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A Systematic Review of Selected Musculoskeletal Late Effects in Survivors of Childhood Cancer

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Abstract

Survivors of childhood cancer are at risk for treatment-related musculoskeletal late effects. Early detection and orthopedic intervention can help ameliorate musculoskeletal late effects and prevent subsequent complications. This systematic review summarizes the literature describing associations between cancer, its treatment, and musculoskeletal late effects. We searched PubMed and Web of Science for English language articles published between January 1970 and December 2012. The search was limited to investigations with at least 15 participants and conducted at least 2 years after completion of therapy for childhood, adolescent, or young adult cancer. Some late skeletal effects, including low bone mineral density, osteonecrosis, slipped capital femoral epiphyses, oncogenic rickets, and hormone-related growth disturbances have been previously reviewed and were excluded, as were outcomes following amputation and limb-salvage procedures. Of 2347 references identified, 30 met inclusion criteria and were retained. An additional 54 studies that met inclusion criteria were found in reference lists of retained studies. Of 84 studies, 60 focused on associations between radiotherapy, six between chemotherapy, and 18

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between surgery and musculoskeletal late effects. We found that younger age, higher radiation dosage, and asymmetric or partial bone radiation volume influences the effects of radiation on the musculoskeletal system. Methotrexate and vincristine are associated with long-term muscular strength and flexibility deficits. Laminectomy and chest wall resection are associated with spinal malalignment, and enucleation is associated with orbital deformities among survivors. Radiotherapy, chemotherapy, and surgery are associated with musculoskeletal late effects independently and additively. Associations are additionally influenced by host and treatment characteristics.

Keywords

craniofacial abnormalities; musculoskeletal diseases; neoplasms; pediatrics; radiation; scoliosis; thoracic wall

INTRODUCTION

The 5-year survival rate among children with malignancies is over 80%. As of January 1, 2010, there were nearly 380,000 survivors of childhood cancer in the United States (1). This growing population is the result of progress in cancer treatment and supportive care. However, survivors remain at risk for significant treatment-related late effects (2, 3), including musculoskeletal complications (4).

Late musculoskeletal effects such as low bone mineral density (BMD) (5), osteonecrosis (6), slipped capital femoral epiphyses (7), oncogenic rickets (8), hormone-related growth disturbances (9), and limb salvage and amputation-related outcomes (10), have been comprehensively reviewed. However, the current state of knowledge about other, equally important, musculoskeletal late effects has not been systematically evaluated. Clinicians providing care to survivors should anticipate musculoskeletal late effects such as muscular atrophy, fibrosis, skeletal hypoplasia, and craniofacial and spinal deformity. Although these late effects influence physical functioning and quality of life of survivors (11–13), they have not been rigorously studied compared to the aforementioned well-reviewed late effects. Early detection and orthopedic intervention can help ameliorate musculoskeletal late effects and prevent subsequent complications.

To aid clinicians in the provision of individualized care through the identification of at-risk survivors and provision of timely intervention, we systematically review and summarize the existing knowledge about musculoskeletal late effects of childhood cancer treatment.

METHODS

Data Sources

We searched the PubMed and Web of Science database (Limits: English, human, dates: 01/01/1970 to 12/31/2012) for clinical trials, observational studies, case series, and reviews using the search terms “musculoskeletal abnormalities”, “adverse effects”, “infant”, “child”, “adolescent”, “adult, young”, “neoplasms”, “survivors”. Studies were selected after

reviewing the abstracts for relevance. This search was augmented with selected publications from reference lists of studies retrieved from databases.

Study Selection

The systematic review was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines (14). Reports were limited to studies with at least 15 participants that discussed late musculoskeletal effects among childhood cancer survivors evaluated a minimum of 2 years after completion of therapy. Previous literature reviews were excluded. Specific musculoskeletal effects, including low BMD (5), osteonecrosis (6), slipped capital femoral epiphyses (7), limb salvage and amputation related late effects (10), oncogenic rickets (8), and hormone-related growth complications after cranial radiation (9) were excluded because comprehensive reviews have been published. Primary outcomes were defined as the occurrence of musculoskeletal complications at least 2 years after completion of cancer therapy.

