Systematic review of charged-particle therapy for chordomas and sarcomas of the mobile spine and sacrum

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OBJECTIVE Long-term local control in patients with primary chordoma and sarcoma of the spine and sacrum is increasingly reliant upon en bloc resection with negative margins. At many institutions, adjuvant radiation is recommended; definitive radiation is also recommended for the treatment of unresectable tumors. Because of the high off-target radiation toxicities associated with conventional radiotherapy, there has been growing interest in the use of proton and heavy-ion therapies. The aim of this study was to systematically review the literature regarding these therapies.

METHODS The PubMed, OVID, Embase, and Web of Science databases were queried for articles describing the use of proton, combined proton/photon, or heavy-ion therapies for adjuvant or definitive radiotherapy in patients with primary sarcoma or chordoma of the mobile spine and sacrum. A qualitative synthesis of the results was performed, focusing on overall survival (OS), progression-free survival (PFS), disease-free survival (DFS), and disease-specific survival (DSS); local control; and postradiation toxicities.

RESULTS Of 595 unique articles, 64 underwent full-text screening and 38 were included in the final synthesis. All studies were level III or IV evidence with a high risk of bias; there was also significant overlap in the reported populations, with six centers accounting for roughly three-fourths of all reports. Five-year therapy outcomes were as follows: proton-only therapies, OS 67%–82%, PFS 31%–57%, and DFS 52%–62%; metastases occurred in 17%–18% and acute toxicities in 3%–100% of cases; combined proton/photon therapy, local control 62%–85%, OS 78%–87%, PFS 90%, and DFS 61%–72%; metastases occurred in 12%–14% and acute toxicities in 84%–100% of cases; and carbon ion therapy, local control 53%–100%, OS 52%–86%, PFS (only reported for 3 years) 48%–76%, and DFS 50%–53%; metastases occurred in 2%–39% and acute toxicities in 26%–48%. There were no studies directly comparing outcomes between photon and charged-particle therapies or comparing outcomes between radiation and surgical groups.

CONCLUSIONS The current evidence for charged-particle therapies in the management of sarcomas of the spine and sacrum is limited. Preliminary evidence suggests that with these therapies local control and OS at 5 years are comparable among various charged-particle options and may be similar between those treated with definitive charged-particle therapy and historical surgical cohorts. Further research directly comparing charged-particle and photon-based therapies is necessary.

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KEYWORDS chordoma; carbon ion therapy; proton therapy; radiotherapy; local control; adjuvant

EN BLOC resection with negative margins (R0 resection) improves local control (LC) and disease-free survival (DFS) in patients with chordoma and primary sarcomas of the spinal column and sacrum.^{1–5} R0 resection may also improve overall survival (OS).^{1,6} Sur-

gery has been the mainstay of therapy for years as these tumors are radioresistant and the doses required to improve LC were unacceptably toxic to local healthy tissues. Certain locations, such as the mobile spine, offer unique challenges given the often close approximation of tumor

ABBREVIATIONS CIRT = carbon ion radiotherapy; CTC = Common Toxicity Criteria; DFS = disease-free survival; DSS = disease-specific survival; LC = local control; LFU = last follow-up; MGH = Massachusetts General Hospital; OS = overall survival; PFS = progression-free survival; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RBE = relative biological effectiveness; RFS = relapse-free survival.

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and eloquent nervous tissue. In the latter part of the 20th century, though, more advanced radiation modalities became clinically available as adjuvant or definitive therapy, including focused photon radiotherapy modalities and charged-particle therapies, notably proton therapy and carbon ion radiotherapy (CIRT). Charged particles have superior behaviors in soft tissue that theoretically enable them to provide more focused delivery of radiation energy to the target site with minimal off-target effects.

Preliminary studies, such as those from the Massachusetts General Hospital (MGH),^{7,8} found that the addition of modern radiation therapy could improve LC in patients operated on for spinal chordoma. Importantly, LC rates improved even in patients with positive surgical margins. More recent evidence has suggested that adjuvant radiation with these advanced modalities may be even more important to LC than surgical margins,⁹ perhaps due to the presence of micrometastatic disease located immediately outside the tumor pseudocapsule. As such, there is increased interest among spine surgeons, medical oncologists, and radiation oncologists in the use of proton therapy and hadron therapy as either definitive or adjuvant radiotherapy for patients with chordoma and sarcoma of the spinal column. In this study, we sought to systematically review the existing literature with a focus on radiation regimens, LC, DFS, progression-free survival (PFS), OS, and postradiotherapy complications. Our main objective was to compare the efficacy of proton, mixed proton/photon, and carbon ion radiotherapy in terms of the above outcomes, focusing on LC, PFS, DFS, and OS at 5 years following radiation treatment. We included both surgery- and radiation-only series to address the second question of whether definitive radiotherapy with charged particles can produce 5-year LC, OS, DFS, and PFS rates similar to the rates reported in historical surgical series.

Methods

A literature search was conducted on November 13, 2020, to identify all published reports of proton therapy, combined proton therapy/photon tomotherapy, and hadron therapy for patients with primary chordoma or sarcoma of the mobile spine and sacrum. Queried databases included PubMed/Medline, Embase, OVID Medline, and Web of Science. We also queried the bibliographies of included articles to identify additional articles. The search query for the PubMed/Medline database was (“chordoma” OR “chondrosarcoma” OR “osteosarcoma” OR “osteogenic sarcoma” OR “Ewing sarcoma” OR “Ewing’s sarcoma” OR “Ewings sarcoma” OR “primary bone tumor” OR “primary vertebral tumor” OR “primary spine tumor”) AND (spine OR spinal OR vertebral OR vertebra OR vertebrae OR sacrum OR sacral) AND (“carbon ion” OR “hadron” OR “proton” OR “proton therapy” OR “carbon ion therapy” OR “hadron therapy” OR “charged ion” OR “charged ion therapy”). The individual queries for each database are listed in the *Appendix*.

