1) **Study title:** Long-term outcomes associated with local control method (radiotherapy, amputation, or limb salvage/reconstructive options) in survivors of lower extremity bone sarcoma diagnosed between 1987 and 1999.

2) **Working group and investigators:** The study will be performed under the primary oversight of the Childhood Cancer Survivor Study (CCSS) Chronic Disease Working Group. Secondary oversight will be provided by the CCSS Psychology Working Group

Name	*Contact information*
Duncan Ramsey	duncan.ramsey@utrgv.edu
Andrew Murphy	Andrew.Murphy@stjude.org
Kevin Raskin	kraskin@mgh.harvard.edu
Erik Geiger	erikgeiger23@gmail.com
David Shulman	David_Shulman@dfci.harvard.edu
Kiri Ness	kiri.ness@stjude.org
Rebecca Howell	rhowell@mdanderson.org
Kevin Krull	Kevin.Krull@stjude.org
Gregory Armstrong	Greg.Armstrong@stjude.org
Eric Chow	ericchow@uw.edu
Steven Dubois	Steven_Dubois@dfci.harvard.edu
Yutaka Yasui	Yutaka.Yasui@stjude.org
Wendy Leisenring	wleisenr@fredhutch.org
Kevin Oeffinger	kevin.oeffinger@duke.edu
Brent Weil	Brent.Weil@childrens.harvard.edu
Christopher Weldon	Christopher.Weldon@childrens.harvard.edu

3) **Background and rationale:**

Osteosarcoma (OS) and Ewing sarcoma (ES) together account for 90% of all primary bone cancers in children.[1–3] The long bones of the lower extremity (particularly the distal femur and proximal tibia) are the most common location for primary bone sarcomas.[4] Patients with OS or ES are treated with neoadjuvant chemotherapy followed by local control and adjuvant chemotherapy. Local control for OS consists of surgical resection.[5] Radiotherapy exists as a local control option for ES given its radiosensitivity. Surgical options for both OS and ES are similar and include amputation, rotationplasty, or limb-salvage via bone allograft, endoprosthesis, or allograft-prosthesis composite. Each has its own host of short- and long-term complications, and it is unclear from the literature which modality results in better long-term outcomes with respect to function, psychological well-being, or socioeconomic attainment.[6,7]

Before modern chemotherapy, the 5-year overall survival for OS was roughly 20%, and ES prognosis fared worse at roughly 10% in some series.[8–10] In this era local control was obtained primarily via amputation or, for ES, occasionally radiotherapy. The 1970s saw the introduction of methotrexate,[11] doxorubicin,[12] and cisplatin,[13] the backbone of today's OS chemotherapy regimen. The now-standard regimen of vincristine, doxorubicin, and cyclophosphamide plus ifosfamide/etoposide for ES similarly was developed during the 1970s - 1990s, and long-term overall survival for localized OS and ES rose to 60%-80%, roughly where it stands today.[9,14–16]

This improved long-term survival required stronger consideration of patients' long-term function, ushering the need for improved limb salvage techniques. Principles of limb salvage require first and foremost that the operation respects oncologic goals, i.e., the attainment of negative margins and acceptably low local recurrence rates. Chemotherapeutic advancements coincided with the advent of cross-sectional imaging, which allowed surgeons to better characterize the extent of tumors and margins needed to achieve an oncologically optimal surgery.[17] A very large body of literature has since shown that limb salvage, when combined with appropriate adjunctive chemotherapy, can be done safely and with local recurrence rates equivalent to amputation.[18–21]

Options for local control

Radiotherapy for local control of ES uses doses of 45-65Gy. Although effective for local control, it carries a significant risk of developing chronic medical and psychological conditions, subsequent neoplasms, and orthopaedic complications such as limb length discrepancy, arthrofibrosis, and fracture.[22–24] Due to this, use of RT as frontline local control for extremity ES has declined, and it is now primarily utilized in cases in which surgery is deemed highly morbid.[25]

One reconstructive option after bone sarcoma resection is an endoprosthesis (EP). Though available since the 1970's, the transition to modular prostheses that could be customized intraoperatively to any resection occurred in the early 1980's. Soon after this advancement, the rotating hinge platform for EP reconstruction of the knee was developed.[26,27] This advancement drastically improved mechanical and aseptic loosening rates, and the general design continues to be used today.[28,29] Surgical techniques such as gastrocnemius rotational flap also came into widespread use during this time period, further improving complication rates and affirming EP as a viable reconstructive option.[30]