Data Extraction and Synthesis

One reviewer (P.L.G.) screened all titles and abstracts for relevance and validity. The methodological quality of the selected studies was independently evaluated by two reviewers (P.L.G. and K.K.N.) (15). Criteria used to determine the quality of the studies included comparability of subjects, clear definition of exposure or intervention, standard outcome measurement and appropriate statistical analysis. Discrepancies in assessment of validity and quality of studies were resolved by discussion between reviewers. We extracted information about sample size, age at diagnosis, type of diagnosis, follow-up period, type and details of treatment and musculoskeletal late effects from the selected studies.

RESULTS

Search Results

Our initial search of PubMed database identified 2347 studies; 30 were retained as relevant. An additional 54 studies that met inclusion criteria were found in reference lists of initially retained studies. No additional studies were identified in the Web of Science database. The 84 studies selected were evaluated according to the predominant anticancer therapy exposure (radiotherapy [n = 60], chemotherapy [n = 6], or surgery [n = 18]) associated with the late musculoskeletal effects (Figure 1).

Study Quality and Risk of Bias

Studies included in this review had clearly defined exposure and outcome measures. Most of the studies were cross-sectional, retrospective in design, from single institutions, and did not mention the eligible source population. Although we excluded studies with fewer than 15 participants, several studies included were conducted among small convenience cohorts because data from larger cohorts documenting musculoskeletal late effects were not available. These study designs may have either excluded patients with the most severe musculoskeletal effects because of death or inability to participate in follow-up testing, or oversampled them because of their concerns regarding late effects. Longitudinal studies included in this review were likely subject to selection bias due to attrition.

Muscular Late Effects of Radiotherapy (Table 1)

The underlying pathophysiology linking radiation to muscular late effects is unclear. However, acutely, radiation prevents mitosis of progenitor myosatellite cells (16), disrupts cell membrane permeability and lipid fluidity, and can result in sodium-potassium pump failure at the neuromuscular junction (17). Additionally, in the long-term, post-radiation inflammation, mediated by the transforming growth factor- β family, may prevent muscle growth (18), radiation-induced vascular and parenchymal damage may interfere with muscle nutrition (19), and mantle radiation may result in nemaline myopathy (20), potentially contributing to muscular atrophy (21–26), fibrosis (25–27), and hypoplasia (28).

Younger age and radiation doses ≥ 20 Gy influence the impact of radiation on muscle (28, 29). Thus, muscular late effects are most common among survivors of dysontogenetic tumors such as Wilms tumor (21–24, 29, 30) and neuroblastoma (27, 30) because these tumors typically present in early childhood and require radiation in cases of advanced disease (31). In contrast, while sarcomas (25, 26, 32) present across a wider age spectrum, survivors of these tumors are vulnerable to muscular late effects, not exclusively because of young age at exposure but because high doses of radiation (> 30 Gy) are required to achieve local control if complete surgical resection is not feasible.

All but two studies (24, 29) describing associations between radiotherapy and muscular late effects had small sample sizes (21–23, 25–28, 30, 32–36). Among 185 survivors of Wilms tumor treated at a median age of 3.7 and followed for a median of 18.9 years, Van Dijk *et al.* (29) reported an increased risk of tissue hypoplasia with increased dose of chest (Odds Ratio [OR]: 1.10 Gy⁻¹; 95% Confidence Interval [CI]: 1.03–1.18) and flank/abdominal (OR: 1.17 Gy⁻¹; 95% CI: 1.10–1.24) radiation. The authors also observed that female sex, younger age at diagnosis, and treatment with anthracyclines increased risk of tissue hypoplasia. A National Wilms Tumor Study (NWTs) analysis ($n = 680$) reported a higher prevalence of muscular atrophy five years after radiotherapy among survivors of Wilms tumor diagnosed between 1969 and 1979 who received radiation (30.2%) than among those who did not (1%) (24). Post-radiation muscular atrophy is uncommon for survivors of Wilms tumor treated after 1980 because unlike the historical age-adjusted 18–40 Gy radiotherapy, contemporary Wilms tumor patients are treated with 10.8 Gy (31).

Skeletal Late Effects of Radiotherapy (Table 1)

Acutely, radiation damages DNA in osteocytes by causing single or double strand breaks, sugar damage, base damage, by creating protein crosslinks, or by producing free hydroxyl radicals (37, 38). Animal and clinical evidence suggests that radiation may affect bone formation by: 1) arresting chondrogenesis at the epiphyseal growth plate, 2) inducing absorption failure of calcified cartilage and bone at the metaphysis, and 3) altering diaphyseal periosteal activity (39–41). Flat bones grow primarily by membranous ossification may present with diminished or asymmetrical growth after irradiation (Figure 2) (33).