Included studies had full-text English translations and included a minimum of 5 adult patients (> 16 years of age) being treated for a primary sarcoma or chordoma of the mobile spine or sacrum. Articles had to provide pri-

mary data on one of the following outcomes of interest: OS, PFS, disease-specific survival (DSS), DFS, LC, rates of metastasis, and radiation-associated toxicities. Articles were excluded if they pooled adult and pediatric patients, pooled spine/sacral lesions with lesions of other sites, pooled patients treated with pure photon regimens with those receiving proton/charged-particle regimens, or presented nonprimary data (i.e., fit one of the following article types: commentary, opinion, perspective, systematic review, narrative review). Articles were screened by two reviewers (Z.P. and J.E.), with a third reviewer (D.M.S.) serving as referee in case of disagreement. Screening was performed using Covidence v2313 (Covidence) according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.¹⁰

We collected details about patient demographics (age, sex, median tumor clinical target volume), radiation treatment modality (protons, mixed protons and photons, CIRT, or other hadron therapy), dosing schema (total dose, fractionation, duration), and concomitant treatments given with radiation (including surgery, chemotherapy, and hyperthermia). All studies were case series and were deemed to have a high risk of bias.

Results

In total, 595 unique articles were identified, of which 64 underwent full-text screening and 36 were included in the final qualitative synthesis (Fig. 1).^{1,11–45} The most common exclusion reasons were pooling of spine/sacrum lesions with other lesion locations (n = 14), the use of photon-only radiotherapy (n = 9), and failure to report one of the outcomes of interest (n = 3). Of the included articles, 8 examined proton-only therapy (Table 1),^{11,22,33,40–44} 11 examined combined proton/photon radiotherapy (Table 2),^{1,12–20,45} 14 examined CIRT (Table 3),^{21,23–32,34–36} and 3 examined a combination of proton radiotherapy and CIRT or another hadron therapy (Table 4).^{37–39} All included studies were at high risk of reporting bias. All were level IV evidence based on the North American Spine Society Levels of Evidence,⁴⁶ except the study by Mima et al.³⁷ (level III evidence). Most studies were published by five centers: the Heidelberg Ion Beam Therapy Center (n = 3),^{21,31,34} the Hyogo Ion Beam Medical Center in Japan (n = 4),^{11,23,37,39} the MGH (n = 9),^{1,13–17,19,20,22} the National Institute of Radiological Sciences in Chiba, Japan (n = 10),^{23–29,32,33,36} and the Paul Scherrer Institute (n = 4).^{41–44} Unless otherwise stated, the results are reflective of adjuvant particle radiation before, after, or combined with surgery.

Proton-Only Series

All 8 studies^{11,22,33,40–44} were small (5–116 patients). The median age was 50–71 years, the median follow-up was 18–65 months, and patients were 55%–100% male. Excluding the study by Murray et al.,⁴¹ which separated chordoma and chondrosarcoma outcomes, the most common pathologies were chordoma (67%–100% of patients) and chondrosarcoma (0%–33%). Five series^{11,22,42–44} described outcomes for only chordoma patients, and 0%–75% of lesions involved the mobile spine; 2 reported only outcomes for sacral chordoma.^{11,44} LC was 56%–68% at 5

FIG. 1. PRISMA flow diagram for study queries.

years and 62%–100% at the last follow-up (LFU). Five-year outcomes were OS 67%–82%, PFS 31%–57%, and DFS 52%–62%. Metastases occurred in 17%–18% by the LFU. Acute toxicities were seen in 3%–100% of patients with National Cancer Institute Common Toxicity Criteria (CTC) events $\geq$ grade 3 noted in 0%–20%. Late toxicities occurred in 34%–60%, with 0%–16% suffering toxicities $\geq$ grade 3. The median dose relative biological effectiveness (RBE) ranged from 70 to 74; most used fractions of 1.8–2.2 RBE. No common outcomes were reported by the 2 studies of nonsurgical patients.^{11,44} However, Aibe et al.¹¹ reported the following 3-year outcomes: LC 82%, OS 93%, PFS 90%, and DFS 81.9%.

Mixed Proton/Photon Series

Eleven studies described combined proton/photon therapy.^{1,12–20,45} All series were small (11–126 patients) with a median age of 39–70 years, sex makeup of 45%–63% male, and median follow-up of 12.9–99.6 months; 54%–100% of patients were treated for chordoma with 6 series^{1,12–14,19,20} including only chordoma patients. The median dose was 68.4–77.4 RBE, most commonly given in 1.8–2 RBE fractions. LC rates were 36%–98% (1 year), 18%–90% (2 years), 84%–97% (3 years), 62%–85% (5 years), and 49%–58% (10 years). The OS rates were 93%–96% (2 years), 87%–92% (3 years), 78%–87% (5 years), and 53%–63% (10 years). PFS was only reported by Chen et al.,¹³ who reported 90% at 5 years and 80% at 10 years. DFS was 68%–77% at 3 years and 61%–72% at 5 years. Metastases occurred in 12%–14% (3 years), 20%–27% (5 years), and 8%–24% (LFU). Acute toxicities occurred in 84%–100% (2%–16% suffered toxicities $\geq$ CTC grade 3), and late tox-

icities occurred in 10%–100% (0%–28% suffered toxicities $\geq$ CTC grade 3). Chen et al.¹³ and Kabolizadeh et al.¹⁹ described nonsurgical patients. Both cohorts were from the MGH and used a median dose of 77.4 RBE delivered in 1.8–2 RBE fractions. At 3 years, the OS was 89%–92% and DSS was 96%–97%. Metastasis was seen in 12%–14% and the OS at 5 years was 78%–82%.

