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Childhood Cancer Survivor Study
Analysis Concept Proposal

Title: Long-Term Survivors of Childhood Osteosarcoma

Working Group: Chronic Disease Working Group

Investigators:

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Background and Rationale:

One particular group of childhood cancer survivors with potentially increased sequelae are adult survivors of pediatric osteosarcoma.[1] Children diagnosed with osteosarcoma often require extensive surgical intervention (amputation or limb sparing procedures), and are exposed to significant amounts of chemotherapy. Evidence of the surgical treatment can be quite noticeable because bone tumors predominantly occur in the extremities (lower > upper). [2] Disfigurement or dysfunction related to muscle and bone loss or amputation may interfere with everyday physical function and may alter self image. Additionally, the intensive chemotherapy (and/or radiation therapy) may alter celluar structure and organ function resulting in cardiac impairments, fertility problems, second cancers, etc[3]... and have a lifelong impact on daily living. The impact these treatments have on an individual are compounded by varying levels of emotional maturity (pre-adolescence and adolescence) and skeletal maturity of the child at the time of diagnosis. Emotional maturity may play an important role in psychosocial functioning because of one's development of body image, independence and relationships during adolescence. Skeletal maturity is another potential determinant of psychosocial sequelae because of its importance in determining the type of

surgical local control (amputation/rotationplasty/expanding prosthesis vs. limb sparing surgeries) which can alter one's body image and infringe on self-reliance.

Specific Aims/Objectives/Research Hypotheses:

This study will use data from the Childhood Cancer Survivor Study (CCSS) to determine survival rates, rates of relapse, late mortality, late medical complications, and socioeconomic (education, marriage, employment, insurance) factors in survivors of childhood osteosarcoma.

Hypotheses:

1) Overall and event-free survival will be significantly lower among survivors of childhood osteosarcoma compared to the general U.S. population.

2) Survivors of childhood osteosarcoma therapy will experience significant late morbidity compared with a sibling control group (i.e. early cardiovascular disease, endocrine disorders, second cancers, etc.)

3) Survivors of childhood osteosarcoma will be less educated, and less likely to be employed, have insurance coverage, or be married than the sibling control group and the general population

4) Survivors of childhood osteosarcoma will have increased disability and increased physical limitations compared to the sibling control group

Analysis Framework:

A. Subject population:
   1. all osteosarcoma survivors in the CCSS cohort who have survived 5 years from diagnosis (733 have completed a baseline, 552 have completed Follow-up1 and 488 have completed Follow-up2),
   2. all eligible siblings
   3. U.S. Census Bureau data

B. Outcomes of interest: (see table of variables)
   1. Survival rates
   2. Medical Complications:
      a. Hearing
         i. Baseline: C4 (tinnitus), C5 (vertigo) and Composite of C1 (hearing aid), C2 (deafness not corrected), and C3 (deafness corrected)
         ii. Follow-up 1: Composite of 12a(hearing aid), 12b(deafness not corrected), 12c (deafness corrected)
      b. Kidney function: D4 (dialysis) from Baseline
      c. Fertility
         i. Low Sperm Count: E15 from Baseline

ii. Have you ever had a menstrual period: E16 from Baseline and 19 from Follow-up 1
iii. Pregnancy: M9 from Baseline and 8 from Follow-up 1

d. Cardiovascular
    i. Coronary Artery Disease: Composite of F2, F5, F6, F10 from Baseline
    ii. Coronary Artery Disease: Composite of 10b, 10e, 10f, 10h from Follow-up 1
    iii. Congestive Heart Failure: F4 from Baseline
e. Pulmonary
    i. Lung Fibrosis: Baseline G12
    ii. Lung Fibrosis: Follow-up 1 11l
    iii. O2 need: Baseline G9
    iv. O2 need: Follow-up 1 11i
f. Surgery Frequencies
    i. Amputation: Baseline I1, Follow-up 1 21
    ii. Leg shortening: Baseline I4
    iii. Joint Replacement: Baseline I5
    iv. Other bone surgery: Baseline I6
g. Bone Health: Follow-up 2: Section N