Spinal Malalignment—One reported effect of radiotherapy is alteration in axial alignment, often presenting long after treatment as scoliosis or kyphosis (Supplementary

figure). In this review, the prevalence of post-radiotherapy scoliosis ranged from 10–80% (42, 43) and kyphosis from 2–48% (23, 43). In a cohort of 123 Wilms tumor survivors followed for a median of 18.9 years, the authors reported a 36.6% prevalence of scoliosis or kyphosis. Most cases (93.3%) were among survivors with a history of radiation (29). An NWTs analysis (n = 680) also reported a higher prevalence of scoliosis or kyphosis among survivors who had received radiation (51.4%) compared to those who had not (4.1%) (24). The evidence for the association between radiotherapy and spinal malalignment is strengthened by other studies (4, 21–23, 27, 28, 30, 34, 36, 42–55).

The effect of radiation on spinal malalignment is influenced by younger age, higher doses, and asymmetric radiation. Differential effects of radiation are reported based on age cutoffs of six months (51), one year (45), five years (23), or six years (44), depending on the population being studied. Similarly, varied thresholds for radiation dose are reported to increase risk for spinal malalignment including, > 20 Gy (34), > 23 Gy (52), > 24 Gy (28), and > 26 Gy (23). Asymmetric radiation increases the risk of spinal deformity in two ways (27, 34, 47). It is possible that radiation impairs the vertebral growth plate more on one side than the other. However, because vertebral bodies are small, it is likely difficult to impair only a portion of a vertebra. Two authors have speculated that spinal deformity is the result of tethering in atrophied paraspinal muscles (23, 34). Butler *et al.* (47) found that the prevalence of scoliosis after an average follow-up of 9.9 years after diagnosis was higher among survivors of Wilms tumor (63%) and neuroblastoma (83%), who had received asymmetric radiation, than among Hodgkin lymphoma survivors (39%), who received symmetric radiation. High rates of post-irradiation spinal deformity have gradually declined with refinement in radiotherapy techniques for solid tumors and with the use of lower radiation doses (31).

Spinal Growth Retardation—Although growth retardation is reported as an indirect result of growth hormone deficiency after cranial radiation (56), there is also evidence to suggest an association between spine directed radiation and abnormal vertebral growth. Survivors with this impairment are not only shorter in stature but are also cosmetically challenged as their trunk length is not congruent with normal length arms and legs. In a study of 124 Hodgkin lymphoma survivors treated when younger than 16 years of age, those treated before puberty with 33 Gy radiation to the entire spine and evaluated 2 years later had both standing (7.7%) and sitting height (8.2%) deficits (57). Other studies support the association between spinal radiation and growth retardation (42, 44, 58–61).

Both younger age (42, 58–61) and higher radiation doses (61–63) are associated with spinal growth retardation. Age-related effects of radiotherapy on spinal growth are described with age cutoffs of one year (59), three years (42), six years (58), and before the onset of puberty (60). Hartley *et al.* (63) found impaired vertebral growth among survivors of medulloblastoma and supratentorial primitive neuroectodermal tumor (median follow-up: 44 months) who received 36–39.6 Gy craniospinal irradiation (n = 26) than among those who received 23.4 Gy (n = 35).

Vertebral Asymmetry—Among cohorts of Wilms tumor survivors treated before 1980, spinal radiotherapy is associated with anterior beaking of vertebrae (23, 43, 45, 46), which

results in progressive spinal deformity, typically kyphosis, later in life (64, 65). Riseborough *et al.* (23) reported beaking of vertebral bodies among 16 of 81 Wilms tumor survivors followed a median of 12 years; 74 had received 31 Gy orthovoltage radiation.

Skeletal Hypoplasia—The inhibitory effect of radiation on osteogenesis commonly manifests as hypoplasia of bones among survivors of childhood cancer (45, 48, 50, 51, 55, 66), reported especially in flat bones (21, 33, 42, 45–47, 50, 66–69). In a study of 89 survivors of various childhood cancers treated at a median age of 3.8 years and followed for an average of 10.8 years, Crooks *et al.* (48) observed a higher prevalence of skeletal hypoplasia among survivors treated with > 25 Gy than among those treated with ≤ 25 Gy radiation (9/16 vs. 0/8).