CIRT Series

Fourteen studies described CIRT.^{21,23–32,34–36} Studies were small (7–219 patients), with only 2 studies from the National Institute of Radiological Sciences in Chiba, Japan, including more than 100 patients.^{23,27} The median age was 54–67 years, patients were 48%–80% male, and the median follow-up was 18–80 months. Except in the study by Matsumoto et al.,⁴⁷ in all treated patients (94%–100%) chordoma was the most common disease, with 12 studies including only chordoma patients.^{21,23–27,29,30,32,34–36} The median dose was 64–86 RBE given in 2.2–4.6 RBE fractions. LC rates were 90%–94% (1 year), 76%–85% (2 years), 53%–95% (3 years), and 53%–100% (5 years). The OS rates were 97%–100% (2 years), 59%–86% (3 years), and 52%–86% (5 years). The PFS rates were 90%–95% (1 year), 70%–80% (2 years), 48%–76% (3 years), and 48%–94% (10 years). The DFS was 50%–53% at 5 years, and Imai et al.²⁷ reported a 10-year DFS of 31.3%. Metastases occurred in 7%–9% (1 year), 32%–52% (5 years), and 2%–39% (LFU). Acute toxicities occurred in 26%–48% (0%–18% suffered CTC grade $\geq$ 3 events), and late toxicities occurred in 59%–89% (0%–21% suffered CTC grade $\geq$ 3 events). Eight studies examined strictly nonsurgical patients,^{23,26–30,32,35} and in 6 of these studies patients were

TABLE 1. Series describing outcomes for patients treated with proton-only regimens

Authors & Year (LOE)	Neuropathology	Pt Demogr:			RT Regimen	Op Outcome	LC & Mets	OS	PFS, DFS, DSS, &/or RFS	Toxicity	
		Sex; Med	Age; Med FU;	Med CTV						Acute	Late
Albe et al. 2018 ^{11*} (IV)	33 chrd, 11 w/ pre-RT surgical spacer placement; 100% S	55% M; 71 yrs; 37 mos; 284.4 cm ³	TD 70.4 RBE, frx 2.2 RBE, 5 days/wk x 6 wks		NA	3-yr LC: 81.8%; mets 11.8%; med time to mets 28 mos	3-yr 92.7% LFU 77%, med 61.5 mos	3-yr PFS 89.6% & DFS 81.9%	Overall: ≥64%, ≥3% grd ≥3; skin: 32% grd 2; 2% grd 3; GI: 2% grd 3; GU: 5% grd 2; pain: 47% grd 2; other: 9% grd 2	Overall: ≥58%, ≥6% grd ≥3; pain: 43% grd 2; sacral frac: 9% grd 2, 5% grd 3; GI: 5% grd 2, 2% grd 3; GU: 5% grd 2; neurop: 5% grd 2	RT toxicity not separated from nilotinib toxicity
Cote et al., 2018 ^{22†} (IV)	22 high-risk chrd; LOC: 1 T, 8 L, 13 S	59% M; 65 yrs; 44.8 mos; NG	TD med 73.8 RBE, preop 50.4 RBE, frx 1.8; 5 days/wk x 6 wks; current nilotinib 200 mg 2/day x 56 days		45% op, 55% no op	LC: NG; mets: NG	2-yr 95% LFU 77%, med 61.5 mos	2-yr med PFS 58.2 mos, ~90% of pts	RT toxicity not separated from nilotinib toxicity	RT toxicity not separated from nilotinib toxicity	RT toxicity not separated from nilotinib toxicity
Demizu et al., 2017 ^{33*†} (IV)	28 spine chrd sarcoma; LOC: 8 C, 5 L, 2 L/S, 13 S	NG; NG; NG; NG	TD med 70.0 Gy; frx NG; time NG		61% op, 39% no op	5-yr 55.6%; mets: NG	5-yr 70.7% PFS 30.7%	5-yr PFS 30.7%	Not separated from skull base outcomes	Not separated from skull base outcomes	Not separated from skull base outcomes
Indelicato et al., 2016 ⁴⁰ (IV)	34 chrd; 17 cndr; LOC: 20 C, 10 T/L, 21 S	66% M; 58 yrs; 3.7 yrs; NG	TD med 70.2 RBE (chrd 70.2, cndr 72 RBE); frx NG; time NG; 28 prRT; 23 prRT + phRT		NG; instrumentation in 47%	LC: 4-yr 58%, mets: 14%; LR: 35% med 1.7 yrs	4-yr 72% PFS med 1.7 yrs; DFS: 57%; DSS 4-yr 72%	PFS med 1.7 yrs; DFS: 57%; DSS 4-yr 72%	Overall: 16% grd ≥3; 2 secondary cancer	Overall: 16% grd ≥3; 2 secondary cancer	Overall: 16% grd ≥3; 2 secondary cancer
Murray et al., 2020 ^{41§} (IV)	116 chrd; LOC: 50 C, 8 T, 13 L, 45 S	60% M; 57 yrs; 64.7 mos; 809 cm ³	TD med 74 RBE; frx NG; time NG; 90% prRT only; 10% prRT + phRT		57% R0/R1; 43% R2/biopsy only; instrumentation in 43%	LC: 67.9% 5 yrs; mets: 17.2% LFU; LR: 32.8% LFU	81.6% 5 yrs DFS 5-yr 62.1%	DFS 5-yr 62.1%	Chrd + cndr pooled; overall: 33.5%; 7.7% grd ≥3	Chrd + cndr pooled; overall: 33.5%; 7.7% grd ≥3	Chrd + cndr pooled; overall: 33.5%; 7.7% grd ≥3
Murray et al., 2020 ^{41§} (IV)	39 cndr; LOC: 11 C, 21 T, 0 L, 1 S; 6 pelvis	64% M; 50 yrs; 64.7 mos; 386 cm ³	TD med 70 RBE; frx NG; time NG; 85% prRT only; 15% prRT + phRT		64% R0/R1; 36% R2/biopsy only; instrumentation in 41%	LC: 55.9% 5 yrs; mets: 17.9% LFU; LR: 38.5% LFU	67.3% 5 yrs DFS 5-yr 51.7%	DFS 5-yr 51.7%	Chrd + cndr pooled; overall: 33.5%; 7.7% grd ≥3	Chrd + cndr pooled; overall: 33.5%; 7.7% grd ≥3	Chrd + cndr pooled; overall: 33.5%; 7.7% grd ≥3
Snider et al., 2018 ^{42§} (IV)	100 spinal chrd; LOC: 46 C, 4 T, 12 L, 38 S	57% M; 56 yrs; 65 mos; NG	TD med 74 RBE; frx 1.8–2 RBE; time NG; 88% prRT; 12% phRT-prRT combo		40% R0/R1 rsxn; 60% R2 rsxn; 39% w/ instrumentation in 41%	LC: 5-yr 63% med 103 mos; 63% LFU; mets: NG	81% 5 yrs; med 157 mos	PFS 5-yr 57%, med 82 mos	Overall: 8% grd ≥3; skin: 6% grd 3; mucositis: 2% grd 3	Overall: 8% grd ≥3; skin: 6% grd 3; mucositis: 2% grd 3	Overall: 8% grd ≥3; skin: 6% grd 3; mucositis: 2% grd 3
Staab et al., 2011 ^{43§} (IV)	40 chrd; LOC: 16 C, 3 T, 1 T/L, 10 L, 11 S	63% M; 58 yrs; 43 mos; NG	TD med 74 RBE; frx 1.8–2.0 RBE; 4 days/wk x 8–10 wks; 78% prRT; 22% prRT + phRT		53% R0/R1; 47% R2; 53% prior instrumentation	LC: 62% 5 yrs; mets: NG	80% 5 yrs DFS 5-yr 57%	DFS 5-yr 57%	Overall: 5% grd ≥3; 1 secondary malignancy, 1 vertebral frac requiring op	Overall: 5% grd ≥3; 1 secondary malignancy, 1 vertebral frac requiring op	Overall: 5% grd ≥3; 1 secondary malignancy, 1 vertebral frac requiring op