With the development of cadaveric bone banking centers and improved graft availability, the use of bone allografts became another option for limb salvage reconstruction. Allografts are an attractive alternative to EPs as they maintain native soft tissue reconstructions and do not sacrifice the opposing bone across the joint in question.[31] However, they do have a significant risk of complications such as infection, host/allograft nonunion, allograft fracture, and joint degeneration.[32,33] Studies examining long-term outcomes of massive bone allografts report 10-year graft survival of 60%.[33–36]

Allograft-prosthesis composites (APC) entail the insertion of a revision-type prosthesis into a massive bone allograft that is then affixed to remaining native bone. These provide the theoretical advantage of biological healing at both the allograft-host bone interface and at soft tissue attachment sites, as well as a durable articulation provided by EPs.[37–40] Allograft-prosthesis composites may be superior to EPs in terms of functional outcome and joint stability, although they carry risks inherent to allografts such as nonunion, fracture, and infection.[41–44] Some studies (and at least one systematic review) have shown APCs to give superior function in the lower limb, though this is not consistent and studies are of generally low-quality evidence.[40–46]

Finally, biological autograft reconstruction by rotationplasty is another reconstructive option used in childhood bone sarcomas. This operation is technically an ablative procedure where the distal femur or proximal tibia is removed and the distal portion of the extremity is translated proximally, rotated 180°, and secured to the residual proximal femur. This creates a new "knee" joint with the ankle, thereby allowing use of a modified below-knee amputation (BKA) prosthesis. The procedures produce a durable reconstruction resulting in better functional outcomes and ambulatory efficiency than above-knee amputations (AKA).[47,48]

It is unclear from the literature whether amputation or limb salvage results in better long-term outcomes with respect to function, psychological well-being, or socioeconomic attainment.[6,7,49–52] Similarly, there is no consensus whether rotationplasty, allograft, APC, or EP reconstruction is an optimal reconstructive strategy, as each has its own host of long-term complications as noted above.[32,46,53–56] Of note, a recent CCSS study recently reported a 25-year cumulative incidence of amputation after primary limb salvage surgery of 18%, though it is unknown if this number varied based upon the different limb salvage reconstruction options.[52]

Therefore, the proposed study will evaluate and compare functional, psychological, socioeconomic, and surgical outcomes of different local control modalities in long-term survivors of lower extremity bone sarcomas. The study population will be narrowed to the Expansion Cohort only (1987-1999). This era coincides with the standardization of chemotherapeutic regimens, advancements in modern imaging techniques, and the development of reconstructive operations and implants whose design rationales are still used today.[9,57] Previous CCSS studies have partitioned surgical techniques into "limb salvage" or "amputation" only. Therefore, we will commence a review of the Expansion Cohort operative notes and coding dataset to define amputations by level (below- and above-knee), further partition limb salvage into EP, allograft, and APC reconstructions, and account for rotationplasty procedures. Of note, operative notes for the original cohort were not captured by CCSS data abstraction. This increased granularity over the time frame of the Expansion Cohort will allow a more accurate examination of the long-term outcomes of local control techniques in the modern era of orthopaedic oncology. This will enrich our understanding of survivor health and wellbeing as a function of local control methods and will inform surgical decision-making, patient counseling, and targeted late interventions.

4) **Specific aims:**
   a) **Specific aim 1.** Describe late health-related quality of life (HRQoL), functional impairment, activity limitations, and psychosocial outcomes among lower extremity bone sarcoma survivors according to local control treatment method.
   Hypothesis: Amputation will have poorer HRQoL, functional impairment, activity limitations, and psychosocial outcomes than limb salvage or radiotherapy-only treatment. Limb salvage methods will not differ between themselves.

   b) **Specific aim 2.** Describe late socioeconomic outcomes including education, marital status, and income, and recent healthcare utilization among lower extremity bone sarcoma survivors according to local control treatment method.
   Hypothesis: Null: Limb salvage surgical methods and radiotherapy (alone) will be associated with superior socioeconomic outcomes than amputation.

   c) **Specific aim 3.** Estimate the cumulative incidence (CI) of cardiac, pulmonary, endocrine, metabolic, and musculoskeletal Common Terminology Criteria for Adverse Events (CTCAE) chronic health conditions among lower extremity bone sarcoma survivors according to local control treatment method.
   Hypothesis: After controlling for other treatment variables such as chemotherapeutic regimen, the definitive radiotherapy group treated without surgical local control will have a lower CI of CTCAE chronic health conditions compared with those undergoing limb salvage surgeries.

   d) **Specific aim 4.** If statistically powered to do so, we will determine the rate of secondary malignancy, overall survival, and cause-specific mortality according to local control treatment method, including: definitive radiotherapy, surgery plus radiotherapy, amputation alone, rotationplasty alone, and primary limb salvage procedures alone further stratified by technique (EP, allograft, or APC reconstruction).