Limb Length Discrepancy—Limb length discrepancy may develop in survivors treated with extremity radiation for Ewing sarcoma (25, 26, 32, 70) or abdominal radiation for Wilms tumor when the hemipelvis is included in the radiation field (28, 29, 49). Because the proximal femoral epiphysis accounts for only 30% of growth (71), most of the discrepancy observed among Wilms tumor survivors is likely due to the tilt resulting from iliac wing hypoplasia. Jentzsch *et al.* (26) observed limb length differences of > 1.5 cm among 9 of 22 lower extremity Ewing sarcoma survivors 2 years after treatment with a median dose of 50 Gy. Among 42 Wilms tumor survivors treated with abdominal radiation of 10–40 Gy (28), five survivors developed limb length differences ranging from 0.8 to 2.5 cm. Although cutoff criteria for defining limb length discrepancy varies across studies, the prevalence is higher among Ewing sarcoma (25, 26, 47) than among Wilms tumor survivors (29, 49). The severity of limb length discrepancy is influenced by younger age at radiation (25, 26). In a study of extremity sarcoma survivors followed for a median of 13 years, those radiated when younger than 10 years had greater limb length discrepancy than those radiated when older than 10 years of age (median: 4.4 vs. 1.2 cm) (25).

Craniofacial Deformities—Craniofacial deformities are reported after radiotherapy for head and neck tumors (72–74) including retinoblastoma (68) and rhabdomyosarcoma (69, 75–80). In a recent study, all of 25 retinoblastoma survivors treated with 35–54.9 Gy and followed for 5 to 21 years presented with midfacial hypoplasia (68). Another study reported facial deformity in 73% of survivors of head and neck rhabdomyosarcoma exposed to 41.4–65.0 Gy and followed for a median of 20 years (75).

The impact of radiation on craniofacial structure is age (73, 74, 77, 81) and dose dependent (72, 81). Younger age at diagnosis (2–9 vs. 11–13 years) was associated with a higher prevalence of craniofacial deformities (16/16 vs. 0/4) in survivors of head and neck sarcoma (77). Craniofacial deformity assessed using cephalometric analysis of lateral radiographs was present among 18 of 20 ALL survivors treated when younger than 5 years of age with 24 Gy but not among those treated when older than 5 years of age or those treated with < 24 Gy cranial irradiation (81).

Orbital Deformities—Several observational studies (68, 75, 78, 82–86) have reported associations between radiotherapy and orbital hypoplasia. This association is also influenced by younger age at radiation (82). Imhof *et al.* (82) examined 68 retinoblastoma survivors

(120 affected orbits) diagnosed at a mean age of 11 months, treated with 42 Gy radiation, and followed for 96 months. Among 16 unilateral retinoblastoma survivors treated with radiotherapy alone, the mean orbital width, height, and edge-tragus distance were shorter in irradiated orbits when compared to contralateral non-irradiated orbits. Mean orbital widths, heights, and edge-tragus distances of irradiated orbits improved with increasing age at radiation (82).

Chest Wall Deformities—Although usually reported as a late effect of surgery, chest wall deformities may result from radiotherapy (22, 47, 55, 66, 87). These deformities are not only important cosmetically but also impact risk for scoliosis and restrictive lung disease. Among 143 survivors treated with 19.5–50 Gy spinal and/or extremity radiation at a mean age of 8 years and followed for an average of 10 years, Butler *et al.* (47) observed chest and rib deformities in 36%. A higher prevalence of chest and rib deformities (63%) was observed in a subsample of 30 Wilms tumor survivors following asymmetric radiation (median dose 20 Gy) that included caudal ribs (47). Among 15 early-stage Hodgkin lymphoma survivors treated with 15 Gy asymmetric mantle radiation at a median age of 13 years (median follow-up of 39.6 months), Merchant *et al.* (87) observed impaired growth in fully versus partially irradiated clavicles (1.3 ± 1.1 vs. 1.8 ± 1.2 cm).

Osteochondroma—Osteochondromas are observed after exposure to TBI (53, 88) or local radiotherapy (23, 24, 28, 43, 45, 46, 51, 55), with a suggested higher prevalence reported following TBI. Assessments of TBI-exposed survivors reported osteochondroma among 9% (88) to 42% (53). Evans *et al.* (24) noted osteochondroma in 3.5% Wilms tumor survivors treated with local radiation, and Pastore *et al.* (55) observed osteochondroma in 8% survivors treated with an average of 21 Gy radiation. Although most osteochondromas do not require any treatment, some may require intervention if the tumor becomes abnormally large or symptomatic (89) or undergoes malignant transformation to secondary chondrosarcomas (90).