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TABLE 1. Series describing outcomes for patients treated with proton-only regimens

Authors & Year (LOE)	Neuropathology	Pt Demogr:		RT Regimen	Op Outcome	LC & Mets	OS	PFS, DFS, DSS, &/or RFS	Vol		Toxicity	
		Sex; Med Age; Med FU; Med CTV							Resp	Acute	Late	
Tran et al., 2020 ⁴⁸ (IV)	5 unresec chrd; LOC: 100% S	100% M; 67 yrs; 18 mos; NG	TD 70 RBE; frx 2.5 RBE; 41 days w/ 39°–42°C hyperthermia	NA	NA	LC: 100%; mets: 0%	Med >18 mos	PFS med >18 mos; DSS >18 mos	Initial ↑ in 4/5; 9–72% ↓ (med 48%) LFU	Overall: 100%; 20% grd ≥3; pain: 100% grd 2–3; skin: 60% grd 2; GI: 20% grd 3	Overall: 60%; 0% grd ≥3, 20% grd 3, iliac frac; skin: 20% grd 2; GI: 20% grd 1	

C = cervical spine; chrd = chordoma; cndr = chondrosarcoma; CTV = clinical target volume; demogr = demographic; frx = fracture; frx = fraction; FU = follow-up; GI = gastrointestinal toxicity; grd = grade; GU = genitourinary toxicity; L = lumbar spine; LOC = location; LOE = level of evidence; LR = local recurrence; med = median; mets = metastasis; NA = not applicable; neuro = post-RT neuropathy; NG = not given; phRT = photon radiotherapy; phRT = proton radiotherapy; pt = patient; R0 = complete tumor removal on macroscopic and microscopic histology; R1 = complete tumor removal on macroscopic but not microscopic examination; R2 = tumor identified on both macroscopic and microscopic examination; resp = response; rsxn = resection; RT = radiotherapy; S = sacrum; T = thoracic spine; TD = total dose; unresec = unresectable; Vol = volumetric; ↓ = decrease; ↑ = increase.

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treated at the National Institute of Radiological Sciences,^{23,26–29,32} so much of the data from these sources were from a similar and likely overlapping set of nonsurgical patients treated at the National Institute of Radiological Sciences. Five-year outcomes were LC 72%–100%, OS 52%–86%, and DFS 50%–53%. Metastasis occurred in 14%–36% by the LFU.^{23,26–30,32,35}

Other Series

In the 3 remaining series, 2 reported pooled outcomes for patients treated with proton therapy and CIRT,^{37,39} and 1 series described patients treated with helium, neon, or combination helium/neon-based therapies.³⁸ All 3 series studied sacral chordoma; the median patient age was 61–72 years, and 48%–86% of patients were male. The median dose was 70.4–79.2 RBE given in fractions of 2–4.4 RBE over a period of 4 weeks to 61 days. Only 5-year OS (85%–100%) and rates of metastases at the LFU (14%–29%) were reported by more than 1 study.^{38,39} Both studies from the Hyogo Ion Beam Medical Center employed a surgical spacer implanted posterior to the rectum to reduce dosing to the anus and rectum, whereas the study of Schoenthaler et al.³⁸ treated a mixture of surgical and nonsurgical patients. Only Tsugawa et al.³⁹ reported outcomes for nonsurgical patients.

