1) **Study title:** Late complications based on local control modalities for childhood pelvic sarcoma

2) **Working groups and investigators:** The study will be performed with the assistance of the Childhood Cancer Survivor Study (CCSS) Chronic Disease Working Group. Secondary oversight will be provided by the CCSS Epidemiology/Biostatistics Working Group, Psychology Working Group, and Second Malignancies Working Group.
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3) **Background and rationale:**
Compared with other anatomic locations, pelvic sarcoma is associated with increased rates of mortality, tumor recurrence, and morbidity[1,2]. The deep space of the pelvis may result in a longer interval between disease development and diagnosis for pelvic sarcomas. Specifically, pelvic sarcomas are more likely to present with advanced stage at diagnosis, higher rates of metastasis, and anatomic difficulties with the delivery of local control therapies including surgery and radiation[1,2]. Despite these inherent treatment challenges, the advent and refinement of multimodality therapies for pelvic sarcoma have resulted in improvement in overall survival from 20% to greater than 70% during the past 30 years[1]. In general, surgical resection of a pelvic sarcoma is challenging due to adjacent structures (e.g. neurovasculature, viscera, and musculoskeletal structures) and therefore definitive radiotherapy may be an attractive alternative to avoid short-term complications. However, the short-term risks of surgical resection may be counterbalanced by the long-term risk of late effects from pelvic radiotherapy.

With improving rates of long-term survival, these long-term morbidities from pelvic sarcoma treatment are increasingly important to identify, in order to implement preventative strategies or early treatment. The pelvis is an especially important area in which to consider the late effects of either method of local control (i.e., surgery or radiotherapy), because vital structures are included in the area of treatment and, as such, are at risk of damage. Specific structures at risk include

vasculature (e.g., iliac vessels and their branches), nerves (e.g., lumbosacral plexus and autonomics), visceral organs (e.g., rectum, ureter/bladder, uterus, cervix, ovaries, and prostate), musculature (e.g., pelvic floor), external organs (anus, vagina, phallus, and testes), and bones (e.g. pelvis, 4-5th lumbar vertebrae [L4-5], sacrum, and coccyx).

The three predominant tumor histologies that account for pediatric pelvic sarcomas are Ewing sarcoma, osteosarcoma, and rhabdomyosarcoma[1]. Ewing sarcoma and osteosarcoma of the pelvis almost always originate from bones (L4-5 vertebrae, sacrum, coccyx, and pelvis), whereas pelvic rhabdomyosarcoma originates from a wider variety of visceral and muscular structures including the bladder, prostate, uterus, cervix, and pelvic musculature. Nearly all patients with these three tumor histologies receive systemic chemotherapy. Local control therapy for osteosarcoma almost always involves surgical resection. In contrast, local control therapy for Ewing sarcoma and rhabdomyosarcoma can involve surgery, definitive radiation without surgery, or a combination of surgical resection and radiotherapy. The disparate role of local control therapies for each of these three malignancies in the pelvis presents the unique opportunity to determine the effects of pelvic surgery and radiotherapy on late mortality, secondary malignancy, functional outcomes, and quality of life outcomes in pelvic sarcoma survivors. A more complete understanding of these effects is needed to explain long-term risks and benefits of each local control modality to patients when making initial cancer therapy decisions.

The late effects of multimodality therapy for pelvic sarcomas have been incompletely explored in prior studies. Using the SEER database to investigate predictors of late death in patients who survived greater than 60 months after treatment for Ewing sarcoma, Dubois et. al. determined that a pelvic primary site was associated with late death in univariate analysis, and that axial/pelvic tumor location was an independent predictor of late mortality[3].

