CCSS Analysis Concept Proposal
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1. Title: Predictors of physical activity in survivors of lower extremity sarcoma: a report from the Childhood Cancer Survivor Study

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3. Background and rationale:

Cure rates for children and adolescents with lower-extremity sarcoma have improved significantly over the past few decades with current 5 year overall survival percentages ranging from 58.6% for those with Ewing sarcoma to 65.8% for those with osteosarcoma[1]. Progress is related to improvements in both medical care and oncology intervention. With improved survival, the focus of research now includes investigations into the long term impact of not only these diseases, but also the therapeutic interventions used to treat these diseases on organ system impairments, physical performance limitations, and participation restrictions in these young survivors. Such studies are important because these young survivors face the challenges of living productive lives in the context of these impairments and limitations.

Children with lower-extremity sarcoma undergo toxic chemotherapeutic regimens, limb-altering surgical procedures,[2-5] and/or vigorous localized radiotherapy interventions that place them at risk for cardiopulmonary, musculoskeletal, and neuromuscular impairments in adult life. Cardiomyopathy, lung fibrosis, chest wall abnormalities,[6, 7] bony deformity, low bone mineral density and osteonecrosis,[8] limited range of motion[9], reduced muscular strength and control,[10] peripheral neuropathy[11], and balance dysfunction[12] have all been reported. These impairments interfere with physical performance, which may limit the ability of these survivors to fully participate in regular physical activity.

Physical activity is an important health behavior that has the potential to ameliorate or prevent further deterioration of cardiopulmonary, musculoskeletal and neuromuscular health, and provides an opportunity for intervention among survivors at risk for poor health outcomes. Identification of individuals least likely to participate in physical activity will help researchers understand and identify possible targets for intervention. Evidence from the chronic disease literature suggests that impairments of cardiopulmonary, musculoskeletal and neuromuscular

function are amenable to rehabilitation interventions, thus potentially enhancing the ability of those treated to better participate in physical activity to enhance their own health[13-17].

A recent investigation of physical activity in the overall Childhood Cancer Survivor Study cohort[18] found that survivors of childhood cancer are less likely than their siblings to meet physical activity guidelines and more likely to be inactive. More importantly, those with lower extremity amputation, a common treatment for lower extremity sarcoma, had some of the highest risks for inactivity. Given that physical activity is known to provide benefits even to those who have substantial functional loss[19-21], it is important to identify the factors related to inactivity so that interventions may be developed to help these survivors attain optimal physical activity levels. **The primary aim of this manuscript is to refine the analysis of Ness et al. so as to more specifically identify the predictors of physical activity in childhood survivors of sarcoma of the lower extremity.** We propose to identify disease related, treatment related, demographic, and personal factors that impact physical activity levels in these survivors.

4. Purpose/aims:

The primary aim of this manuscript is to identify predictors of physical activity in survivors of sarcoma of the lower extremity. A secondary aim is to determine how the duration of survivorship impacts physical activity in this patient population. There have been other general analyses describing the physical activity patterns of the CCSS cohort. However to date, only the physical activity patterns of acute lymphocytic leukemia (ALL) survivors have been examined in detail.[22] We propose to identify factors (including disease and treatment related factors, demographic characteristics, and personal factors) that impact physical activity levels in sarcoma survivors. By understanding these factors, interventions may then be devised and implemented to improve physical activity levels among survivors of lower extremity sarcoma and thereby improve their overall health, activity levels, and participation.

Hypothesis #1: The following variables will be associated with reporting an inactive lifestyle, and with reporting not meeting the CDC physical activity guidelines at the second follow-up questionnaire: hemipelvectomy or amputation above the knee, lung surgery (excluding biopsy), chest or whole lung radiation, localized radiation, greater anthracycline dose, greater platinum dose, greater bleomycin dose, vinca alkaloid in treatment history, baseline BMI, older age at diagnosis, older age at the second follow-up, persistent cancer related pain, higher levels of anxiety, symptoms of depression, tobacco use, lower annual household income (TABLE 1).

Hypothesis #2: The following variables will be associated with the total number of minutes per week of at least moderate intensity physical activity at the second follow-up questionnaire: hemipelvectomy or amputation above the knee, lung surgery (excluding biopsy), chest or whole lung radiation, local radiation, anthracycline dose (tertiles), platinum dose (tertiles), bleomycin dose (tertiles), vinca alkaloid in treatment history, baseline BMI, older age at diagnosis, older age at the second follow-up, persistent cancer related pain, higher levels of anxiety, symptoms of depression, tobacco use, lower annual household income (TABLE 2).