Discussion

Recent evidence has begun to suggest that adjuvant radiation⁹ may be the most significant predictor of LC in primary sarcomas of the spine and sacrum. The reasons for this are at present unknown; however, preliminary histology-based studies suggest it may be due to micrometastatic disease outside of the tumor capsule.⁴⁸ Additionally, some lesions are not amenable to surgery, meaning that definitive radiotherapy may be the only option. Given the radioresistance of primary bone sarcomas to conventional radiation, there is great interest in the utility of charged-particle therapies for the definitive or adjuvant management of these lesions. Previous reviews focusing on chordoma and chondrosarcoma of the skull base have found these modalities to produce high rates of OS and LC of up to 5 years. Here, we provide a similar analysis of the efficacy of these treatment methods in the mobile spine and sacrum. Relative to the reported rates for skull base lesions, we find that OS and LC rates are lower. However, given the findings from population-level studies,⁴⁹ it is possible that these differences may be due to the overall better prognosis of skull base lesions relative to those of the spine/sacrum.

Of particular interest are the reported efficacies of the various radiation modalities as definitive therapies. The available data are severely limited. Of those studies including only nonsurgical patients, LC is similar for patients treated with protons (82% at 3 years)¹¹ and CIRT (72%–100% at 5 years). OS is likewise similar for combined photon/proton radiotherapy and CIRT at 5 years (78%–82% vs 52%–86%). Of note, statistical comparisons were not possible given the significant overlap in the reported study populations. Despite this, Mima et al.³⁷ directly compared outcomes between proton and hadron therapy for sacral chordoma and saw no significant differences in LC, PFS,

TABLE 2. Series outcomes for patients treated with combined proton/photon therapy regimens

Authors & Year (LOE)	Neuropathology	Pt Demogr:		RT Regimen	Op Outcome	LC & Mets	OS	PFS, DFS, DSS, &/or RFS	Vol		Toxicity	
		Sex; Med Age; Med FU; Med CTV							Resp	Acute	Late	
Austin et al., 1993 ⁴⁵ (IV)	Recurrent lesions; 10 chrd; 1 cndr; LOC: 100% C	55% M; 39 yrs; NG; 76.1 cm ³	TD med 68.4 RBE; frx 1.8–2 RBE; med 38 RBE; 5 days/wk × 7–8 wks	NG	LC: 36% 1 yr; 18% 2 yrs; mets: NG; LR: 100% LFU; 64% 1 yr	NG	NG	NG	NG	NG	NG	NG
Beddok et al., 2021 ¹² (IV)	41 chrd; LOC: 100% S	NG; 64 yrs; 46 mos; 255 cm ³	TD 70–73.8 RBE; frx 1.8–2 RBE; med 64 days; 28 prRT/phRT combo; 13 phRT only	15 R0/R1; 15 R2, 11 no op	LC: 90% 2 yrs; 75% 5 yrs; mets: 11% 2 yrs; 27% 5 yrs; LR: 19.5% LFU	96% 2 yrs; 80% 5 yrs	NG	NG	Overall: 100%; 7% grd ≥3; skin: 100%; 7% grd 3; neurop: 17% grd 1; pain: 54% grd 1; 2.4% grd 2; GU: 5–15% grd 1	NG	Overall: 82–100%; 4% grd ≥3; skin: 45%; GU: 14–19%; pain: 34% grd 1; 7% grd 2; 2% grd 3	
Chen et al., 2013 ^{13*} (IV)	24 unresec chrd; LOC: 2 C, 1 T, 2 L, 19 S	54% M; 70 yrs; 56 mos; 198 cm ³	TD med 77.4 RBE; frx 1.8–2 RBE; 5 days/wk × med 60 days	NA	LC: 79% LFU; mets: 13.5% 3 yrs; 19.5% 5 yrs	91.7% 3 yrs; 78.1% 5 yrs	DFS: 3-yr 77.2%; DSS 5-yr 72.0%, 3-yr 95.7%, 5-yr 81.5%; PFS 3-yr 90.4%, 5-yr 79.8%	NG	Overall: NG; skin: ≥3; 8 sacral frac; skin: 100% grd 1–2; GU: 8.3%; GI: 17–29% 8.3%; GI: 16.7%; neurop 13%	NG	Overall: 100%; 0% grd ≥3; 8 sacral frac; skin: 100% grd 1–2; GU: 8.3%; GI: 16.7%; neurop 13%	
Cheney et al., 2014 ^{14*} (IV)	20 chrd; LOC: 1 C, 3 L, 16 S	45% M; NG; 1.8 yrs; NG	TD med 70.2 RBE; frx NG; time NG; 10% got nilotinib w/ RT	70% R0; 15% R1/R2; 15% biopsy only	LC: NG; mets: 15% med 10.7 mos	NG	NG	NG	NG	NG	NG	NG
Chowdhry et al., 2016 ^{15*} (IV)	50 chrd; 28 cndr; 3 ost; 11 other sarcoma; LOC: T/L	NG; 54 yrs; 12.9 mos; NG	TD med 70.2 RBE; frx NG; time NG; 7.5 Gy ⁹⁰ Y or 10 Gy ¹⁹² Ir dural plaque in 10/68	16 ops, margin NG; 52 no op	LC: NG; mets: NG; LR: 10.3% LFU	86.9% 5 yrs	NG	NG	Overall: NG; neurop: 11.7%	NG	Overall: NG; neurop: 7.1% grd ≥2 5 yrs; 19.1% 6 yrs, 8 yrs	
DeLaney et al., 2009 ^{16*} (IV)	29 chrd; 14 cndr; 1 ost; 6 other; LOC: 11 T, 13 L, 26 S	NG; NG; 48 mos; NG	TD med 76.6 RBE; frx 1.8 RBE; time: 2 wks preop (S) or 6 wks (spine); 7.5 Gy ⁹⁰ Y or 10 Gy ¹⁹² Ir dural plaque in 3 pts, 2 pts, respectively	8 R0; 17 R1; 12 R2; 13 biopsy only; instrumentation in 16	LC: 98% 1 yr; 84% 3 yrs; 78% 5 yrs; mets: NG; LR: 18% LFU	98% 1 yr; 87% 5 yrs	RFS: 94% 1 yr; 68% 3 yrs; 63% 5 yrs	Overall: 1 grd ≥3; sacral frac: 1 grd 3	Overall: 10%; 31% 6 yrs; 28% grd ≥3 6 yrs; neurop: 4% grd 3; sacral frac: 2% grd 3; GU: 2% grd 3; GI: 2% grd 3	NG	Overall: 10%; 31% 6 yrs; 28% grd ≥3 6 yrs; neurop: 4% grd 3; sacral frac: 2% grd 3; GU: 2% grd 3; GI: 2% grd 3	

