1) Study title: Treatment regimens and late outcomes among survivors of Ewing sarcoma diagnosed between 1970 and 1999

2) Working group 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, Subsequent Malignant Neoplasms and Psychology Working Groups
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3) Background and rationale:
Among individuals diagnosed with Ewing sarcoma, five-year overall survival has increased from 36% (diagnosed 1973-82) to 60% (diagnosed 1993-2004) and ten-year overall survival has likewise increased from 34% (diagnosed 1973-82) to 55% (diagnosed 1993-2004).[1] Among five-year survivors, prior Childhood Cancer Survivor Study data demonstrate a 35-year conditional cause-specific survival of 70% and, similarly, SEER data reflect a 30-year overall survival of 72%.[2, 3]

Ewing sarcoma survivors have previously been shown to have a high burden of chronic conditions.[2, 4, 5] There are several potential explanations for this finding, which warrant further investigation. First, Ewing sarcoma is presumed to have subclinical metastasis in the majority of patients. As such, intensive chemotherapy (including anthracyclines, alkylating agents, ifosfamide, and etoposide) has been employed to improve survival, with concomitant potential for late chemotherapy-related complications.[6–8] Additionally, unlike osteosarcoma, Ewing sarcoma is radiosensitive. While radiotherapy (RT) plays a role in local control of a subset of

patients with Ewing sarcoma, it also contributes to the late burden of chronic conditions, the risk of developing subsequent neoplasms, and multiple orthopaedic complications such as limb length discrepancy and fracture.[9–11] Radiotherapy has also been associated with psychosocial perturbations and somatization.[24] A subset of patients with Ewing sarcoma are treated with RT approaches (high dose RT to large pelvic fields; hemithorax RT; or whole lung RT) that are used less commonly in other pediatric conditions. In both its primary or metastatic manifestations, Ewing sarcoma has the potential to affect multiple different anatomic areas, necessitating specific local control interventions. The proposed study may provide insight into the burden of late effects from these specific interventions. Finally, with the introduction of effective chemotherapy regimens, options for near-total surgical resections permitting limb salvage became possible.[12] However, compared with amputation, limb salvage is associated with increased number of procedures and greater potential for infection, implant or allograft failure, and peri-prosthetic fracture.[13–16] Each of these changes may predispose Ewing sarcoma survivors to late complications. In a CCSS study examining 35-year outcomes from the original cohort (diagnosed between 1970 and 1986), 85% and 74% of Ewing sarcoma survivors developed ≥1 and ≥2 chronic health conditions, respectively[2, 17]

The most recent CCSS report describes 35-year outcomes of 403 Ewing sarcoma survivors diagnosed between 1970-1986.[2] Since 1986, the field has seen significant changes in management of both localized and distant (metastatic) disease.[6, 7, 18] Of particular note, the INT-0091 trial, initiated in 1986, demonstrated a significant survival advantage with the addition of ifosfamide and etoposide (IE) (compared to vincristine, doxorubicin, and cyclophosphamide [VDC] alone) in patients with localized Ewing sarcoma.[19] As a result only 9% and 11% of patients in the Original Cohort received ifosfamide or etoposide, respectively. A much greater proportion of patients in the Expansion Cohort (1987-1999) will have received IE, comprising a regimen more representative of the contemporary standard of care (Figure A). At this same time, reliance on radiotherapy for frontline management of these patients has also decreased significantly, largely due to risk of secondary malignancies and improvements in surgical techniques.[20, 21]

Given these changes in multimodal treatment strategies and survival over time, we propose to update the prior work and incorporate an additional 335 survivors who were diagnosed with Ewing sarcoma between 1987-1999. The changes in chemotherapy, RT, and surgery treatments expected to be represented in the Expansion Cohort will allow us to identify several specific outcomes with which these changes may be associated. These include late mortality, late recurrence, and the development of subsequent malignant neoplasms (SMNs). Although the addition of IE is known to improve five-year event-free survival, its impact upon late mortality is unclear, though it has been hypothesized that the Expansion Cohort may show lower rates of late recurrence within CCSS partly due to this change.[2] Chronic medical conditions brought on by the addition of IE or RT may further be elucidated, as well. Finally, the interplay between health-related quality of life (HRQoL), physical function, and emotional distress and Expansion Cohort-era treatment regimens is also unclear.[22, 23]