Hypothesis: After controlling for chemotherapeutic exposure, secondary malignancies will be more prevalent in the non-surgery (radiotherapy-only) group. Survival and cause-specific mortality will not differ between local control methods.

5) **Analysis framework:**

a) **Study Population**

The study population will include all long-term survivors (N ≥ 501) of lower extremity primary bone sarcoma in the Expansion Cohort (diagnosed 1987-1999) who underwent any form of local control management of the primary tumor, including primary limb salvage procedures, rotationplasty, amputation, or radiotherapy. "Lower extremity" will include primary tumors of the proximal femur and distally. Patients will be evaluated in an intention-to-treat manner.

b) **Data acquisition:**

We will lead a review of Expanded Cohort operative notes for this study population that will further partition limb salvage into endoprosthetic, allograft, or allograft-prosthesis composite reconstructions as well as define amputations by level (below- and above-knee) and account for rotationplasty procedures.

c) **Outcomes of interest – most recent questionnaire results for each patient**

Primary outcomes: HRQoL, functional, and psychosocial outcomes

- HRQoL: SF-36 mental and physical sub-scores (Table 3a) (Numeric, binary [< 40 or ≥ 40], categorical (below/within/above MCID of general population mean and below /within/above MCID of siblings; LTFU 2014 O1-P3, LTFU 2017 E1-F3)
- Physical activity and function:
  - Physical activity: (Based on Florin2007[58]. Binary: active vs inactive; BaseExp O15, 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
  - Activity limitations: (Based on Ness 2017[59]. Binary: limited [vs not] for more than 3 months over last two years to any of: LTFU 2007 N26, LTFU 2014 N29, etc)
  - Functional impairment: (Based on Ness 2017[59]. Binary: Limited or not limited; BaseExp O20a-f, LTFU 2014 N29a-f)
- Psychosocial: Brief Symptoms Inventory (BSI) (Numeric, 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]; Baseline #J16-35 (excluding J25 and J28), Baseline Expansion #K1-K18. LTFU 2014 L1-20; anti-depressants and anxiolytics LTFU C2;9, 11)

Secondary outcomes:

- Socioeconomic (For patients >25 years of age)
  - Education (Categorical; BaseExp R1, LTFU 2014 A4)
  - Employment (Categorical; BaseExp S2, LTFU 2014 A5)
  - Income: (Binary "Poverty yes/no"; ; BaseExp T1-3, LTFU 2014 A7-9) Poverty based on 2014 poverty guidelines https://aspe.hhs.gov/topics/poverty-economic-mobility/poverty-guidelines/prior-hhs-poverty-guidelines-federal-register-references/2014-poverty-guidelines#threshholds

Marriage: (BaseExp M3-4, LTFU 2014 M2-3)
Insurance (Binary; BaseExp U2, LTFU 2014, LTFU 2017)
Medical care/follow up (Binary y/n and Categorical; BaseExp B1-B3, LTFU 2014 B1-B3, LTFU 2017 B1-B3)
Late (> 5 years after diagnosis) chronic health conditions defined by CTCAE-graded conditions
Number of conditions (any grade)
Number of severe, life-threatening, or fatal conditions (Grade 3-5)
CTCAE Grade 3-5 cardiac conditions
CTCAE Grade 3-5 pulmonary conditions
CTCAE Grade 3-5 endocrine conditions
CTCAE Grade 3-5 metabolic conditions
CTCAE Grade 3-5 musculoskeletal conditions
Body mass index (categorical; underweight (BMI < 18.5), normal (between 18.5 and 25), overweight (between 25 and 30) and obese (> 30); BaseExp LTFU A1-2, most recent)
Number of surgeries at site of local disease **<5** years from diagnosis, excluding biopsies (numeric)
Number of late (**>5** years from diagnosis) musculoskeletal surgeries (numeric, LTFU 2014 J1-J6 , LTFU 2017)
Number of amputations in non-amputation treatment groups (numeric, LTFU 2014 J1, LTFU 2017; *should be available from Geiger et al 2022 work*)
Scoliosis surgery y/n (binary; BaseExp I2-3; LTFU 2014 J2-3, LTFU 2017)
Late cancer-specific (due to the original sarcoma), SMN, and all-cause mortality

d) **Exploratory variables**

Patient variables

- Attained age (Interval)
- Sex (categorical, EBL-A2)
- Race, ethnicity (categorical, EBL-A5)