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TABLE 2. Series outcomes for patients treated with combined proton/photon therapy regimens

Authors & Year (LOE)	Neuropathology	Pt Demogr:		RT Regimen	Op Outcome	LC & Mets	OS	PFS, DFS, DSS, &/or RFS	Toxicity		
		Age; Med FU; Med CTV	Sex; Med						Vol Resp	Acute	Late
DeLaney et al., 2014 ^{17*} (IV)	29 chrd; 14 cndr; 1 ost; 6 other; LOC: 11 T, 12 L, 27 S	NG; NG; 7.3 yrs; NG		TD med 76.6 RBE (w/ 7.5 Gy ⁹⁰ Y or 10 Gy ¹⁹² Ir dural plaque in 3 pts); frx 1.8 RBE; 2 wks preop (S) or 6 wks (spine)	8 R0; 17 R1; 12 R2; 13 biopsy only; in- strumenta- tion in 16	LC: 81% 5 yrs; 74% 8 yrs; mets: 8%	84% 5 yrs; 65% 8 yrs	RFS: 64% 5 yrs; 52% 8 yrs	NG	Overall: NG; sacral frac: 1 grd 3	Overall: 16% 5 yrs; 19% 8 yrs; grd ≥3 10% 5 yrs; 13% 8 yrs; RT-induced sarcoma in 1; neurop: 2 grd 3; GU: 4% grd 3; 6% sacral frac (4% grd 2, 2% grd 3); GI: 2% grd 3; other: 4% grd 1
Holliday et al., 2015 ¹⁸ (IV)	13 chrd post- rsxn; 6 cndr post-rsxn; LOC: 6 mobile spine; 13 S	M: 47%; NG; 34.5 mos; NG		TD med 70 RBE; frx 2 RBE; ~7 wks; 14 prRT only; 5 prRT/phRT combo	NG	LC: 58% 2 yrs; LR: 63.2%; mets: NG	93.3% 2 yrs	RFS: 51.9% 2 yrs	NG	Overall: ≥84%; ≥16% grd ≥3; skin: 68% grd 1, 16% grd 2; esophagitis: 21% grd 1–2	NG
Kaboliza- deh et al., 2017 ^{19*} (IV)	40 unresec chrd; LOC: 9 C, 1 T, 3 L, 27 S	53% M; 67 yrs; 50 mos; 174 cm ³		TD med 77.4 RBE; frx 1.8–2 RBE; NG	NA	LC: 96.9% 3 yrs; 85.4% 5 yrs; mets: 11.7% 3 yrs; 20.2% 5 yrs	89.1% 3 yrs; 81.9% 5 yrs	DSS: 97.2% 3 yrs; 89.4% 5 yrs	Med max ↓ = 43.2%; med ↓ 20% 6 mos; 36% 1 yr; 55% 2 yrs; 64% 36–60 mos	Overall: NG; GI: 10–23%; mucosi- tis: 13% mos; 36% 1 yr; 55% 2 yrs; 64% 36–60 mos	Overall: NG; 25 sacral frac; neurop: 8%; GU: 5%; GI: 3%
Park et al., 2006 ^{20*} (IV)	27 chrd; LOC: 100% S	63% M; 58 yrs; 99.6 mos; NG		TD med 73 RBE; frx med 39 RBE; med 67 days	5 R0; 16 R1/2; 6 no op	LC: 71.7% 5 yrs; 57.5% 10 yrs; mets: 24% med 86 mos; LR: 41% LFU	82.5% 5 yrs; 62.5% 10 yrs	DFS: 60.5% 5 yrs; 48.6% 10 yrs	NG	Not separated from op complications	Not separated from op complications
Rotondo et al., 2015 ^{1*} (IV)	126 chrd; LOC: 16 T, 40 L, 71 S	62% M; 53.2 yrs; 47 mos; NG		TD med 72.4 RBE; frx 1.8–2 RBE; 11–25 days preop + 10–11 days postop; 7 pts w/ 10 Gy ⁹⁰ Y & 4 w/ 42 Gy ¹⁹² Ir intraop dural plaque	27% R0; 45% R1; 24% R2; 5% unknown	LC: 62% 5 yrs; 49% 10 yrs; mets: 23% 5 yrs; 37% 10 yrs	81% 5 yrs; 53% 10 yrs	NG	NG	Overall: 13% grd ≥3; wound infection: 8–13% grd ≥3; sacral frac: 5% grd ≥3; neurop: 3% grd ≥3; GI: 1% grd ≥3; 1 second- ary malignancy	Acute & late toxicities pooled

Ost = osteosarcoma.