Muscular Late Effects of Chemotherapy (Table 2)

Recent studies have reported muscular late effects of chemotherapeutic agents including L-asparaginase, methotrexate, and vincristine that commonly present as loss of muscular strength (91–93) and/or flexibility (92). The inhibitory effect of L-asparaginase on protein synthesis (94) and the neurotoxicity (95) of methotrexate and vincristine may be responsible for these long-term muscular late-effects. In a study of 43 female survivors of ALL (mean follow-up: 8 years), Hovi *et al.* (91), even after accounting for physical activity levels, reported an association between L-asparaginase exposure and muscle weakness (effect sizes: 0.83–1.01). A more recent study of 415 survivors of ALL (median follow-up: 29.9 years) observed that survivors treated with cumulative dose of intrathecal methotrexate 215 mg/m² were at a higher risk for impaired strength, walking efficiency, and ankle range of motion than those not treated with methotrexate (92). Restricted ankle range of motion was also associated with a cumulative dose of vincristine 39 mg/m² (92).

Skeletal Late Effects of Chemotherapy (Table 2)

The skeletal late effects of chemotherapy have been observed as a result of additive effect with radiotherapy (96) or as an independent effect due to renal injury (97). Medulloblastoma survivors treated with both chemotherapy and craniospinal irradiation had lower growth velocities than those who received craniospinal irradiation alone (SDS: -3.57 vs. -0.88) when assessed for four consecutive years after treatment (96). However, the mechanism of this additive effect is unclear. Ifosfamide induces proximal tubular injury to the kidneys, presenting as loss of glucose, proteins, phosphate and bicarbonates (98), and is associated with rickets after an average of 5 years follow-up (97).

Skeletal Late Effects of Surgery (Table 3)

Spinal Malalignment—Surgeries such as laminectomy for any type of spinal tumor (99), neuroblastoma (52, 100–102) or intraspinal neuroblastoma (103–106), and chest wall resection (107) are associated with spinal malalignment. A study of 954 neuroblastoma survivors treated primarily with surgery reported a 20-year cumulative incidence of 5.8% for scoliosis requiring surgical correction (101). The authors also found that neuroblastoma survivors were 27 times (95% CI: 13.6–53.4) more likely to develop severe scoliosis than their siblings. Laminectomy (Relative Risk [RR]: 11.0; 95% CI: 5.8–21.1), spinal radiotherapy (RR: 5.6; 95% CI: 1.7–18.4) and thoracotomy (RR: 3.1; 95% CI: 1.6–6.1) were independently associated with severe scoliosis (101). In a study of 26 intraspinal neuroblastoma survivors followed for a median of 10 years, Hoover *et al.* (105) reported scoliosis among 66.7% of those treated with, compared to 36.4% among those treated without, laminectomy.

Follow-up time (52, 99) and concomitant radiotherapy (107, 108) influence the effects of surgery on spinal malalignment. In a study of neuroblastoma survivors, Paulino *et al.* (52) observed that those treated with laminectomy developed scoliosis after a median of 23 months, and those treated with radiotherapy developed scoliosis after a median of 68.5 months. Among 98 neuroblastoma survivors with symptomatic epidural compression, the prevalence of spinal deformity among those who had chemotherapy, radiotherapy and surgery was 62.5% compared to those who had chemotherapy and surgery (30%) or surgery alone (50%) (108).

Orbital Deformities—Orbital hypoplasia (84, 85, 109–112) and orbital asymmetry (84, 85, 112) occur in retinoblastoma survivors after enucleation. Among 65 retinoblastoma survivors treated with unilateral enucleation, Osborne *et al.* (109) observed a higher mean percent difference in orbital volume (enucleated – contralateral) among those enucleated at 0–2 years (10.4%) and 3–12 years (9.6%) than those enucleated when older than 13 years of age (3.6%). In a cohort of 54 retinoblastoma survivors treated at a median age of 13 months and followed for a median of 7.5 years, Kaste *et al.* (85) observed that orbital volume of survivors treated with enucleation alone were smaller than the contralateral orbits (median volume difference = 1.5 cm^3 ; $p = 0.01$).