Oncologic variables

- Age at diagnosis
- Histology (categorical; osteosarcoma, Ewing sarcoma, other and ordinal; high, low grades)
- Tumor location: bone and proximal/diaphyseal/distal
- Metastatic disease upon presentation (binary y/n)

Treatment variables

- Surgery for local control (binary y/n)
- Type of initial local control surgery (categorical: AKA, BKA, rotationplasty, EP, allograft, APC)
- Radiotherapy only for local control (binary y/n and continuous [dosage])
- Radiotherapy used in addition to surgery for local control (binary y/n and continuous [dosage] and timing as pre- vs. post-op radiotherapy)
- Chemotherapy by agent and/or regimen (binary y/n)
    - Anthracycline (binary y/n)
    - Alkylating agent (binary y/n)
    - Vinca alkaloid (binary y/n)
    - MTX (binary y/n)

  - Cyclophosphamide (binary y/n)
  - Cisplatin/platinum (binary y/n)
  - Etoposide (binary y/n)
  - Regimen: (categorical; VDC, VDC/IE, MAP, MAP/IE, AP, other)

e) **Statistical methods**

Descriptive statistics will compare demographic, tumor, and treatment variables between local control modalities (radiotherapy, AKA, BKA, rotationplasty, and primary limb salvage procedures: endoprosthetic, allograft, or allograft-composite reconstruction) and identify potential baseline differences in the groups. (Tables 1,2)

Aim 1: Univariate analysis will be used to describe/explore associations of potential risk factors with SF-36 PCS and MCS scores below the population norm minus MCID = 5. This includes local control modality, chemotherapy (either by specific agents or by regimens), demographic variables, and treatment variable. Similar analysis will describe/explore potential risk factors for BSI, using threshold > 63 and binary as noted above. Physical activity will be evaluated as a binary variable indicating whether they meet the CDC guidelines for "active[58]." Activity limitations will be evaluated as a binary outcomes based on self-reporting as "limited" for at least three months in the past two years[59]. Functional impairment similarly reported as a binary variable based on self-reporting[59].

Multivariable modified-Poisson or log-binomial regression analysis will then be used to estimate adjusted associations of each of these outcomes with potential risk factors, based on previously identified unadjusted associations in the univariate analysis. Adjusted risk ratio estimates will be estimated and reported with 95% confidence intervals. (Table 3)

Aim 2: We will evaluate differences by local control modalities in socioeconomic outcomes including educational attainment, marital status, personal income under the poverty level, and health insurance status. Demographic variables (age, sex, race/ethnicity) and other potential covariates (e.g., chemotherapy exposures) will be controlled for in multivariable analysis, using a similar approach as Aim 1. Adjusted risk ratios will be estimated and reported with 95% confidence intervals. (Table 4) We will tabulate the number and proportion of each local control modality group that have seen healthcare providers within 2 years and what type. (Table 5)

Aim 3: We will graph and tabulate cumulative incidence of relevant CTCAE chronic health conditions, taking death as the competing risk event. Regression analysis will also be performed evaluating relationship between local control methods and CTCAE chronic health conditions. (Tables 6a/b, 7, Figure 3)

Aim 4: We will estimate time-dependent rates and cumulative incidence curves for overall survival, cancer-specific mortality, and second malignancy according to local control treatment method. (Figures 2-3), adjusting for variables considered in Aim 1, using piecewise exponential models.

f) **Examples of tables and figures**

Table 1: Demographics

	All Survivors (N=)	No surgery	AKA	BKA	Rotationplasty	Endoprosthetic	Allograft	APC	*p*
Age at diagnosis, mean (SD)									
Gender (%M)									
Race									
Non-Hispanic white									
Non-Hispanic black									
Hispanic									
Other									
BMI, mean (SD)									
Histology									
Osteosarcoma									
Ewing sarcoma									
Other									
Location									
Proximal femur									
Distal femur									
Proximal tibia									
Distal tibia									
Other									