* Massachusetts General Hospital.

TABLE 3. Series describing outcomes for patients treated with CIRT

Authors & Year (LOE)	Neuropathology	Pt Demogr: Sex; Med Age; Med FU; Med CTV	RT Regimen	Op Outcome	LC & Mets	OS	PFS, DFS, DSS, &/or RFS	Vol Resp	Toxicity	
									Acute	Late
Bostel et al., 2020 ^{21*} (IV)	68 chrd; LOC: 100% S	68% M; 61 yrs; 60 mos; 182 cm ³	TD med 66 RBE; 60 RBE in 16; 63 RBE in 2; 64 RBE in 14; 66 RBE in 14; frx 3–4 RBE; NG; 22 w/ phRT; 46 CIRT alone	14 R0/R1 rsxn; 26 R2 rsxn; 28 no op	LC: 90% 1 yr; 80% 2 yrs; 65% 3 yrs; 53% 5 yrs; mets: 9% 1 yr; 19% 2 yrs; 29% 3 yrs; 52% 5 yrs; LR: 46% med 25 mos	97% 1 yr; 97% 2 yrs; 86% 3 yrs; 74% 5 yrs	PFS 90% 1 yr; 80% 2 yrs; 65% 3 yrs; 53% 5 yrs	NG	NG	Overall: 59%; 21% grd ≥3; 49% sacral frac (16% w/ grd ≥3); neurop: 9%; 5% grd ≥3; GI: 3% (both grd 2); skin: 9% (all grd 1)
Demizu et al., 2021 ^{22††} (IV)	219 chrd w/o prior op; LOC: 100% S	69% M; 67 yrs; 56 mos; NG	TD 67.2 RBE in 143; 70.4 RBE in 75; 79.2 RBE in 1; frx 2.2–4.4 RBE; 4 days/wk × 4 wks	NA	LC: 72% 5 yrs; mets: >9%; LR: 18% & regional/distant in 27%	84% 5 yrs	PFS 48% 5 yrs	NG	Overall: 4% grd ≥3; skin: 8 grd 3–4	Overall: 6% grd ≥3; myositis: grd 3 in 3; pain: grd 3 in 2; skin: grd 2 in 2
Imai et al., 2004 ^{23†} (IV)	30 chrd; LOC: 100% S	80% M; 66 yrs; 30 mos; 556 cm ³	TD med 70.4 RBE; all pts had 16 frx; 4.4 RBE; 4 days/wk × 4 wks	0 R0; 2 R1; 3 R2; 2 unknown; 23 no op	LC: 96% 5 yrs; mets: 7% 1 yr; 23% LFU	52% 5 yrs	94% 5 yrs	NG	Overall: NG; skin: 10% grd ≥3	Overall: NG; skin: 13% grd ≥3; GI: 3% grd ≥3; neurop: 20% grd ≥3
Imai et al., 2010 ^{24†} (IV)	38 unresec chrd; 8 w/ prior op; LOC: 100% S	76% M; 66 yrs; 80 mos; 523 cm ³	TD 54.8 RBE in 1; 64.0 RBE in 1; 70.4 RBE in 29; 73.6 RBE in 7; all had 16 frx; 4 days/wk × 4 wks	3 R1 rsxn; 2 R2 rsxn; 3 unknown rsxn; 30 no op	LC: 95% 3 yrs; 89% 5 yrs; mets: 39% LFU; med time to mets 40 mos	86% 5 yrs; med 70 mos	PFS 76% 3 yrs; 54% 5 yrs	NG	Overall: ≥26%; ≥13% grd ≥3; skin: 7% grd 3; 4% grd 4; neurop: 10 (no grade)	Overall: ≥5%; ≥5% grd ≥3; skin: 4% grd 3; 1 sacral frac 9 mos post-RT; GI: 2% grd 1
Imai et al., 2011 ^{25†} (IV)	95 unresec chrd; 11 w/ prior op; LOC: 100% S	72% M; 66 yrs; 42 mos; 370 cm ³	TD 54.8 RBE in 1 pt; 64.0 RBE in 1 pt; 73.6 RBE in 7 pts; 86 RBE in 86 pts; all had 16 frx; 4 days/wk × 4 wks	NA	LC: 88% 5 yrs; mets: NG; LR: 6.3% med 35 mos	86% 5 yrs	NG	NG	Overall: NG; skin: 7% grd 3	Overall: NG; skin: 4% grd 3; 4% grd 4; GI: 2% grd 1
Imai et al., 2016 ^{26†} (IV)	188 unresec chrd; no prior radiation; no instrumentation; LOC: 100% S	68% M; 66 yrs; 62 mos; mean 345 cm ³	TD 64.0 RBE in 1 pt; 67.2 RBE in 106 pts; 70.4 RBE in 74 pts; 73.6 RBE in 7 pts; all pts had 16 frx; 4 days/wk × 4 wks	NA	LC: 77.2% 5 yrs; 52.0% 10 yrs; LR: 22%; mets: 32% 5 yrs; med time to mets 34 mos	81.1% 5 yrs; 66.8% 10 yrs; 10 yrs; postrecurrence: 52% 3 yrs, 52% 5 yrs	DFS: 50.3% 5 yrs, 31.3% 10 yrs	NG	NG	Overall: ≥89%; ≥3.2% grd ≥3; neurop: 11% grd 1, 7% grd 2, 3% grd 3; skin: 89% grd 1, 6% grd 2, 2% grd 3–4; GI: 2% grd 1