A study from the Swedish Cancer Registry showed that a primary pelvic location for Ewing and osteosarcoma was associated the secondary development of genitourinary malignancies[4]. The highest standardized incidence ratio for development of any secondary malignancy was found in patients with primary pelvic Ewing sarcoma in this study, suggesting that the development of secondary malignancies was due to radiation effect[4]. Pelvic or spinal Ewing and osteosarcoma have also been associated with the secondary development of treatment-related myelodysplastic syndrome and acute leukemia[5]. A recent study from the St. Jude life cohort showed that Ewing sarcoma survivors frequently exhibited hypogonadism/infertility and male survivors had abnormally low sperm concentrations associated with exposure to gonadotoxic alkylating agents and pelvic radiation exposure[6]. This study also showed that osteosarcoma survivors with a primary pelvic resection or lower extremity amputation had inferior physical performance (aerobic function, mobility, walking efficiency) when compared to patients with an upper extremity primary tumor or a lower extremity primary tumor who underwent limb salvage surgery[6]. This difference was not seen among surgical groups in the Ewing sarcoma cohort, perhaps indicating that definitive radiotherapy could spare late impairment of physical performance[6]. A large, single-institution study examining patient-reported functional and quality of life outcomes in long-term survivors of Ewing sarcoma found that patients with pelvic tumors had inferior functional outcomes as assessed by Toronto Extremity Salvage Scores (TESS) when compared to patients with a nonpelvic tumor location[7]. Survivors of childhood bone sarcomas have been shown to have higher rates of moderate-to-severe chronic pain relative to other cancer diagnoses[8]. Bladder function and related outcomes in survivors of pediatric pelvic sarcoma have not been specifically assessed in the CCSS cohort. Erectile dysfunction has been associated with pelvic surgery during treatment in male survivors of childhood cancer[9]. Long-term medical effects of childhood

rhabdomyosarcoma include need for medications to induce puberty and loss of sensory motor function[10]. Survivors of bladder/prostate rhabdomyosarcoma have been shown to have persistent abnormal bladder function and erectile dysfunction[9,11,12].

A prior publication including survivors from the baseline cohort of the Childhood Cancer Survivorship Study with pelvic and lower extremity osteosarcoma and Ewing sarcoma determined that patients with a pelvic primary tumor and those receiving pelvic radiation were more likely to be disabled as judged by a Quality of Life Cancer Survivor (QOL-CS) score below the 25th percentile[13]. In this prior publication from the CCSS, the proportion of survivors of primary pelvic Ewing and osteosarcoma was much smaller than predicted, likely due to suboptimal oncologic treatment outcomes of pelvic sarcoma achieved during the treatment era of the original cohort[13]. Subsequent studies from the CCSS have combined pelvic and lower extremity sarcomas, focused on lower extremity sarcomas exclusively, or not stratified the analysis of late effects based on the anatomic location of the primary tumor, and therefore have not specifically interrogated the late effects of pelvic sarcoma treatment in more recent treatment eras[14-18]. Overall, conclusions regarding the late effects of treatment in pelvic sarcoma survivors from prior studies have been limited by a small number of patients or combined analyses of pelvic and lower extremity sarcomas.

Furthermore, there is currently no consensus strategy for local control. Among long-term survivors of pelvic sarcoma, it is unknown whether those who underwent primary surgery have fewer (or more) late complications than those who underwent primary radiotherapy. Many existing studies are limited only to outcomes of mortality and recurrence. The findings of this proposed study will have potential implications for local treatment recommendations as well as prognostication among children diagnosed with pelvic sarcoma. The study population comprises 508 survivors of pelvic sarcoma who participated in the original cohort and expanded cohort baseline questionnaire. This includes 343 survivors of pelvic soft tissue sarcoma (including 281 with rhabdomyosarcoma), 135 Ewing sarcoma, 24 osteosarcoma, and 6 other bone tumors of the pelvis.