Table 2: Treatment

	All Survivors (N=)	No surgery n (%)	AKA n (%)	BKA n (%)	Rotationplasty n (%)	Endoprosthetic n (%)	Allograft n (%)	APC n (%)	*p*
Chemotherapy regimens									
VDC									
VDC/IE									
MAP									
MAP/IE									
AP									
Other									
Local radiotherapy (y/n)									
Local radiotherapy (median dose of y's)									

Table 3a: HRQoL

	All Survivors (N=)	No surgery	AKA	BKA	Rotationplasty	Endoprosthetic	Allograft	APC	*p*
SF-36: Physical component score, mean (SD)									
Physical health, mean (SD)									
Physical role, mean (SD)									
Bodily pain, mean (SD)									
General health, mean (SD)									
SF-36: Mental component score, mean (SD)									
Vitality, mean (SD)									
Emotional role, mean (SD)									
Social function, mean (SD)									
Mental health, mean (SD)									
SF-36: Number below 40 (%)									
SF-36: Number below [pop mean - MCID] (%)									
BSI: Global Status Index, mean (SD)									
BSI: Global Status Index <63									
Depression or antidepressants vs not, n (%)									
Anxiety or anxiolytics vs not, n (%)									
Somatization, n (%)									

Table 3b: Risk of poor HRQoL by local control method*

Physical Activity	All Survivors (N=)	No surgery (Definitive XRT)	AKA	BKA	Rotationplasty	Endoprosthetic	Allograft	APC
Recommended activity, OR (vs less than rec)								
Activity limitations, OR (vs not)								
Functionally impaired OR (vs not)								

***Adjusted for demographics, chemotherapy, and lung/whole body radiation.**

Table 4: Socio-economic outcomes

	All Survivors (N=)	No surgery n (%)	AKA n (%)	BKA n (%)	Rotationplasty n (%)	Endoprosthetic n (%)	Allograft n (%)	APC n (%)	*p*

Employed									
Education									
College graduate									
High school graduate									
Below high school									
Marriage status									
Married									
No longer married									
Never married									
Income, personal									
Less than $20,000									
$20,000 - $39,999									
$40,000 - $59,999									
$60,000 - $79,999									
$80,000 - $99,999									
Over $100,000									
Health insurance									
Yes									
Canadian									

Table 5: Healthcare follow-up patterns

	All Survivors (N=)	No surgery n (%)	AKA n (%)	BKA n (%)	Rotationplasty n (%)	Endoprosthetic n (%)	Allograft n (%)	APC n (%)	
Healthcare provider in last 2 years (%)									
Primary care									
Cancer specialist									
Physical or occupational therapist									
Psychiatrist/psychologist									
Other									
Times seen a doctor, last 2 years									
Most recent routine check-up, cancer									

<1 year ago									
1-2 years									
2-5 years									
>5 years									
Never									

Table 6a: Chronic Health Conditions

	All Survivors (N=)	No surgery n (%)	AKA n (%)	BKA n (%)	Rotationplasty n (%)	Endoprosthetic n (%)	Allograft n (%)	APC n (%)
Chronic health conditions								
Any grade 1-5 condition								
Any grade 3-5 condition								
Grade 3-5 conditions								
Cardiac								
Pulmonary								
Endocrine								
Metabolic								
Musculoskeletal								

Table 6b: Risk of Chronic Health Conditions by Local Control Method*

	No surgery (Definitive XRT)	AKA	BKA	Rotationplasty	Endoprosthesis	Allograft	APC
Any Grade 3-5 CTCAE chronic condition	Ref	RR (95% CI)					
≥2 Grade 3-5 CTCAE chronic conditions							

***Adjusted for demographics, chemotherapy, and lung/whole body radiation.**

Table 7: Misc outcomes

	All Survivors (N=)	No surgery n (%)	AKA n (%)	BKA n (%)	Rotationplasty n (%)	Endoprosthetic n (%)	Allograft n (%)	APC n (%)	*p*
Spine/scoliosis surgery y/n									
Overall 10-year survival									
Cancer-related 10-year survival									

Figure 1 Distribution of each local control method by era (4yrs each, 1987-1999)
Figure 2, a and b Cumulative incidence curves: all-cause of overall survival, separated by local control modality
Figure 3, a and b Cumulative incidence curves: Relevant CTCAE: overall and separated by local control modality