The purpose of this study is to characterize the outcomes (including survival, late complications, and functional status) in Ewing sarcoma survivors with respect to different multimodal treatment strategies. Importantly, this study will identify risk factors for late mortality, recurrence, and other complications as well as HRQoL and functional deficits that reflect a more contemporary cohort of survivors than previously reported.

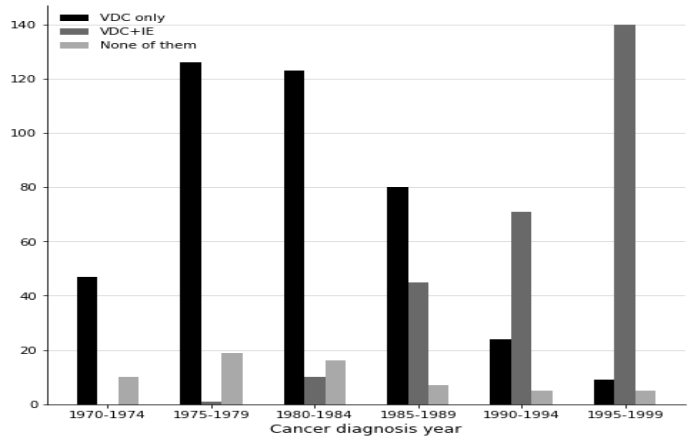

Figure A: Chemotherapeutic regimens of CCSS Ewing sarcoma survivors, partitioned in five-year intervals. (CCSS data, unpublished)

4) Specific aims:

Aim 1. To estimate and compare incidence of all-cause and cause-specific (primary malignancy, SMN, health-related, or other) late mortality among 1A) all eligible Ewing sarcoma survivors and their siblings in the complete cohort and 1B) among participants stratified by treatment group (chemotherapy regimens of VDC, VDC+IE, and other) and treatment era (diagnosis between 1970-1986 vs 1987-1999).
Hypothesis: There is a higher cumulative incidence of all-cause late mortality among survivors of Ewing sarcoma, compared with sibling controls, which vary with treatments received.

Aim 2. To estimate the rate and cumulative incidence of late recurrence among all eligible Ewing sarcoma survivors and stratified by treatment regimen.
Hypothesis: The rate of late recurrence will vary by treatment regimen.

Aim 3. To estimate cumulative incidence of subsequent malignant neoplasms among all eligible Ewing sarcoma survivors in the complete cohort and compare by treatment era and treatment regimen.
Hypothesis: There will be a higher than expected cumulative incidence of subsequent malignant neoplasms among survivors of Ewing sarcoma compared with the SEER database; cumulative incidence of subsequent neoplasm will be higher among survivors receiving treatment regimens of the later era and more intensive treatment regimens containing IE or radiotherapy.

Aim 4. To estimate the cumulative incidence of relevant CTCAE-graded chronic health conditions (defined below; including, cardiac, neurologic, pulmonary, renal, and musculoskeletal outcomes) among 1) all eligible Ewing sarcoma survivors and their siblings in the complete cohort and 2) among participants stratified by treatment era and treatment regimen as above.
Hypothesis: There is a higher cumulative incidence of each category of CTCAE chronic health conditions among survivors of Ewing sarcoma, compared with sibling controls; cumulative incidence of each CTCAE category will be higher with later and more intensive treatment regimens.