4) **Specific aims:**

a) **Specific aim 1**. To describe the difference in **all-cause and health-related-cause late mortality** among childhood cancer survivors of pelvic sarcomas treated for local control overall, and with A) surgical resection alone vs. B) radiotherapy alone vs. C) surgical resection and radiotherapy.

i) All-cause and health-related-cause late mortality will be compared between pelvic sarcoma survivors and age-matched sibling controls.

ii) All-cause and health-related-cause late mortality will be compared among the three local control treatment groups and also to a cohort of similarly treated sarcoma survivors from other anatomic sites.

b) **Specific aim 2**. To describe the difference in **late effects** including functional outcomes (e.g., physical function, bladder function and related outcomes, sexual function, chronic pain), reproductive outcomes (fertility/infertility), second neoplasm, and CTCAE chronic health conditions among survivors of childhood pelvic sarcomas treated for local

control overall, and with A) surgical resection alone vs. B) radiotherapy alone vs. C) surgical resection and radiotherapy.

i) Functional outcomes, fertility, and CTCAE chronic health conditions will be compared between pelvic sarcoma survivors and age-matched sibling controls.

ii) The incidence of secondary malignant neoplasms (SMN) in survivors of pelvic sarcoma will be compared to the incidence of malignant neoplasms in the general population using the SEER databse.

iii) Functional outcomes, reproductive outcomes, second neoplasm, and CTCAE chronic health conditions will be compared among the three local control treatment groups and also to a cohort of similarly treated sarcoma survivors from other anatomic sites.

c) **Specific aim 3**. To compare **quality of life measures** among childhood cancer survivors of pelvic sarcoma treated for local control with A) surgical resection alone vs. B) radiotherapy alone vs. C) surgical resection and radiotherapy.

i) Quality of life measures will be compared between pelvic sarcoma survivors and age-matched sibling controls.

ii) Quality of life measures will be compared among the three local control treatment groups and also to a cohort of similarly treated sarcoma survivors from other anatomic sites.

5) **Analysis framework:**

a) **Outcomes of interest**

(1) Late mortality

(a) All-cause late mortality

(b) Health-related-cause late mortality

(2) **Late effects** (late effects will be evaluated individually and chronic health conditions listed below will be evaluated individually and as a composite outcome by CTCAE grades).

(a) Physical function and activity: based on constructs from prior studies (e.g., Ness et al., 2017, Florin et al., 2007)[19,20]

(i) Functional impairment (report of needing help with personal care or routine needs or difficulty attending school or work Baseline #N.10-12, ExpBaseline #O16-18, LTFU 2007 #N22-24, LTFU 2014 #N25-27)

(ii) Physical performance limitation (e.g., problem walking 1 block for 3 months or more in the past two years Baseline #N.14a-f, ExpBaseline #O20a-f, LTFU 2007 #N26a-f, LTFU 2014 #N29a-f)

(iii) Physical activity (binary: active vs. inactive; Baseline #N9, ExpBaseline #O15, LTFU 2003 #D1-7, LTFU 2007 #N15-21; LTFU 2014 #N15-24)

1. Active defined per Centers for Disease Control and Prevention guidelines as: ≥150 minutes/week of moderate intensity physical activity or ≥60 minutes/week of vigorous activity per week[6]
2. Inactive if not meeting above definition or if reported no leisure-time physical activity in the month prior to survey completion (LTFU 2003 #D1, LTFU 2007 #N16 and N19, LTFU 2013 #N16 and #N19, LTFU 2017 #D1)

(b) Reproductive outcomes[21-24]:
   (i) Fertility/Ever pregnant (defined as becoming pregnant or siring a pregnancy; binary/yes no): Baseline #M9, ExpBaseline #N6, LTFU 2000 #8; LTFU 2003 #N1; LTFU 2007 Q1; LTFU 2014 #V1 (females) or #V3 (males).
   (ii) Infertility (based on construct from 2013 CCSS infertility study)[24]
      1. Clinical Infertility (defined as a period in life when subject and partner tried greater than one year to become pregnant without success; binary yes/no): Baseline #M.5, ExpBaseline #N5, Men's Health Questionaire (MHQ) #C7.
      2. Total Infertility: Clinical Inferility (as determined above) OR Primary ovarian insufficiency (defined as cessation of menses ≥6 months in duration occurring 5 years after diagnosis and before age 40, not due to surgery, pregnancy or medications; binary: yes/no). "Yes" is defined as response of < 40 years on LTFU 2000 #19b and answer of "Normal or early menopause" to #19d on LTFU 2000, and/or response of < 40 years to question #G14 and answer of "Normal or early menopause" on question #G16 on LTFU 2014.