References

1. Lee DH, Hills JM, Jordanov MI, Jaffe KA: Common Tumors and Tumor-like Lesions of the Shoulder. *J Am Acad Orthop Surg* 2019;27:236–245.
2. Jaffe N, Bruland OS, Bielack S: *Pediatric and Adolescent Osteosarcoma*. (Springer US: Netherlands, 2010).
3. Esiashvili N, Goodman M, Marcus RB: Changes in incidence and survival of ewing sarcoma patients over the past 3 decades: Surveillance epidemiology and end results data. *J Pediatr Hematol Oncol* 2008;30:425–430.
4. WHO Classification of Tumours Editorial Board: *Soft Tissue and Bone Tumours*. (International Agency for Research on Cancer: Lyon, 2020).
5. Anderson ME: Update on Survival in Osteosarcoma. *Orthop Clin North Am* 2016;47:283–292.
6. Nagarajan R, Neglia JP, Clohisy DR, Robison LL: Limb salvage and amputation in survivors of pediatric lower-extremity bone tumors: What are the long-term implications? *J Clin Oncol* 2002;20:4493–4501.
7. Ottaviani G, Robert RS, Huh WW, Palla S, Jaffe N: Sociooccupational and physical outcomes more than 20 years after the diagnosis of osteosarcoma in children and adolescents: Limb salvage versus amputation. *Cancer* 2013;119:3727–3736.
8. COVENTRY MB, DAHLIN DC: Osteogenic sarcoma; a critical analysis of 430 cases. *J Bone Joint Surg Am* 1957;39 A:
9. Allison DC, Carney SC, Ahlmann ER, et al.: A meta-analysis of osteosarcoma outcomes in the modern medical era. *Sarcoma* 2012;2012:
10. Hustu HO, Holton C, James D, Pinkel D: Treatment of Ewing’s sarcoma with concurrent radiotherapy and chemotherapy. *J Pediatr* 1968;73:249–251.
11. Jaffe N, Frei E, Traggis D, Bishop Y: Adjuvant Methotrexate and Citrovorum-Factor Treatment of Osteogenic Sarcoma. *N Engl J Med* 1974;291:994–997.
12. Cortes EP, Holland JF, Wang JJ, Sinks LF: Doxorubicin in Disseminated. *JAMA J Am Med Assoc* 1972;221:1132–1138.
13. Baum ES, Gaynon P, Greenberg L, Krivit W, Hammond D: Phase II study of cis-dichlorodiammineplatinum(II) in childhood osteosarcoma: Children’s cancer study group report. *Cancer Treat Rep* 1979;63:1621–1627.
14. Link MP, Goorin AM, Miser AW, et al.: The Effect of Adjuvant Chemotherapy on Relapse-Free Survival in Patients with Osteosarcoma of the Extremity. *N Engl J Med* 1986;314:1600–1606.
15. Nesbit ME, Gehan EA, Burgert EO, et al.: Multimodal therapy for the management of primary, nonmetastatic Ewing’s Sarcoma of bone: A long-term follow-up of the first intergroup study. *J Clin Oncol* 1990;8:1664–1674.
16. Davenport JR, Vo KT, Goldsby R, West DC, Dubois SG: Conditional Survival and Predictors of Late Death in Patients With Ewing Sarcoma. *Pediatr Blood Cancer* 2016;63:1091–1095.
17. Hounsfield GN: The E.M.I. scanner. *Proc R Soc London - Biol Sci* 1977;195:281–289.
18. Eilber FR, Morton DL, Eckardt J, Grant T, Weisenburger T: Limb salvage for skeletal and soft tissue sarcomas multidisciplinary preoperative therapy. *Cancer* 1984;53:2579–2584.
19. Simon MA, Aschliman MA, Thomas N, Mankin HJ: Limb-salvage treatment versus amputation for osteosarcoma of the distal end of the femur. *J Bone Jt Surg - Ser A* 1986;68:1331–1337.
20. Forsberg JA, Eberhardt J, Boland PJ, Wedin R, Healey JH: Estimating survival in patients with operable skeletal metastases: An application of a Bayesian belief network. *PLoS One* 2011;6:1–7.
21. Petrilli AS, Gentil FC, Epelman S, et al.: Increased survival, limb preservation, and prognostic factors for osteosarcoma. *Cancer* 1991;68:733–737.
22. Turcotte LM, Neglia JP, Reulen RC, et al.: Risk, risk factors, and surveillance of subsequent malignant neoplasms in survivors of childhood cancer: A review. *J Clin Oncol* 2018;36:2145–2152.
23. Zeltzer LK, Recklitis C, Buchbinder D, et al.: Psychological status in childhood cancer survivors:

A report from the childhood cancer survivor study. *J Clin Oncol* 2009;27:2396–2404.
24. Kuttesch JF, Wexler LH, Marcus RB, et al.: Second malignancies after Ewing's sarcoma: Radiation dose-dependency of secondary sarcomas. *J Clin Oncol* 1996;14:2818–2825.
25. Jairam V, Roberts KB, Yu JB: Historical trends in the use of radiation therapy for pediatric cancers: 1973-2008. *Int J Radiat Oncol Biol Phys* 2013;85:e151–e155.
26. Walker PS, Emerson R, Potter T, Scott R, Thomas WH, Turner RH: The kinematic rotating hinge: Biomechanics and clinical application. *Orthop Clin North Am* 1982;13:187–199.
27. Choong PFM, Sim FH, Pritchard DJ, Rock MG, Chao EYS: Megaprostheses after resection of distal femoral tumors. A rotating hinge design in 30 patients followed for 2-7 years. *Acta Orthop Scand* 1996;67:345–351.
28. Myers GJC, Abundu AT, Carter SR, Tillman RM, Grimer RJ: Endoprosthetic replacement of the distal femur for bone tumours. *J Bone Jt Surg - Ser B* 2007;89:521–526.
29. Shih LY, Sim FH, Pritchard DJ, Rock MG, Chao EYS: Segmental total knee arthroplasty after distal femoral resection for tumor. *Clin Orthop Relat Res* 1993;269–281.doi:10.1097/00003086-199307000-00036.
30. Malawer MM, Price WM: Gastrocnemius transposition flap in conjunction with limb–sparing surgery for primary bone sarcomas around the knee. *Plast Reconstr Surg* 1984;73:741–750.
31. Mankin HJ, Springfield DS, Gebhardt MC, Tomford WW: Current status of allografting for bone tumors. *Orthopedics* 1992;15:1147–1154.
32. Mankin HJ, Gebhardt MC, Jennings LC, Springfield DS, Tomford WW: Long-term results of allograft replacement in the management of bone tumors. *Clin Orthop Relat Res* 1996;86–97.doi:10.1097/00003086-199603000-00011.
33. Aponte-Tinao LA, Ayerza MA, Albergo JI, Farfalli GL: Do Massive Allograft Reconstructions for Tumors of the Femur and Tibia Survive 10 or More Years after Implantation? *Clin Orthop Relat Res* 2020;478:517–524.
34. Toy PC, White JR, Scarborough MT, Enneking WF, Gibbs CP: Distal femoral osteoarticular allografts: Long-term survival, but frequent complications. *Clin Orthop Relat Res* 2010;468:2914–2923.
35. Bus MPA, Van De Sande MAJ, Taminiau AHM, Dijkstra PDS: Is there still a role for osteoarticular allograft reconstruction in musculoskeletal tumour surgery? *Bone Jt J* 2017;99B:522–530.
36. Ogilvie CM, Crawford EA, Hosalkar HS, King JJ, Lackman RD: Long-term results for limb salvage with osteoarticular allograft reconstruction. *Clin Orthop Relat Res* 2009;467:2685–2690.
37. Abdeen A, Hoang BH, Athanasian EA, Morris CD, Boland PJ, Healey JH: Allograft-prosthesis composite reconstruction of the proximal part of the humerus. Functional outcome and survivorship. *J Bone Jt Surg - Ser A* 2009;91:2406–2415.
38. Gitelis S, Piasecki P: Allograft prosthetic composite arthroplasty for osteosarcoma and other aggressive bone tumors. *Clin Orthop Relat Res* 1991;197–201.doi:10.1097/00003086-199109000-00026.
39. Moon BS, Gilbert NF, Cannon CP, Lin PP, Lewis VO: Distal Femur Allograft Prosthetic Composite Reconstruction for Short Proximal Femur Segments following Tumor Resection. *Adv Orthop* 2013;2013:1–5.
40. Benedetti MG, Bonatti E, Malfitano C, Donati D: Comparison of allograft-prosthetic composite reconstruction and modular prosthetic replacement in proximal femur bone tumors: Functional assessment by gait analysis in 20 patients. *Acta Orthop* 2013;84:218–223.
41. Farid Y, Lin PP, Lewis VO, Yasko AW: Endoprosthetic and allograft-prosthetic composite reconstruction of the proximal femur for bone neoplasms. *Clin Orthop Relat Res* 2006;223–229.doi:10.1097/01.blo.0000181491.39048.fe.
42. Wunder JS, Leitch K, Griffin AM, Davis AM, Bell RS: Comparison of two methods of reconstruction for primary malignant tumors at the knee: A sequential cohort study. *J Surg Oncol* 2001;77:89–99.