3. Second Cancers:
    a. Baseline: section K
    b. Follow-up 1: question 17
    c. Follow-up 2: section R
4. Education:
    a. Baseline: section O, questions 1-4
    b. Follow-up 1: question 1
    c. Follow-up 2: question 1
5. Employment:
    a. Baseline: section O, questions 5-11, section Q, questions 8, 9
    b. Follow-up 2: question 3
    c. Follow-up 3: questions 4, 5, 6
6. Insurance:
    a. Baseline: section Q, questions 1-6
    b. Follow-up1: question 16
    c. Follow-up 2: section M
7. Marriage:
    a. Baseline: section L
    b. Follow-up 1: question 2
    c. Follow-up 2: questions 2 and 3
8. Pregnancy history:
    a. Baseline: section M
    b. Follow-up 1: question 8
    c. Follow-up 2: section N
9. Physical Disability
    a. Baseline: N10 and N11
    b. Follow-2: SF-36 - Role Physical

10. Physical Limitation
    a. Baseline: N12, N14a, N14b, N14c, N14d, N14e
    b. Follow-2: SF-36 - Physical Function

C. Explanatory variables: (see table of variables)
    1. Age at cancer diagnosis
    2. Age at response to CCSS questionnaire
    3. Time from diagnosis
    4. Gender
    5. Type of treatment (chemotherapy, radiation, surgery) – Yes/No
    6. Type and cumulative doses of chemotherapy
        a. Anthracycline Yes/No
        b. Anthracycline <300 or > 300 mg/m2
        c. Cisplatinum Yes/No
        d. Alkylator use
            i. Cytoxan
                1. Yes/No
                2. <5gm. 5-10 gm, and > 10gm
            ii. Ifosfamide
                1. Yes/No
                2. <30gm, 30-60gm, and >60 gm
    7. Radiation site and dose
        a. Site: Pelvis, abdomen, thorax/lung, arm, leg, head/neck
            i. Yes/No to site
            ii. Dose: Gross doses (<2000, 2000-4000, >4000)
    8. Types of surgery
    9. Site of disease

Dependent and Outcome Variables	
Dependent Variable	**Outcome Variables**
Age at Cancer Dx Age at questionnaire Gender Type of Treatment (chemo/XRT/surgery) Type and cumulative dosages of chemotherapy Radiation (site and dose) Types of Surgery Site of Disease	Medical Complications Baseline: Section C (Hearing) Baseline: Section D (Urinary) Baseline: Section E (Hormonal) Baseline: Section F (cardiovascular) Baseline: Section G (Pulmonary) Baseline: Section H (GI) Baseline: Section I (Surgical) Follow-up 1: Question 9 (medical condition) Follow-up 1: Question 10 (cardiovascular) Follow-up 1: Question 11 (Respiratory) Follow-up 1: Question 12 (Hearing) Follow-up 1: Ovarian failure and menopause data Follow-up 2: Section N (bone health)
	Second Cancers

	Education
	Employment
	Insurance
	Marriage
	Pregnancy History
	Physical Disability
	Physical Limitations

D. Analysis Plan:

1. Descriptive Epidemiology/Summary statistics:
   a. Characteristics of osteosarcoma survivors and siblings will be described using frequencies, means (SD) or medians (range).