(c) Sexual function:
   (i) Male erectile dysfunction: Male Health Questionnaire (MHQ)**: International Index of Erectile Function (IIEF) erectile function domain score OR the presence of any of the following medications in the "Other prescribed drugs" write-in box: sildenafil (Viagra), vardenafil (Levitra, Staxyn), tadalafil (Cialis), avanafil (Stendra); Baseline #B.8(16), ExpBaseline #B8(16), LTFU 2000 #6 (q), LTFU 2003 #Q (9), LTFU 2007 #C8 (10), LTFU 2014 #C2 (11).
   (ii) Sexual Function Questionnaire (SFQ) overall score from MHQ and WHQ**

   **Analyses dependent on the MHQ, WHQ, or SFQ to be performed if statistically feasible based on number of participants.

(d) Bladder function and related outcomes:
   1. "REPEATED (>3 in any 12 month period) kidney or bladder infections": ExpBaseline #D2, LTFU 2007 #E2, LTFU 2014 #E2.
   2. "Blood in your urine": ExpBaseline #D4, LTFU 2007 #E4, LTFU 2014 #E4.
   3. "Urinary incontinence": ExpBaseline #D5, LTFU 2007 #E5, LTFU 2014 #E5.

(e) Pain:

(i) Current pain: Baseline #J36; ExpBaseline #K19; LTFU 2003 #G19; LTFU 2014 #L20 ("Do you currently have pain as a result of your cancer or similar illness, or its treatment?).

(f) Secondary malignant neoplasms (SMN)

(g) Burden of CTCAE chronic health conditions
  (i) Subset analysis of grade 3-4 conditions
  (ii) CTCAE condition groups to include: renal, musculoskeletal, neurological, gastrointestinal, endocrine, SMN, cardiovascular, pulmonary

(3) Quality of life measures

a) Emotional health: evaluated by the 18-item Brief Symptom Inventory (BSI-18)
  i. Summary scale (Global Status Index)
  ii. Subscales: Depression, Anxiety, and Somaticization

b) Health related quality of life: evaluated by the 36-item Medical Outcomes Short Form Health Survey (SF-36)
  i. Two Summary scales:
    a. Physical Component Summary
      i. Physical health
      ii. Physical role
      iii. Bodily pain
      iv. General health
    b. Mental Component Summary
      i. Vitality
      ii. Emotional role
      iii. Social function
      iv. Mental health

b) **Subject population**

We will include all childhood cancer survivors in the CCSS cohort (diagnosed 1970-99) who participated in the baseline or expanded baseline survey, and were diagnosed with pelvic sarcoma, defined as osteosarcoma, Ewing sarcoma, rhabdomyosarcoma, or other soft tissue or bone sarcoma involving the following structures based on ICD-O-3 topographical codes:

- Vasculature: iliac artery or vein ("C49.5")
- Nerves: lumbosacral plexus and autonomics ("C47.5")
- Visceral and genital organs: intestine, ureter, bladder, vagina, uterus, cervix, ovaries, and prostate ("C20.9","C19.9","C18.7","C52.9","C53.1","C53.8","C53.9","C54.0","C54.1","C54.2","C54.3","C54.8","C54.9","C55.9","C56.9","C57.0","C57.1","C57.2","C57.3","C57.4","C57.7","C57.8","C57.9","C61.9","C66.9","C67.0","C67.1","C67.2","C67.3","C67.4","C67.5","C67.6","C67.7","C67.8","C67.9","C68.0","C68.1","C68.8","C68.9")
- Musculature: pelvic floor / perineum ("C76.3")
- Bones: L4-5, sacrum, coccyx, and pelvis ("C41.4")