Hypothesis #3: The average number of days per week of participation in at least 20 minutes of moderate intensity physical activity will decline in this cohort from the baseline questionnaire to the second follow-up questionnaire relative to members of the sibling comparison group, after adjusting for age and gender (FIGURE 1).

5. Analysis framework:

Sample

Survivor participants (N=519) diagnosed with soft tissue sarcoma, osteosarcoma, Ewing sarcoma or other bone tumor of the lower extremity or pelvis (ICD-O-3 site codes C40.2 C40.3, C41.4,C41.8, C49.2, C49.5)) who completed the baseline and the second follow-up questionnaire and who consented to and had a medical record abstraction will be included. Members of the sibling comparison group who filled out both the baseline and the second follow-up questionnaire will be included for analysis of hypothesis #3.

Outcomes of interest

Physical activity levels: Questions D1 – D7 from the second follow-up questionnaire:

- The average number of minutes per day (or week) of moderate physical activity
- The average number of minutes per day (or week) of vigorous physical activity
- A binary variable for whether subjects meet the nationally recommended guidelines for physical activity (30 minutes of moderate intensity physical activity on 5 or more days of the week or 30 minutes of vigorous physical activity on 3 or more days of the week).
- A binary variable indicating if subjects reported no physical activity over the past month

Independent (exploratory) variables

A. Diagnosis and treatment variables
    - Cancer diagnosis (dx group variable)
        - Ewing Sarcoma
        - Osteosarcoma
        - Other bone tumor
        - Soft Tissue Sarcoma
    - Age at diagnosis (Date of diagnosis and date of birth), explored as:
        - specific categories
            - 0-4 years
            - 5-9 years
            - 10-14 years
            - 15-20 years
        - continuous
    - Treatment
        - Surgery—Amputation-- ICD-9 codes 84.1, 84.3, or 84.4 (Baseline Questionnaire I.1 and medical record abstraction form)
            - Transtibial
            - Transfemoral
            - Hemipelvectomy
        - Surgery—Limb sparing procedure ICD-9 codes 77.05, 77.07, 77.09, or 77.60 (Baseline Questionnaire I.1, I.4, I.6 and medical record abstraction form)
        - Surgery to lungs (Medical record abstraction form)--ICD-9 codes 32.0-32.9, 34.3, 34.4, 34.5, 34.9
        - Chest radiation (yes/no, cumulative dose from diagnosis to cohort eligibility – first five years)
        - Local radiation—defined as radiation to site of surgery/amputation (yes/no, cumulative dose from diagnosis to cohort eligibility—first five years)
        - Anthracyclines: Daunorubicin (Daunomycin), Doxorubicin (Adriamycin) (explored as yes/no, overall score, < 300 mg/m2 vs. >=300 mg/m2 and cumulative dose with appropriate conversion to equivalent doxorubicin dose)

    - Platinum compounds: Carboplatin, Cis-platinum (explored as yes/no, tertiles, and cumulative dose)
    - Bleomycin (explored as yes/no, and cumulative dose)
    - Vinca alkaloids: Vinblastine (Velban), Vincristine (explored as yes/no)

B. Demographic and personal factors

- BMI at baseline and the second follow-up (weight in kilograms/height in meters squared) (A10-A11). We realize that BMI and physical activity are likely to be correlated and that the direction of this association will not be able to be determined. We will take this into account in our analysis.
- Age at second follow-up (Completion date second follow-up and date of birth)
    - specific categories
    - continuous
- Gender (A.2 – baseline)
- Race/ethnicity (A4 and A4a baseline)
    - White not Hispanic (reference)
    - Black
    - Hispanic
    - Other
- Annual household income at second follow-up (S1)
    - <$40,000/year
    - $40-59,999/year
    - 60+/year
    - Not indicated
- BSI questions/BPI from baseline (J16-J36 adult/J16-J21 under 18)
    - Depression T-score from BSI
    - Depression scale score from behavioral problem index
- Pain and anxiety question from second follow-up (G19-G20)
    - None or mild vs. moderate or greater for both variables
- Smoking/tobacco (L1-6 second follow-up)
    - Never user, current user, former user
- Participation in physical activity at baseline (N 15)
    - Yes/no

Statistics

Descriptive statistics including means and standard deviations, medians and ranges will be calculated for the baseline demographic, diagnosis, and treatment variables and then compared with eligible participants and non-participants using compared with two-sample t-tests or Chi-square statistics. These descriptors will be used to describe the cohort and present information in the manuscript on the generalizability of the results to the greater population of survivors of childhood onset lower extremity sarcoma.