Aim 5. To estimate the impact of childhood Ewing sarcoma on psychosocial and functional outcomes on survivors.
Hypothesis: Survivors will have poorer quality of life and greater functional and physical limitations, and emotional distress compared with siblings. Among survivors, tumor location will be associated with quality of life among childhood survivors of Ewing sarcoma. Further, when stratified by tumor location, treatment regimens will similarly be associated with differential levels of quality of life, functional and physical limitations, and emotional distress.

Aim 6. To identify specific treatment exposures associated with the development of the above outcomes among Ewing sarcoma survivors.

5) Analysis framework:

Survivors will be compared with respect to mutually exclusive treatment groups based on 1) clinically relevant chemotherapy regimens (VDC, VDC+IE, and 'other') after stratification by whether they received RT for local control as well as 2) temporal groups based on the timing of these treatment changes noted above (1970-1986 vs 1987-1999).

The following treatment variables will be evaluated as potential effect modifiers:

1. Lung field RT
2. Total body radiation
3. Hematopoietic stem cell transplant (HSCT)*
4. Limb salvage surgery (vs amputation vs no surgery)

a) Outcomes of interest

Aim 1. Late all-cause mortality (occurring > five years after diagnosis), defined by the National Death Index. Cause-specific (disease recurrence, SMN, or health-related) mortality will be reported. Additionally, the most common causes of death among Ewing sarcoma survivors will be reported (Supplementary table).

Aims 2 and 3. Late recurrence and subsequent malignant neoplasm (SMN)

- Baseline & ExBaseline #K1 and K4, LTFU 2003 R1-2; LTFU 2007 P1; LTFU 2014 #S1-3 and S5; LTFU 2017 H1-3, H5
- Additionally, the most common SMNs developed by survivors will be collected (Supplementary table) and these specific SMNs may be evaluated separately pending these findings.

Aim 4. Late chronic health conditions, defined by CTCAE chronic health conditions:[25]

- No condition, Grade 1 condition (mild), Grade 2 condition (moderate), Grade 3 condition (severe or disabling), Grade 4 condition (life-threatening), Grade 5 condition (fatal)
- Number of conditions (any grade)
- Number of severe, life-threatening, or fatal conditions
- CTCAE-graded conditions classified by organ system
    - CTCAE Grade 3-5 cardiac conditions

- CTCAE Grade 3-5 pulmonary conditions
- CTCAE Grade 3-5 neurologic conditions
- CTCAE Grade 3-5 renal conditions
- CTCAE Grade 3-5 musculoskeletal conditions

Aim 5. Psychosocial and Functional Outcomes, defined by:

- Health-related quality of life (HRQOL), as assessed by Short Form 36 (SF-36), physical function questions, and Brief Symptom Inventory (BSI) surveys.
  - HRQOL: SF-36 (LTFU 2003 #F1-14, LTFU 2007, LTFU 2014 O1-P3, LTFU 2017 E1-F3) Binary (t-score >40 vs. ≤40). Compare whether within MCID of sibling controls.
  - Physical function/activity (based on Florin2007):
    - Physical limitations: (Binary: Limited or not limited; BaseExp O20a-f, LTFU 2014 N29a-f).
    - Physical activity: (binary: active vs inactive; BaseExp O15, LTFU 2003 D1-D7; LTFU 2014 N15-24). "Active" definition based on CDC guidelines: ≥150 minutes/week of moderate intensity physical activity or ≥60 minutes/week of vigorous activity per week
  - Emotional Distress: BSI results are based on Baseline #J16-35 (excluding J25 and J28), Baseline Expansion #K1-K18. LTFU 2014 L1-20; anti-depressants and anxiolytics LTFU C2;9, 11. Continuous and binary (Depression or use of anti-depressants vs. no depression; anxiety or use of anxiolytics vs. no anxiety; somatization vs. no somatization; <63 vs. ≥63)

b) Subject population

We will include all childhood cancer survivors in the CCSS Original (diagnosed 1970-86) and Expansion (diagnosed 1987-1999) cohorts who were diagnosed with Ewing sarcoma (N = 738). For the purposes of this analysis, Ewing sarcoma will include patients determined to have been diagnosed with Ewing sarcoma, peripheral (non-CNS) PNET, and Askin tumor. Patients coded as having undifferentiated round cell sarcoma of bone or soft tissue will not be included. All participating siblings will be used as non-cancer comparison subjects.