43. Zehr RJ, Enneking WF, Scarborough MT: Allograft-prosthesis composite versus megaprosthesis in proximal femoral reconstruction. *Clin Orthop Relat Res* 1996;207–223.doi:10.1097/00003086-199601000-00026.
44. Ippolito J, Thomson J, Beebe K, Patterson F, Benevenia J: Outcomes following periacetabular tumor resection: A 25-year institutional experience. *J Surg Oncol* 2020;122:949–954.
45. Wang J, Shen J, Dickinson IC: Functional outcome of arthrodesis with a vascularized fibular graft and a rotational latissimus dorsi flap after proximal humerus sarcoma resection. *Ann Surg Oncol* 2011;18:1852–1859.
46. Gautam D, Arora N, Gupta S, George J, Malhotra R: Megaprosthesis Versus Allograft Prosthesis Composite for the Management of Massive Skeletal Defects: A Meta-Analysis of Comparative Studies. *Curr Rev Musculoskelet Med* 2021;14:255–270.
47. Cammisa FP, Glasser DB, Phil M, et al.: The van nes tibial rotationplasty. *J Bone Jt Surg - Ser A* 1990;72 A:1541–1547.
48. McClenaghan BA, Krajbich JI, Pirone AM, Koheil R, Longmuir P: Comparative assessment of gait after limb-salvage procedures. *J Bone Jt Surg - Ser A* 1989;71:1178–1182.
49. Robert RS, Ottaviani G, Huh WW, Palla S, Jaffe N: Psychosocial and functional outcomes in long-term survivors of osteosarcoma: A comparison of limb-salvage surgery and amputation. *Pediatr Blood Cancer* 2010;54:990–999.
50. Malek F, Somerson JS, Mitchel S, Williams RP: Does limb-salvage surgery offer patients better quality of life and functional capacity than amputation? *Clin Orthop Relat Res* 2012;470:2000–2006.
51. Mason GE, Aung L, Gall S, et al.: Quality of life following amputation or limb preservation in patients with lower extremity bone sarcoma. *Front Oncol* 2013;3 AUG:1–6.
52. Geiger EJ, Liu W, Srivastava DK, et al.: What Are Risk Factors for and Outcomes of Late Amputation After Treatment for Lower Extremity Sarcoma: A Childhood Cancer Survivor Study Report. *Clin Orthop Relat Res* 2022;Publish Ah:1–13.
53. Henderson ER, O’Connor MI, Ruggieri P, et al.: Classification of failure of limb salvage after reconstructive surgery for bone tumours: A modified system including biological and expandable reconstructions. *Bone Jt J* 2014;96B:1436–1440.
54. Grimer RJ, Aydin BK, Wafa H, et al.: Very long-term outcomes after endoprosthetic replacement for malignant tumours of bone. *Bone Jt J* 2016;98-B:857–864.
55. Muscolo DL, Ayerza MA, Aponte-Tinao LA, Ranalletta M: Partial epiphyseal preservation and intercalary allograft reconstruction in high-grade metaphyseal osteosarcoma of the knee. *J Bone Jt Surg - Ser A* 2004;86:2686–2693.
56. Interiano RB, Kaste SC, Li C, et al.: Associations between treatment, scoliosis, pulmonary function, and physical performance in long-term survivors of sarcoma. *J Cancer Surviv* 2017;11:553–561.
57. Cripe TP: Ewing sarcoma: An eponym window to history. *Sarcoma* 2011;2011:
58. Florin TA, Fryer GE, Miyoshi T, 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;16:1356–1363.
59. Ness KK, Hudson MM, Jones KE, et al.: Effect of temporal changes in therapeutic exposure on self-reported health status in childhood cancer survivors. *Ann Intern Med* 2017;166:89–98.