The frequencies and percents (or means and standard deviations for continuous variables) of individuals who do not meet the CDC guidelines for physical activity or who report no physical activity over the past month will be reported overall and by categories for each independent variable. The association between hemipelvectomy or transfemoral amputation, lung surgery (excluding biopsy), chest or whole lung radiation, local radiation, anthracycline dose, platinum dose, bleomycin dose, vinca alkaloid in treatment history, baseline BMI, older age at diagnosis, older age at the second follow-up, persistent cancer related pain, higher levels of anxiety,

symptoms of depression, tobacco use, lower annual household income and either not meeting the CDC physical activity guidelines or reporting no physical activity over the past month will be evaluated in univariate and multiple variable log linear models. Results will be reported as risk ratios and 95% confidence intervals. Analyses will be stratified by sex.

The mean number of minutes per week of at least moderate intensity physical activity will be calculated by category or unit of hemipelvectomy or transfemoral amputation, lung surgery (excluding biopsy), chest or whole lung radiation, local radiation, anthracycline dose, platinum dose, bleomycin dose, vinca alkaloid in treatment history, baseline BMI, older age at diagnosis, older age at the second follow-up, persistent cancer related pain, higher levels of anxiety, symptoms of depression, tobacco use, lower annual household income and compared in single variable and multiple variable models. Results will be reported as means and standard errors by category or unit, with p-values and R-squared values to represent the contribution of each independent variable to the overall prediction model. Analyses will be stratified by sex.

The change in the mean number of days per week of at least 20 minutes of moderate intensity physical activity at baseline compared to the mean number of days per week of at least moderate intensity physical activity at the second follow-up questionnaire will be calculated and reported with standard errors in age and gender adjusted models for both siblings and survivors. General linear mixed models will be used to compare the change in survivors to the change in siblings to add a variance term for potential within family correlation.

6. References

1. Ries L, Melbert D, Kraphcho M, Stinchcomb D, Howlader N, Horner M et al. SEER Cancer Statistics Review 2007 [cited 2009 March 30]. Available from: URL: http://seer.cancer.gov/csr/1975_2005/.
2. Dormans JP, Garg S. Images in clinical medicine. Rotationplasty for Ewing's sarcoma of the distal femur. N Engl J Med 2004;351(8):e7.
3. Hosalkar HS, Dormans JP. Limb sparing surgery for pediatric musculoskeletal tumors. Pediatr Blood Cancer 2004;42(4):295-310.
4. Marina N, Gebhardt M, Teot L, Gorlick R. Biology and therapeutic advances for pediatric osteosarcoma. Oncologist 2004;9(4):422-41.
5. Muscolo DL, Ayerza MA, Aponte-Tinao L, Farfalli G. Allograft reconstruction after sarcoma resection in children younger than 10 years old. Clin Orthop Relat Res 2008;466(8):1856-62.
6. Mertens AC, Yasui Y, Liu Y, Stovall M, Hutchinson R, Ginsberg J et al. Pulmonary complications in survivors of childhood and adolescent cancer. A report from the Childhood Cancer Survivor Study. Cancer 2002;95(11):2431-41.
7. Paulides M, Kremers A, Stohr W, Bielack S, Jurgens H, Treuner J et al. Prospective longitudinal evaluation of doxorubicin-induced cardiomyopathy in sarcoma patients: a report of the late effects surveillance system (LESS). Pediatr Blood Cancer 2006;46(4):489-95.
8. Kadan-Lottick NS, Dinu I, Wasilewski-Masker K, Kaste S, Meacham LR, Mahajan A et al. Osteonecrosis in adult survivors of childhood cancer: a report from the childhood cancer survivor study. J Clin Oncol 2008;26(18):3038-45.
9. Carty CP, Dickinson IC, Watts MC, Crawford RW, Steadman P. Impairment and disability following limb salvage procedures for bone sarcoma. Knee 2009.
10. De Visser E, Veth RP, Schreuder HW, Duysens J. Altered phase-transitions in tibialis anterior and medial gastrocnemius during walking after limbsaving surgery. Clin Neurophysiol 2005;116(12):2741-7.
11. Citak EC, Oguz A, Karadeniz C, Karaoglan B, Tan MO, Okur V et al. Vincristine-induced peripheral neuropathy and urinary bladder paralysis in a child with rhabdomyosarcoma. J Pediatr Hematol Oncol 2008;30(1):61-2.
12. de Visser E, Deckers JA, Veth RP, Schreuder HW, Mulder TW, Duysens J. Deterioration of balance control after limb-saving surgery. Am J Phys Med Rehabil 2001;80(5):358-65.
13. Aruin AS, Nicholas JJ, Latash ML. Anticipatory postural adjustments during standing in below-the-knee amputees. Clin Biomech (Bristol, Avon) 1997;12(1):52-9.
14. Flynn KE, Pina IL, Whellan DJ, Lin L, Blumenthal JA, Ellis SJ et al. Effects of exercise training on health status in patients with chronic heart failure: HF-ACTION randomized controlled trial. JAMA 2009;301(14):1451-9.
15. Kauzlaric N, Kauzlaric KS, Kolundzic R. Prosthetic rehabilitation of persons with lower limb amputations due to tumour. Eur J Cancer Care (Engl) 2007;16(3):238-43.
16. Knecht S, Henningsen H, Hohling C, Elbert T, Flor H, Pantev C et al. Plasticity of plasticity? Changes in the pattern of perceptual correlates of reorganization after amputation. Brain 1998;121 (Pt 4):717-24.
17. O'Connor CM, Whellan DJ, Lee KL, Keteyian SJ, Cooper LS, Ellis SJ et al. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. JAMA 2009;301(14):1439-50.