There is consistent evidence suggesting that concomitant radiation (83, 112, 113), younger age at enucleation (110, 114), and use of appropriate orbital implants (85, 109–111) impact

the effect of enucleation on orbital deformities. Ameniya *et al.* (83) reported greater differences in size between enucleated and contralateral orbits after an average of 8.8 years of follow-up among 12 retinoblastoma survivors treated with both radiation and enucleation compared to 5 survivors treated with enucleation alone. Another study of 18 unilateral retinoblastoma survivors noted that children younger than 1 year of age at enucleation had higher mean orbital volume differences compared to those treated when older than 1 year of age (1.8 ± 1.5 vs. 0.6 ± 0.6 cm³) (114). Kaste *et al.* (85) also observed that survivors treated with smaller orbital implants (12–14 mm) had higher prevalence (70%) of orbits with smaller volume than survivors treated with larger orbital implants (16 mm: 60% and 18–22 mm: 50%).

CONCLUSION AND FUTURE DIRECTION

This systematic review summarizes the evidence that describes treatment-related musculoskeletal late effects in childhood cancer survivors. It includes information about both well-established musculoskeletal toxicities and novel musculoskeletal toxicities identified in recent studies. This information provides a foundation for providers who care for these children. Providers can identify children most at risk for adverse musculoskeletal outcomes so that they can target surveillance for outcomes amenable to early intervention (*e.g.* limb length differences, muscle weakness), or counsel those children and families who will require intervention when they reach skeletal maturity (*e.g.* mid-facial hypoplasia).

There has been a gradual refinement in therapeutic approaches to reduce late effects (31, 115) and several studies included in this review were instrumental in this process. Identification of adverse musculoskeletal effects after asymmetric and high-dose radiation among children treated for Wilms tumor led to the use of symmetric administration and lowering of radiation dose and restriction of radiation to only those with advanced stage tumor (31). Despite the gradual refinement in therapeutic approaches, many contemporary protocols include the same chemotherapeutic agents used in the past and may also include high-dose radiotherapy for advanced stage disease and radiotherapy for younger patients (31).

Very few studies have evaluated the musculoskeletal late effects of contemporary protocols and most of the studies in our review were conducted in small convenience cohorts. Therefore, continued work is needed to document musculoskeletal outcomes among those treated with newer radiotherapy delivery methods (116), personalized chemotherapy (117), and modern surgical management (118) so that risk factors can be updated for survivors treated on contemporary protocols. Continued observational research will help clinicians identify survivors at high risk of developing musculoskeletal late effects with improved precision and perhaps facilitate the design of interventions structured to ameliorate musculoskeletal late effects.

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Abbreviations

ALL	Acute lymphoblastic leukemia
BMD	Bone mineral density
CI	Confidence interval
DNA	Deoxyribonucleic acid
Gy	Gray
HCT	Hematopoietic cell transplant
NHL	non-Hodgkin lymphoma
NWTS	National Wilms Tumor Study
RR	Relative risk
SDS	Standard deviation score
TBI	Total body irradiation

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Figure 1.
Flow of studies through review.

Figure 2.
Effect of radiation on striated muscles and bones in childhood cancer patients

Table 1

Summary of 60 reports of radiation-associated musculoskeletal late effects in long-term survivors of childhood cancer

Ref. Author Name	Study Size (N)	Diagnosis	Exposure	Time since Exposure (years)	Outcome/ Assoc.	Vascular						Skeletal						Risk Factors																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																													
						Myocardial			Atherosclerosis			Stroke			LAD			Osteoarthritis			Osteoporosis			RT Damage			RT Field Size			RT Parameters																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																	
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Proctor (1975)	22	<15 y	HL (n=10), ALL (n=2)	HL (n=10), ALL (n=2)	9 mo-10 y	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

^a = age at study;

✓ = reported late effect or risk factor;