c) Exploratory variables

- <u>Primary cohort definitions, to be evaluated separately</u>
  - Era of diagnosis (1970-1986 vs 1987-1999)
  - Chemotherapeutic regimen (VDC vs VDC/IE vs "other"), stratified by history of RT for local control (Y vs N)
- <u>Demographic and social variables</u>
  - Age at diagnosis (continuous and categorical; Baseline #A1; ExpBaseline #A1) and attained age
  - Sex (categorical; Baseline #A2; ExpBaseline #A2)
  - Race and ethnicity (categorical: non-Hispanic white, non-Hispanic black, Hispanic, other; Baseline #A4, ExpBaseline #A5)

  - Highest level of education attainment (time dependent; categorical: <high school, high school graduate, college graduate; Baseline #O1-4, LTFU2003 #1, LTFU2007 #A3; ExpBaseline #R1; LTFU2014 #A4)
- Disease variables
  - Tumor location (categorical: upper extremity, lower extremity, pelvis, skull, chest wall, spinal/paraspinal, or other; ICD-O-3)
- Treatment variables (within 5 years of cancer diagnosis)
  - Surgery for local control, *excluding biopsies* (binary [Y vs N] and categorical [amputation vs limb salvage surgery as primary surgical method] and numeric [number of non-biopsy procedures within 5 years]; MRAF)
    - Site of local control surgery (categorical; head upper extremity, lower extremity, pelvis, skull, chest wall, spinal/paraspinal, or other)
    - Late amputation (categorical; Baseline #I1, ExpBaseline #I1, LTFU 2007 #J1, LTFU 2014 #J1)
    - Major joint replacement (categorical; Baseline #I5, ExpBaseline #I5, LTFU 2007 #J5, LTFU 2014 #J5)
    - Limb-lengthening or other osseous procedure (categorical; Baseline #I4, #I6, ExpBaseline #I4, I6, LTFU 2007 #J4, J6, MRAF)
    - As an exploratory approach, review of the primary operative reports to determine granular details of each operation if possible.
  - Any radiotherapy (binary; MRAF)
    - Total body dose (numeric, total Gy)
    - Local control RT dose per dosimetry team algorithm (categorical: 0, <10, 10-29.9, 30-49.9, >50 Gy)
    - Radiotherapy to pelvic field (binary)
    - Hemithorax radiotherapy (binary)
    - Whole lung radiotherapy (binary)
  - Any chemotherapy (binary; MRAF)
    - Alkylating agent:
      - Cyclophosphamide, mg/m^2 (categorical: none, tertiles)
      - Ifosfamide, mg/m^2 (categorical: none, tertiles)
      - We will also consider combining cyclophosphamide and ifosfamide and expressing the cumulative total in cyclophosphamide-equivalent dose
    - Anthracycline, mg/m^2 in doxorubicin-equivalent dose (categorical: none, 1-100, 100-300, 300-450, >450)
    - Epipodophyllotoxin (categorical: none, 1-999, 1000-3999, 4000+)
  - Any hematopoietic stem cell transplant (binary; MRAF)*
    - *Will remove this group if survivors undergoing HSCT cannot be consistently identified

d) Statistical methods

For descriptive purposes, we will first compare the time-independent demographic, treatment, and clinical characteristics of the following groups: i.) Ewing sarcoma survivors vs. siblings (Table 1) and ii.) Ewing sarcoma survivors partitioned by chemotherapeutic treatment groups

and era of diagnosis (Table 2). Wherever possible, chemotherapy regimen will be stratified by whether RT was used for local control.