18. Ness K, Gebhardt MC, Warwisck AB, Hudson MM. Functional Outcomes for Survivors of Pediatric Sarcoma. ASCO. 2008. p 479-84.
19. (CDC) CfDCaP. Physical activity among adults with a disability--United States, 2005. MMWR Morb Mortal Wkly Rep 2007;56:1021-4.
20. Berk DR, Hubert HB, Fries JF. Associations of changes in exercise level with subsequent disability among seniors: a 16-year longitudinal study. J Gerontol A Biol Sci Med Sci 2006;61(1):97-102.
21. Fielding RA, Katula J, Miller ME, Abbott-Pillola K, Jordan A, Glynn NW et al. Activity adherence and physical function in older adults with functional limitations. Med Sci Sports Exerc 2007;39(11):1997-2004.
22. Florin TA, Fryer GE, Miyoshi T, Weitzman M, Mertens AC, Hudson MM et al. Physical inactivity in adult survivors of childhood acute lymphoblastic leukemia: a report from the childhood cancer survivor study. Cancer Epidemiol Biomarkers Prev 2007;16(7):1356-63.

Examples of proposed tables

Table 1. Logistic regression model results

	Did not meet CDC guidelines for physical activity				**Reported no physical activity over past month**			
	N	Row Percent	RR	95% CI	N	Row Percent	RR	95% CI
Lower extremity surgery								
Hemipelvectomy								
Transfemoral amputation								
Transtibial amputation								
Limb sparing surgery								
Lung surgery (excluding biopsy)								
Yes								
No								
Chest or lung radiation								
Yes								
No								
Local radiation								
Yes								
No								
Anthracycline dose								
None								
Lowest tertile								
Middle tertile								
Highest tertile								
Platinum dose								
None								
Lowest tertile								
Middle tertile								
Highest tertile								
Bleomycin dose								
None								
Lowest tertile								
Middle tertile								
Highest tertile								
Vinca alkaloid								
Yes								
No								
Baseline body mass index								
Underweight								
Normal weight								
Overweight								
Obese								
Age at diagnosis								
< 4 years								
5-9 years								
10-14 years								
15-20 years								
Age at second follow-up								
<25 years								
25-34 years								
35+ years								
Persistent cancer related pain								

Moderate or greater								
None or mild								
Anxiety as a result of cancer								
Moderate or greater								
None or mild								
Depression								
T-score 63+ on BSI								
T-score < 63 on BSI								
Annual household income								
<$40,000								
$40,000+								

Table 2. Mean minutes of at least moderate physical activity per week by treatment, demographic and personal factors

	Mean	Standard Error	p-value	Contribution to R^2
Lower extremity surgery				
Hemipelvectomy				
Transfemoral amputation				
Transtibial amputation				
Limb sparing surgery				
Lung surgery (excluding biopsy)				
Yes				
No				
Chest or lung radiation				
Yes				
No				
Local radiation				
Yes				
No				
Anthracycline dose				
None				
Lowest tertile				
Middle tertile				
Highest tertile				
Platinum dose				
None				
Lowest tertile				
Middle tertile				
Highest tertile				
Bleomycin dose				
None				
Lowest tertile				
Middle tertile				
Highest tertile				
Vinca alkaloid				
Yes				
No				
Baseline body mass index				
Underweight				
Normal weight				
Overweight				
Obese				
Age at diagnosis				
< 4 years				
5-9 years				
10-14 years				
15-20 years				
Age at second follow-up				
<25 years				
25-34 years				
35+ years				
Persistent cancer related pain				
Moderate or greater				
None or mild				

Anxiety as a result of cancer				
Moderate or greater				
None or mild				
Depression				
T-score 63+ on BSI				
T-score < 63 on BSI				
Annual household income				
<$40,000				
$40,000+				

Figure 1 Example. Average number of days per week active at moderate intensity or higher for 20+ minutes