Population (N=508)

DX group	Frequency	Percent	Cumulative Frequency	Cumulative Percent
Soft tissue sarcoma*	343	67.52	343	67.52
Ewings sarcoma	135	26.57	478	94.09
Osteosarcoma	24	4.72	502	98.82
Other bone tumors	6	1.18	508	100.00

*Soft Tissue Sarcoma diagnosis codes		
Rhabdomyosarcoma	**Diagnosis codes**	**Frequency**
Yes	**M8900/3 Rhabdomyosarcoma NOS**	101
Yes	**M8910/3 Embryonal rhabdomyosarcoma**	164
Yes	**M8920/3 Alveolar rhabdomyosarcoma**	12
Yes	**M8901/3 Pleomorphic rhabdomyosarcoma**	2
Yes	**M8902/3 Mixed type rhabdomyosarcoma**	2
No	**M8800/3 Sarcoma NOS**	20
No	**M8801/3 Spindle cell sarcoma**	1
No	**M8804/3 Epithelioid sarcoma**	2
No	**M8810/3 Fibrosarcoma NOS**	8
No	**M8830/3 Fibrous histiocytoma, malignant**	3
No	**M8832/3 Dermatofibrosarcoma NOS**	1
No	**M8840/3 Myxosarcoma**	1
No	**M8850/3 Liposarcoma NOS**	4
No	**M8852/3 Myxoid liposarcoma**	1
No	**M8890/3 Leiomyosarcoma NOS**	3
No	**M8894/3 Angiomyosarcoma**	1
No	**M9040/3 Synovial sarcoma NOS**	6
No	**M9044/3 Clear cell sarcoma (except of kidney M8964/3)**	1
No	**M9130/3 Haemangioendothelioma, malignant**	1
No	**M9150/3 Haemangiopericytoma, malignant**	2
No	**M9251/3 Malignant giant cell tumour of soft parts**	1
No	**M9540/3 Neurofibrosarcoma**	3
No	**M9560/3 Neurilemmoma, malignant**	2
No	**M9581/3 Alveolar soft part sarcoma**	1
		343 (**rhabdomyosarcoma** : 281)

As comparators, we will include all survivors of sarcomas from other anatomic sites in the CCSS cohort, a cohort of age-matched sibling controls, and the incidence of malignant neoplasms in the general population from the SEER database (comparisons detailed in specific aims).

c) **Exploratory variables**

- Demographic variables
  - Age (continuous and categorical; Baseline #A1; ExpBaseline #A1)
  - Sex (categorical; Baseline #A2; ExpBaseline #A2)
  - Race and ethnicity (categorical: non-Hispanic white, non-Hispanic black, Hispanic, other; Baseline #A4, ExpBaseline #A5)
- Cancer variables
  - Primary cancer diagnosis
- Treatment variables (within 5 years of cancer diagnosis)

    - Classify into the following strata, based on the following:
        - Surgery + chemotherapy only
        - Radiotherapy + chemotherapy only
        - Surgery + chemotherapy + radiotherapy
    - Surgery: Any resection of pelvic sarcoma (binary; MRAF for any surgery for pelvic sarcoma resection)
        - For the primary analyses outlined in the specific aims, surgery will be considered as a binary yes/no variable. However, type of surgery will be collected for descriptive purposes and included as a supplementary table (Supplementary table 1).
    - Pelvis body region Radiotherapy (dose categories; MRAF):
        - 0 Gy
        - <10 Gy
        - 10-29.9 Gy
        - 30-49.9 Gy
        - 50+ Gy
- Other treatment variables (within 5 years of cancer diagnosis)
    - Any chemotherapy (binary)
        - Alkylating agent (binary; will explore dose categories if sample size permits)
            - Cyclophosphamide equivalent dose (CED) score (categorical: 0, 1-3999, 4000-7999, ≥8000mg/m^2)
        - Anthracycline (binary; will explore dose categories if sample size permits)
            - Anthracycline score (categorical: 0, <250, ≥250 mg/m^2)
        - Platinum agent (binary)
        - Methotrexate (IV or PO administration only; binary)
        - Vinca alkyloids (binary)
        - Epipodophyllotoxins (binary)

d) **Statistical methods**

For descriptive purposes, we will first compare the time-independent demographic, treatment, and clinical characteristics of the following groups: pelvic sarcoma survivors, survivors of sarcomas at other anatomic sites, and siblings.