Next, we will graphically display unadjusted risk of cause-specific mortality (Figure 1; non-external mortality; possible stratified by cause, depending on findings and sample size), late recurrence, and SMN (also possibly stratified, depending on findings and sample size), using cumulative incidence curves of Ewing sarcoma survivors vs. siblings. Time since diagnosis will be used as the time scale; age at last follow-up will also be considered for use as the time scale. The same will be done for Ewing sarcoma survivors stratified by treatment regime (Figure 2; truncated at 15 years post-diagnosis follow-up). We will additionally tabulate 20- to 25-year cumulative incidence (depending on data availability) of recurrence/SMN as well as cardiac, neurologic, renal, and musculoskeletal CTCAE chronic health conditions (Table 3).

Accounting for duration of follow-up and adjusting for relevant covariates (age, gender, race/ethnicity), rate ratios will be estimated for survivors (vs. reference siblings) for the same outcomes (Table 3). SIRs will be provided for SMNs, based on SEER registry data; additionally, for each SMN, inclusion of recurrence location in the field(s) of radiotherapy will be checked.

In order to determine if there is an association between tumor characteristics, treatment regime, and non-external mortality, we will adjust for relevant time-independent baseline variables (age, gender, race/ethnicity, and year category of diagnosis) in a multiple regression (piecewise exponential model; Table 4). Adjusted prevalence ratios (for events <5 years) and rate ratios (for events ≥5 years) will be estimated for the comparison of Ewing sarcoma survivors vs. siblings and the following chronic condition outcomes: any grade 1-4, grade 3-4, ≥2 conditions, ≥3 conditions, specific condition categories as defined above (Table 5). This analysis will additionally be stratified by treatment regimen. Finally, we will consider stratifying relevant analyses by tumor location as an exploratory analysis.

Finally, among participants who completed the Medical Outcome Short Form 36 (SF-36), physical activity and functional limitations, and/or the Brief Symptom Inventory (BSI) surveys, health-related quality of life will be compared between Ewing sarcoma survivors and siblings, with a focus on tumor location and local control strategy (limb salvage vs amputation vs RT). Specifically, the quality of life outcomes will be dichotomized into impaired (vs. not impaired) using population level thresholds. A multivariable logistic regression analysis will then be conducted for the quality of life outcomes adjusted for demographic variables (age, sex, and race), time (years) since diagnosis (or pseudodiagnosis for siblings), and relevant cancer- and treatment-related variables, comparing estimates from different Ewing sarcoma tumor location to sibling estimates (Table 7). Similar tables may be constructed for comparisons of treatment regime and era of diagnosis (as defined above).

e) Examples of tables and figures

Table 1. Baseline characteristics of Ewing sarcoma survivors and siblings

Variable	Survivors	Siblings	Survivors 1970-1986	Survivors 1987-1999
Female				

Age at diagnosis, years 0-3 4-9 10-14 15-20 Attained age, years 0-17 18-29 ≥30 Race/ethnicity Non-Hispanic white Non-Hispanic black Hispanic Other Primary tumor location upper extremity lower extremity pelvis chest wall skull spinal/paraspinal other		
Era of diagnosis: 1970-1986 1987-1999		
Chemotherapeutic regimen VDC, total RT for local control No RT for local control VDC/IE, total RT for local control No RT for local control Other		
Radiation as part of local control (Y/N) Radiation dose to primary tumor Surgery as part of local control strategy (Y/N) Amputation Limb-sparing surgery Hematopoietic stem cell transplant (HSCT) Treatment with chemotherapy		

Alkylating agent (cyclophosphamide equivalent dose, mg/m^2)		
None		
Tertile 1		
Tertile 2		
Tertile 3		
Ifosfamide, mg/m^2		
None		
T1		
T2		
T3		
Cyclophosphamide, mg/m^2		
None		
T1		
T2		
T3		
Anthracycline (mg/m^2)		
None		
1-100		
100-300		
300-450		
>450		
Dexrazoxane		
Epipodophyllotoxin		
None		
1-999		
1,000-3,999		
≥4,000		
Radiotherapy, total body dose (Gy)		
0 (no radiotherapy)		
<10		
10-29.9		
30-49.9		
>50		
Pelvic radiotherapy (Gy)		
0 (no radiotherapy)		
<10		
10-29.9		
30-49.9		
>50		