^x = older age at RT and male sex associated with growth retardation

Abbreviations: **AEWS:** Trial for Chemotherapy Intensification Through Interval Compression in Ewing’s Sarcoma; **ALL:** Acute Lymphoblastic Leukemia; **ADR:** Adriamycin; **AMD:** Actinomycin-D; **B/L:** Bilateral; **CCG:** Children’s Cancer Group; **Chemo:** Chemotherapy; **Co-60:** Cobalt-60; **cont.:** controls; **CPL:** Carboplatin; **CPM:** Cyclophosphamide; **CML:** Chronic Myeloid Leukemia; **CRT:** Cranial Radiotherapy; **CSPL:** Cisplatin; **CSRT:** Craniospinal Radiotherapy; **DOXO:** doxorubicin; **EORTC:** European Organization for Research and Treatment of Cancer; **ES:** Ewing’s Sarcoma; **GCT:** Germ Cell Tumor; **GN:** Ganglioneuroma; **Gy:** Gray; **HL:** Hodgkin lymphoma; **HCT:** Hematopoietic Cell Transplant; **LLD:** limb length discrepancy; **mo:** months; **MB:** Medulloblastoma; **MELPH:** Melphalan; **MeV:** Megavoltage; **MOPP:** Mechlorethamine, Vincristine, Procarbazine and Prednisone; **MP:** Mercaptopurine; **MTX:** Methotrexate; **NA:** Not applicable; **NB:** Neuroblastoma; **NHL:** non-Hodgkin Lymphoma; **NWTS:** National Wilms Tumor Study; **NPC:** Nasopharyngeal carcinoma; **OB:** Osteoblastoma; **OY:** Orthovoltage; **PNET:** Primitive Neuroectodermal Tumor; **POG:** Pediatric Oncology Group; **PRED:** Prednisone; **RB:** Retinoblastoma; **RMS:** Rhabdomyosarcoma; **RT:** Radiotherapy; **SIOP:** International Society of Pediatric Oncology; **TBI:** Total Body Irradiation; **UKW1:** United Kingdom Children’s Cancer Study Group First Wilms Tumor Study; **U/L:** Unilateral; **VCR:** Vincristine; **VP-16:** Etoposide; **WT:** Wilms tumor; **y:** years.

Table 2
Summary of 6 reports of chemotherapy-associated musculoskeletal late effects in long-term survivors of childhood cancer

First Author (Year)	Sample Size (n)	Age at Diagnosis	Diagnosis	Time since Diagnosis	Surgery	Chemotherapy Agents	Radiotherapy (RT) and Dose	Late Effects				Risk Factors				
								Loss of muscle strength	Spinal growth retardation	Nephrotoxicity	Rickets	Younger age at treatment	Accompanied RT	Vincristine & Methotrexate	Ifosfamide	L-asparaginase
Oldhan (96) 1992	38	1.3–11.3 y (mean 6.8 y)	MB	4 consecutive years follow-up	All had surgery	Chemo (n=23), VCR, lomustine and CSPL	CSRT 38.1 Gy and 36.3 Gy with chemo	✓	✓		✓					
Hovi (91) 1993	43 plus 69 controls	2–14 y (mean 7 y)	ALL	1–19 y (mean 8 y)	NA	All had Scandinavian protocol	24 Gy (n=32; CRT) 10–12 Gy (n=6; TBI)	✓	✓							✓
Loebstein (97) 1999	174	0.4–21.2 y (median 8 y)	Various cancers	5 y	NA	All had IF and Mesna CSPL (n=123)	NA		✓	✓				✓		
Chow (60) 2007	2434 plus 3009 siblings	0–18 y	ALL	5 y	NA	All had chemo	RT (65.1%) CRT and CSRT		✓				✓			
Hartman (93) 2008	92 plus 155 cont.	Mean 4.3 ± 2.0 y	ALL, WT, NHL, others	1–7.5 y (mean 3.3 y)	NA	Dutch Childhood Oncology Protocol	RT (n=9)	✓								
Ness (92) 2012	415	0.2–18.8 y (median 4.8 y)	ALL	13.7–46.5 y (median 29.9 y)	NA	VCR (n=415) MTX (n=385)	CRT (n=305)	✓						✓		

✓ = reported late effect or risk factor

Abbreviations: **ALL:** Acute Lymphoblastic Leukemia; **ADR:** Adriamycin; **CRT:** Cranial Radiotherapy; **CSPL:** Cisplatin; **Gy:** Gray; **IF:** Ifosfamide; **MB:** Medulloblastoma; **MTX:** Methotrexate; **NA:** Not applicable; **NHL:** non-Hodgkin Lymphoma; **TBI:** Total Body Irradiation; **VCR:** Vincristine; **WT:** Wilms tumor; **y:** years.