Next, late all-cause mortality, health-related-cause mortality, secondary malignant neoplasms, burden of CTCAE chronic health conditions, reproductive outcomes (fertility/infertility), bladder related outcomes will be analyzed using a time-to-event approach. We will calculate the cumulative incidence and generate cumulative incidence curves for each of these time-dependent outcomes among pelvic sarcoma survivors treated with chemotherapy + surgery, chemotherapy + radiotherapy, or chemotherapy + surgery and radiotherapy using siblings as the reference group. We will estimate the rate ratios of each of these outcomes among groups of pelvic sarcoma survivors treated with chemotherapy + surgery, chemotherapy + radiotherapy, or chemotherapy + surgery and radiotherapy using similarly treated survivors of sarcomas from other anatomic sites as the reference group. For time-to-event analysis, Cox regression will be used and age will be used as the time scale. Age at 5 years after diagnosis will be used as the start of at-risk time for survivors, and corresponding age at 5 years after

sibling-survivor's diagnosis will be used for siblings. Additional analysis will be performed among survivors only using time since diagnosis as the time scale. Multiple imputation will be used for participants who develop an outcome but age of outcome is unspecified. Analyses will be adjusted for age, sex, race/ethnicity, and decade of diagnosis. Reproductive and sexual function outcomes will be assessed for interaction by sex.

Next, we will use a cross-sectional logistic regression analysis to estimate odds ratios evaluating the association of treatment groups and/or individual exposures with the following outcomes: physical function and activity outcomes, sexual function outcomes, pain outcomes, and quality of life outcomes. Analyses will be adjusted for age, sex, race/ethnicity, cancer diagnosis, and decade of diagnosis.

Finally, for participants with available data from the Medical Outcome Short Form (SF-36) and the Brief Symptom Inventory (BSI-18) instruments, we will compare quality of life measures between pelvic sarcoma survivors and age-matched sibling controls. Psychosocial outcomes (quality of life measures) will be dichotomized as impaired and not impaired with thresholds set at the population-norm highest 10^{th} percentile value for the BSI-18 (T score $\geq$ 63) and at the lowest 16^{th} percentile for the SF-36 (T score <40). Then, we will compare quality of life measures in each of the three local control groups of pelvic sarcoma survivors: (surgical resection alone vs. B) radiotherapy alone vs. C) surgical resection and radiotherapy (Table 3). Then we will compare quality of life measures among the cohort of pelvic sarcoma surivvors to a cohort of similarly treated sarcoma survivors from other anatomic sites. The analysis will include a multivariable logistic regression model, adjusting for the above variables (i.e., age, sex, race/ethnicity, diagnosis, chemotherapy (binary and agent/dose), tobacco use, BMI, and year of diagnosis) as well as household income, current smoking status, BMI, education, and health insurance status. Because these models include variables that are known only at the time of specific surveys (e.g., household income, current smoking status, BMI, education, and health insurance status), we will use cross-sectional logistic regression techniques incorporating information at most recent follow-up.

e) **Examples of tables and figures**

Table 1. Baseline characteristics of survivors of childhood sarcoma based on anatomic location and siblings

Variable	***Pelvic sarcoma***	***Sarcoma from other anatomic sites***	***Siblings***
Female			
Age at diagnosis, y			
0-3			
4-9			
10-14			
15-20			
Race/ethnicity			
Non-Hispanic white			
Non-Hispanic black			
Hispanic			
Other			
Sarcoma diagnosis			