Hemithorax radiotherapy (Gy)		
0 (no radiotherapy)		
<10		
10-29.9		
30-49.9		
>50		
Whole lung radiotherapy (Gy)		
0 (no radiotherapy)		
<10		
10-29.9		
30-49.9		
>50		
Follow-up, years (median, IQR)		

CED, cyclophosphamide equivalent dose; *CNS*, central nervous system; IQR, interquartile range
[a]Within five years of diagnosis, [b]Among n=## with Ewing sarcoma of the extremity

Table 2. Summary of treatment for Ewing sarcoma by treatment regimen and treatment era

	Treatment type					**Treatment era**	
	VDC		*VDC+IE*		*Other*	*1970-1986*	*1987-1999*
Variable	*Local RT*	*No local RT*	*Local RT*	*No local RT*			
Treatment with surgery for local control*[a]	# (%)						
Number of surgeries*[a]							
1 surgery							
2 surgeries							
>2 surgeries							
Amputation as primary local control							
Limb salvage as primary local control							
Hematopoietic stem cell transplant (HSCT)							
Treatment with chemotherapy							
Alkylating agent (cyclophosphamide equivalent dose, mg/m^2)							
None							
Tertile 1							
Tertile 2							
Tertile 3							
Ifosfamide, mg/m^2							
None							
T1							
T2							
T3							
Cyclophosphamide, mg/m^2							
None							
T1							

T2		
T3		
Anthracycline (mg/m^2)		
None		
1-100		
100-300		
300-450		
>450		
Dexrazoxane		
Epipodophyllotoxin		
None		
1-999		
1,000-3,999		
≥4,000		
Radiotherapy as part of local control		
0 (no radiotherapy)		
<10		
10-29.9		
30-49.9		
>50		
Pelvic radiotherapy		
0 (no radiotherapy)		
<10		
10-29.9		
30-49.9		
>50		
Hemithorax radiotherapy		
0 (no radiotherapy)		
<10		
10-29.9		
30-49.9		

>50		
Whole lung radiotherapy		
0 (no radiotherapy)		
<10		
10-29.9		
30-49.9		
>50		
Tumor location		
Upper extremity		
Lower extremity		
Pelvis		
Skull		
Chest wall		
Spinal/paraspinal		
Other		

[a]Within five years of diagnosis
*Excluding biopsy

Table 3a. Summary of primary and secondary outcomes

	20-year cumulative incidence (95% CI)		*Rate ratio (95% CI)*[a]	
Outcome	*Survivors*	*Siblings*	*Survivors*	*Siblings*
All-cause mortality				Ref
Mortality due to recurrence				
Mortality due to SMN				
Mortality due to health-related causes				
Cardiac				
Pulmonary				
Other				
Chronic health conditions				
Any Grade 1-5				
≥ 2 Grade 1-5				
Any Grade 3-5				
≥ 2 Grade 3-5				
Grade 3-5 Cardiac				
Grade 3-5 Pulmonary				
Grade 3-5 Neurologic				
Grade 3-5 Renal				
Grade 3-5 Musculoskeletal				
SMN[b]				
Recurrence		NA	NA	NA

[a]Adjusted for age, gender, race/ethnicity.
[b]Primary neoplasm for siblings.