Table 3
Summary of 18 reports of musculoskeletal late effects associated with surgery in long-term survivors of childhood cancer

Ref Study Year	Sample Size (n)	Age at Diagnosis	Diagnosis	Time since Diagnosis	Surgery?	Chemotherapy? Agent	Radiation Dose (Gy)	Late Effects				Risk Factors									
								Strabismic	Exotropia	Myopia	Hyperopia	Orbital growth restriction	Orbital deformity	Orbital bony irregularities	Younger age at treatment	Last treatment	Therapeutic	Number of life social	No orbital implant	Had orbital implant	Follow-up time
Shaw (10/1994)	40	0-15 y	NA	1-14 y	Enucleation (1 unilateral and 10 bilateral)	NA	NA														✓
Boyd (10/1975)	10	0-15 y	NA	7 y	Enucleation (1 unilateral and 1 bilateral)	Chemop-1 (10M)	2 y		✓												
Shaw (10/1997)	17	Mean 6 y	RB, SCL	Mean 6 y	Enucleation	NA	NA														✓
Boyd (10/1977)	22	3.5-25 y (mean 10 y)	ES, RMS, OS, OS	7-12 mo	Enucleation (n=11)	Chemop-2 (1)	210-54 (10 y) per 17 (0-40)														✓
Boyd (10/1992)	42	0-15 y (mean 12.5 y)	Various	21 mo-40 y (mean 12.5 y)	Enucleation (2 unilateral and 1 bilateral)	NA	NA														✓
Boyd (10/1996)	42	1-14 y (mean 6 mo)	Various	0-6 mo	Enucleation (n=10)	Chemop-2 (1)	RT (n=5)														✓
Boyd (10/1997)	54 (60 orbits)	0-15 y (mean 7 y)	RB	40-25 y (mean 7 y)	Enucleation (n=31) and RT (n=20)	NA	22-45 (n=20)														✓
Boyd (10/1998)	26	4-15 y (mean 11 y)	RB	8-20 y (mean 14 y)	Enucleation (n=15)	Chemop-1 (1)	RT (n=10)														✓
De Bore (10/1994)	54	0-15 y (mean 10 mo)	NA	4-30 mo (mean 19 mo)	Enucleation (n=32)	Chemop-3 (1)	RT (n=1)		✓												✓
Shaw (10/2001)	70	0-15 y (mean 10 mo)	NA	Enucleation (n=37) and RT (n=33)	Enucleation (n=37)	Chemop-1 (1)	RT (n=1)														✓
Shaw (11/2001)	31 (39 orbits)	Mean 12 y	RB	Enucleation (n=21)	Enucleation (n=21)	Chemop-0	RT (n=21)														✓
Shaw (10/2001)	20 (26 orbits) and 5 (6 orbits)	Mean 12 mo	RB	12-20 y (mean 16 mo)	Enucleation (n=10) and RT (n=10)	Chemop-1 (1)	RT (n=10) and RT (n=10)														✓
Shaw (09/2002)	76	2 mo-16 y (mean 4.5 y)	NA	Enucleation (n=37) and RT (n=39)	Enucleation (n=37) and RT (n=39)	NA	NA														✓
Shaw (11/2007)	33	1-45 mo (mean 14.2 mo)	RB, SCL	12-20 mo (mean 14.2 mo)	Enucleation (n=14) and RT (n=19)	NA	NA														✓
Shaw (11/2009)	60 (64 orbits)	0-20 y (mean 10 y)	RB	8-20 y (mean 13 y)	Enucleation (n=31) and RT (n=29)	Chemop-1 (1)	RT (n=40)														✓
Shaw (10/2011)	98	0-15 mo (mean 6 mo)	RB	2-25 y (mean 7 y)	Enucleation (n=50)	Chemop-1 (1)	RT (n=10)														✓
Shaw (10/2011)	18	Mean 2-3 mo	RB	Mean 2-3 mo	Enucleation (n=10)	NA	NA														✓
Shaw (11/2011)	133 (138 orbits)	0-15 y (mean 5 y)	RB (120 orbits) and OS (18 orbits)	0-15 y (mean 5 y)	Enucleation (n=60) and RT (n=78)	Chemop-1 (1) and Chemop-2 (1)	RT (n=21)														✓

a = age at study; ✓ = reported late effect or risk factor

ADR: Adriamycin; AMD: Actinomycin-D; CPM: Cyclophosphamide; Co-60: Cobalt-60; CRT: Cranial Radiotherapy; ES: Ewing's Sarcoma; Gy: Gray; mo: months; NB: Neuroblastoma; OS: Osteosarcoma; NA: Not applicable; POG: Pediatric Oncology Group; RMS: Rhabdomyosarcoma; U/L: Unilateral; VCR: Vincristine; y: year