Osteosarcoma		
Ewing sarcoma		
Rhabdomyosarcoma		
Other sarcoma		
Treatment groups		-
Chemo + Surgery		
Chemo + Radiation		
Chemo + Surgery + Radiation		
Surgery		
No		-
Yes		-
1 surgery		-
2 surgeries		-
>2 surgeries		-
Major joint replacement		-
Amputation		-
Pelvic resection (cystectomy, hysterectomy, prostatectomy)		
Any chemotherapy		
Alkylating agent CED, mg/m^2		
0		
1-3999		
4000-7999		
>7999		
Platinum agent		
No		
Yes		
Anthracycline dose, mg/m^2		
None		
<250		
≥250		
Pelvis radiotherapy, Gy		
0 (no radiotherapy)		
<10	-	
10-19	-	
20-29	-	
30-39	-	
40-49	-	
>49	-	
Tobacco use	-	
Current		
Former		
Never		
BMI		
<18.5		
18.5-24.9		

25-29.0	
30-34.9	
35-40	
>40	
Follow-up, years (median, IQR)	

CED, cyclophosphamide equivalent dose; IQR, interquartile range

Table 2. Multiple regression evaluating the association between local control with surgery vs. radiotherapy and late outcomes.

Variable	OR (95% CI) Physical function	OR (95% CI) Infertility	OR (95% CI) Sexual function	OR (95% CI) Urinary incontinence	RR (95% CI) SMN	RR (95% CI) >2 CTCAE grade 3-4 chronic health conditions	RR (95% CI) Health-related-cause late mortality
Local control							
Surgery only							
Radiotherapy only							
Surgery and radiotherapy							
Covariates[a]							

OR, odds ratio; *RR* rate ratio; [a]Age, sex, race/ethnicity, diagnosis, chemotherapy (binary and agent/dose), and tobacco use and BMI (for physical function only)

Table 3. Association between treatment type and impaired health-related quality of life and psychological outcomes

Measure	*Adjusted odds ratio (surgical resection only vs. siblings)*	*Adjusted odds ratio (radiotherapy only vs. siblings)*	*Adjusted odds ratio (surgical resection and radiotherapy vs. siblings)*
SF-36 physical component			
Physical health			
Physical role			
Bodily pain			
General health			
Physical component (summary)			
SF-36 mental component			
Vitality			
Emotional role			
Social function			

Mental health
Mental component (summary)
BSI
Depression
Anxiety
Somatization
Global Status Index

BSI-18, Brief Symptom Inventory-18; *SF-36*, Medical Outcomes Study 36-Item Short-Form Health Survey

Supplemental Table 1. Pelvic operations by disease-type

Operation	***All***	***Soft tissue sarcoma***	***Ewing sarcoma***	***Osteosarcoma***	***Other***
Hemipelvectomy					
Internal					
External					
Hip joint replacement					
Cystectomy					
Prostatectomy					
Hysterectomy					
Other					

Figure 1A-B. Cumulative incidence (40-year) of selected late effects (i.e. SMN [Figure 1A], >1 CTCAE grade 3-4 chronic health conditions [Figure 1B]) among childhood cancer survivors vs. siblings, with mortality as a competing risk, stratified by treatment with pelvic resection vs. pelvic radiotherapy vs. pelvic resection and radiotherapy.

Figure 2A. Cumulative incidence (40-year) of late health-related-cause mortality among childhood cancer survivors stratified by treatment with A) surgical resection alone vs. B) radiotherapy alone vs. C) surgical resection and radiotherapy for the treatment of pelvic sarcoma (as well as compared to a baseline of sibling controls).

Figure 2B. Cumulative incidence (40-year) of late all-cause mortality among childhood cancer survivors stratified by treatment with A) surgical resection alone vs. B) radiotherapy alone vs. C) surgical resection and radiotherapy for the treatment of pelvic sarcoma (as well as compared to a baseline of sibling controls).

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