Table 3b. Cumulative incidence of primary and secondary outcomes by treatment regimen and era

	Treatment regimen			Treatment era	
	VDC	*VDC+IE*	*Other*	*1970-1986*	*1987-1999*
Outcome	*Local RT* / *No local RT*	*Local RT* / *No local RT*			
All-cause mortality	Cum inc (95 % CI)				
Mortality due to primary cancer					
Mortality due to recurrence					
Mortality due to SMN					
Cardiac					
Pulmonary					
Other					
Chronic health conditions					
Any Grade 1-5					
≥ 2 Grade 1-5					
Any Grade 3-5					
≥ 2 Grade 3-5					
Grade 3-5 Cardiac					
Grade 3-5 Pulmonary					
Grade 3-5 Neurologic					
Grade 3-5 Renal					
Grade 3-5 Musculoskeletal					
SMN[b]					
Recurrence					

[a]Adjusted for age, gender, race/ethnicity.
[b]Primary neoplasm for siblings.

Table 3c. Rate ratios for development of outcomes by treatment regimen and era

	Treatment regimen			Treatment era	
Outcome	*VDC*	*VDC+IE*	*Other*	*1970-1986*	*1987-1999*
All-cause mortality	Ref	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
Mortality due to recurrence					
Mortality due to health-related causes					
Cardiac					
Pulmonary					
Other					
Chronic health conditions					
Any Grade 1-5					
≥ 2 Grade 1-5					
Any Grade 3-5					
≥ 2 Grade 3-5					
Grade 3-5 Cardiac					
Grade 3-5 Pulmonary					
Grade 3-5 Neurologic					
Grade 3-5 Renal					
Grade 3-5 Musculoskeletal					

SMN[b]		
Recurrence		

[a]Adjusted for age, gender, race/ethnicity, and local control (surgery, radiotherapy) and surgery type (limb salvage, amputation)
[b]Primary neoplasm for siblings.

Table 4. Rate ratios associated with late all-cause mortality, SMNs, and chronic conditions among Ewing sarcoma survivors by primary tumor site[a]

Variable	*All-cause late mortality*	*SMNs*	*Any Grade 3-5 CTCAE chronic condition*	*≥2 Grade 3-5 CTCAE chronic conditions*
Tumor location				
Upper extremity	Ref			
Lower extremity	RR (95% CI)			
Pelvis				
Skull				
Chest wall				
Spinal/paraspinal				
Other				

[a]Adjusted for age at diagnosis, attained age, gender, race/ethnicity.

Table 6. Odds ratios associated with impaired health-related quality of life and psychological outcomes among Ewings survivors compared to siblings

			Treatment regimen			**Treatment era**	
Measure	*Siblings*	*All Ewing survivors*	*VDC*	*VDC/IE*	*Other*	*1970-1986*	*1970-1986*
SF-36 physical component	Ref	OR (95% CI)					
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-18							
Depression or anti-depressants							
Anxiety or anxiolytics							
Somatization							
Global Status Index							

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

Figures.

Figure 1 Cumulative incidence of all-cause late mortality by (A) treatment era and (B) systemic treatment regimen.

Figure 2 Cumulative incidence of late mortality due to recurrence by (A) treatment era and (B) systemic treatment regimen.

Figure 3 Cumulative incidence of mortality due to health-related causes by (A) treatment era and (B) systemic treatment regimen.

Supplemental Table. Supplemental information requested.

Median follow-up time (range)	
Median age at follow-up (range)	
Median age at diagnosis (range)	
Number of late deaths (any cause)	
Number of late deaths (non-external causes)	
Number of late deaths due to Ewing's recurrence	
Top 5 causes of late death (all causes included)	
1 (#)	
2 (#)	
3 (#)	
4 (#)	
5 (#)	
SIR for all SMNs in Ewing survivors	
Top 5 SMNs and corresponding SIR	
1 (# and SIR)	
2 (# and SIR)	
3 (# and SIR)	
4 (# and SIR)	
5 (# and SIR)	
Top 5 chronic conditions	
1 (#)	
2 (#)	
3 (#)	
4 (#)	
5 (#)	
Standardized mortality ratio (SMR)	
All survivors	
Local disease treatment:	
Surgery	
Radiotherapy (RT)	
Surgery + RT	
Systemic disease	
Lung field RT	
Hematopoietic stem cell transplant (HSCT)	
Other	

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