2. Survival Analysis:
   a. Standardized mortality ratios (SMR) (observed number of deaths divided by the expected number) and their 95% confidence intervals will be calculated. SMR will be calculated using age- and sex-specific United States mortality rates, reported by the National Center for Health Statistics. Patients will be grouped by age into 5-year intervals. (Yausai) All-cause SMRs and cause-specific SMRs for secondary or subsequent cancer (ICD 140 to 239), cardiac causes (ICD 390 to 398, 402, 404, 410 to 429), pulmonary causes (ICD 460 to 519), external causes (accidents, suicides, poisonings, and so on; ICD 800 to 999), and other causes (all other ICD codes) will be computed for all deaths. (Only deaths with known causes not due to recurrence of the original cancer will be included).
   b. Overall survival and event-free survival will be analyzed from the 5^{th} and 10^{th} anniversary dates of diagnosis with the life table method (Kaplan-Meier curves). Survival curves for this cohort will be compared with the comparable United States population, based on the United States age- and sex-specific mortality rates. An expected number of deaths for each year since diagnosis will be calculated based on US age and sex specific mortality rates, yielding and expected survival function for each sex.(Le)
   c. Cumulative incidence of relapse, SMN, pulmonary complications, cardiovascular complications and death during remission will be calculated, treating death prior to the event of interest or relapse, as appropriate, as competing risk events. Hazard ratios for these outcomes comparing the osteosarcoma survivors and siblings will be calculated with Cox proportional hazards regression adjusted for age at diagnosis, and gender, race, treatment era and site of disease.

3. The chi-square test of independence (or Fisher's exact test if expected frequencies are less than 5) will be used to compare proportions of medical complications, educational levels, physical limitations and disability, employment status, insured status, marital status of cases, siblings, and the general population. (Breslow & Day)

4. Multiple logistic regression, log linear regression, or Poisson regression will be used to compare rates of medical complications, physical limitations and disability, educational

levels, employment status, insured status, marital status between cases and siblings. (Homer & Lemeshow) adjusted for current age, age at diagnosis and gender.

5. Multiple logistic regression, log linear regression, or Poisson regression will be used to compare rates of medical complications (cardiovascular, pulmonary and fertility), and physical limitations/disability between those that received radiation and those who did not (Homer & Lemeshow) adjusted for current age, age at diagnosis and gender and site of disease.

6. Multiple logistic regression, log linear regression, or Poisson regression will be used to compare rates of hearing and kidney complications between those that received cisplatinum and those who did not (Homer & Lemeshow) adjusted for current age, age at diagnosis and gender and site of disease.

7. Multiple logistic regression, log linear regression, or Poisson regression will be used to compare rates of medical complications (cardiovascular and fertility) and physical limitations/disability between those that received anthracyclines and those who did not (Homer & Lemeshow) adjusted for current age, age at diagnosis and gender and site of disease.

8. Multiple logistic regression, log linear regression, or Poisson regression will be used to compare rates of medical complications (fertility) between those that received alkylators and those who did not (Homer & Lemeshow) adjusted for current age, age at diagnosis and gender and site of disease.

E. Tables and Figures:

1. Demographic table of CCSS osteosarcoma cases and siblings(if applicable):
    - sex
    - diagnosis
    - site of disease
    - age at diagnosis
    - age at follow-up
    - treatment
        - Radiation
        - Chemotherapy
        - Surgeries
    - treatment era
    - medical complications

2. Survival curves: overall survival, overall survival vs US population
3. SMR tables
4. Table of frequencies of medical outcomes and SMNs
5. Cumulative incidence curves: late medical outcomes (cardiovascular, pulmonary, hearing, kidney), second cancers

6. Tables: educational attainment, employment status, insurance status, marital/family status demonstrating frequencies and rates of each of these social indicators compared to the sibling control group and national data
7. Table: Physical disability and physical limitations compared to sibling control group

Special Consideration:

This concept proposal is submitted in response to the CCSS steering committee's request for disease-focused initiatives within the CCSS cohort.

1. Nagarajan, R., et al., *Limb salvage and amputation in survivors of pediatric lower-extremity bone tumors: what are the long-term implications?* Journal of Clinical Oncology, 2002. **20**(22): p. 4493-501.
2. Ries, L., et al., eds. *Cancer Incidence and Survival among Children and Adolescents: United States SEER Program 1975-1995.* National Cancer Institute, SEER program. Vol. NIH Pub . No 99-4649. 1999: Bethesda, MD.
3. Bhatia, S., W. Landier, and L. Robison, *Late effects of childhood cancer therapy*, in *Progress in Oncology 2002*, V. DeVita, S. Hellman, and S. Rosenberg, Editors. 2003, Jone and Barlett Publications: Sudbury, MA. p. 171-201.