>25		
Primary site of disease		
Upper extremity		
Lower extremity		
Chest wall		
Pelvis		
Vertebral		
Therapy received for primary malignancy		
Chemotherapy alone		
Chemotherapy and radiation therapy		
Chemotherapy and surgery		
Chemotherapy and radiation and surgery		
Received radiation therapy for primary malignancy		
Chest		
Abdomen		
Head and neck		
Extremities		
TBI		
Received anthracycline therapy for primary malignancy		
Yes		
No		
Received alkylator therapy for primary malignancy		
Yes		
No		

Table 2: Specific risk factors for the occurrence of gonadal toxicity (comparison between patients with and without the risk factor)

	ES	RR	95% CI	p-value
Medication needed to Initiate puberty (ovarian failure)				
Cyclophosphamide				
Yes				
No				
Cyclophosphamide dose				
≤5 g				
5-10 g				
>10 g				
Ifosfamide				
Yes				
No				
Ifosfamide dose				
<30 g				
30-60 g				
>60 g				
Abdominal radiation therapy				
Yes				
No				
Pelvic radiation therapy				
Yes				
No				
Spine radiation therapy				
Yes				
No				
Infertility				
Cyclophosphamide				
Yes				
No				
Cyclophosphamide dose				
≤5 g				
5-10 g				
>10 g				
Ifosfamide				
Yes				
No				
Ifosfamide dose				
<30 g				
30-60 g				
>60 g				

Table 3: Specific risk factors for the occurrence of any cardiovascular outcome (comparison between patients with and without the risk factor)

	ES	RR	95% CI	p-value
Anthracyclines exposure				
Yes				
No				
Anthracyclines cumulative dose				
<300 mg/m^2				
≥300 mg/m^2				
Chest RT				
Yes				
No				

Table 4: Specific risk factors for the occurrence of any SMN (comparison between patients with and without the risk factor)

	ES	RR	95% CI	p-value
Radiation therapy				
Yes				
No				
Alkylator therapy				
Yes				
No				
Topoisomerase II Inhibitor				
Yes				
No				

Table 5: Medical outcomes and functional limitations

Medical	Total reported Cases N (%)	Siblings N (%)
Gonadal toxicity		
Premature ovarian failure		
Medication needed to initiate puberty		
Infertility		
Cardiopulmonary impairments		
Arrhythmia		
Congestive heart failure		
Hypertension		
Exercise induced chest pain, shortness of breath, or irregular heartbeat		
Second cancer		
New malignancy		
Recurrence		
Breast lump removal/biopsy		
Non-melanoma skin cancer		
Functional Impairment		
Needs help with personal care		
Needs help with routine activities		
Health prevents school or work attendance		
Activity Limitations		
Limited in vigorous physical activity		
Limited in moderate physical activity		
Limited ability to climb steps		
Limited ability to bend or lift		
Limited ability to walk one block		

Table 6: Marital, employment and health insurance status

Sex of Patients	No. of Patients	Sibling Controls	Rate in patients	Sibling Controls	Rate in Patients	Sibling Controls	Rate in patients
		Married		Divorced or separated		Never married	
Female							
Male							
		Employed FT		Employed PT		Unemployed	
Female							
Male							
		Private health insurance		Public health insurance		No insurance	
Female							
Male							

Table 7: Comparison of the incidence of cardiac event in study group with that in sibling control group

Type of cardiotoxicity	No. of observed events	No. of expected events	Standardized Incidence ratio	95% Confidence interval
Arrhythmias				
Congestive Heart Failure				
MI				
Stroke				
Angina				

Table 8: Comparison of the incidence of premature ovarian failure in study group with that in sibling control group

	No. of observed events	No. of expected events	Standardized Incidence ratio	95% Confidence interval
Premature Ovarian Failure				

Table 9: Descriptive Characteristics of Patients with Second Malignant Neoplasms

Patient Characteristics	#/%
Sex -Male -Female	
Age at dx of primary malignancy	
Age at dx of second malignancy	
Time from diagnosis of second malignancy from primary malignancy diagnosis - 0-4 years - 5-9 years - 10-14 years - 15-20 years - >20 years	
Location of Second Cancer - Brain - Head and Neck - Chest - Abdomen - Extremities - Genito-urinary	
Alkylators - Yes - No	
Anthracycline - Yes - No	
Topo II inhibitor - Yes - No	
Radiation - Yes - No	