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TABLE 3. Series describing outcomes for patients treated with CIRT

Authors & Year (LOE)	Neuropathology	Pt Demogr: Sex; Med Age; Med FU; Med CTV	RT Regimen	Op Outcome	LC & Mets	OS	PFS, DFS, DSS, &lor RFS	Toxicity	
								Acute	Late
Matsumoto et al., 2013 ^{28†} (IV)	48 unresec sarcoma; 13 ost; 13 cndr; 9 chrd; 2 EwS; 11 other; LOC: 10 C, 22 T, 16 L	51% M; 54 yrs; 25 mos; 190 cm ³	TD med 64.0 RBE; all pts had 16 frx; 4 days/wk × 4 wks	NA	LC: 79% 3 yrs; 79% 5 yrs; mets: 36% LFU; LR: 17% LFU	59% 3 yrs; 52% 5 yrs; med 44 mos	PFS 48% 3 yrs; 44% 5 yrs	Overall: NG; skin: 2% grd ≥3	Overall: NG; skin: 4% grd ≥3; myelitis: 2% grd ≥3; 15% vertebral frac med 14 mos
Nishida et al., 2011 ^{29†} (IV)	7 chrd; LOC: 100% S	71% M; 67 yrs; 49 mos; NG	TD med 70.4 RBE; frx 4.4–4.6 RBE; 4 days/wk × 4 wks	NA	LC: 100% 5 yrs; mets: 14% LFU	NG	DSS: 53.3% 5 yrs	Overall: NG; 14% wound infection	Overall: NG; neurop: 0%; GU: 0%
Preda et al., 2018 ³⁰ (IV)	39 unresec chrd; LOC: 100% S	62% M; mean 63 yrs; mean 18 mos; mean 298 cm ³	TD 70.4 RBE; frx 16 RBE	NA	LC: 91% 6 mos; 88% LFU; mets: NG	NG	NG	By volume change: 54% ↓, 36% ↔, 10% ↑ LFU	NG
Schulz-Ekner et al., 2004 ^{31*} (IV)	16 chrd; 1 cndr; LOC: 9 C, 8 S	NG; NG; NG; NG	TD 60 RBE (chrd); 68.4 RBE (cndr); frx 3 RBE/day × 7 days/wk; 3–4 wks	Surgery in all; margins unknown; 1 w/ instrumentation	LC: 88% med 19 mos; mets: 12% med 13 mos	NG	NG	Overall: 18% grd ≥3; mucositis: 18% grd ≥3 (all C)	Overall: 0% grd ≥3; GI: 0% neurop: 0%
Serizawa et al., 2009 ^{32†} (IV)	34 unresec chrd; no prior radiation; 8 prior ops; LOC: 100% S	75% M; 66 yrs; NG; 510 cm ³	TD NG; all pts had 16 frx; 4 days/wk × 4 wks	NA	LC: 93.8% 5 yrs; mets: NG	85.4% 5 yrs	NG	Med 64% ↓ LFU; med 56% ↓ 3 yrs; >10% ↑ in 13 at end of RT → 12/13 ↓ below original tumor size	NG
Uhl et al., 2015 ^{34*} (IV)	56 chrd; LOC: 100% S	64% M; 60 yrs; 25 mos; 522 cm ³	TD med 66 RBE (CIRT 63 RBE; CIRT/IMRT 74 RBE); frx 2 Gy (IMRT) or 3 RBE (CIRT); 5–6 frx/wk × 5–6 wks; 33 CIRT only; 23 CIRT-phRT combo	23% RO/ R1: 34% R2: 43% biopsy only	LC: 76% 2 yrs; 53% 3 yrs; mets: 2% LFU	100% LFU	PFS ~95% 1 yr; ~70% 2 yrs; ~55% 3 yrs	Overall: ≥84% in 1st 24 mos; 13% grd ≥3; pain: 84% in 1st 24 mos; GI: 38%; 13% grd ≥3; GU: 30%; neurop: 39–48% in 1st 24 mos; skin: 34% in 1st 24 mos	Overall: 76% beyond 24 mos; 14% grd ≥3; pain: 76%; GI: 31%; 14% grd ≥3; GU: 31% neurop: 14–24%; skin: 10%

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TABLE 3. Series describing outcomes for patients treated with CIRT

Authors & Year (LOE)	Neuropathology	Pt Demogr: Sex; Med Age; Med FU; Med CTV	RT Regimen	Op Outcome	LC & Mets	OS	PFS, DFS, DSS, &/or RFS	Toxicity	
								Vol Resp	Late
Wu et al., 2019 ³⁵ (IV)	16 chrd; 5 cndr; LOC: 1 T, 19 S; 1 pelvis	48% M; 64 yrs; 22 mos; 513 cm ³	TD 60 RBE; frx NG; time NG	NA	LC: 94% 1 yr; 85% 2 yrs; mets: 19% LFU	100% 2 yrs	PFS 88% 1 yr; 80% 2 yrs	NG	Overall: 48%; 0% grd ≥3; skin: 14% grd 1; myelosup- pression: 33% grd 1
Zhang et al., 2004 ^{36†} (IV)	12 chrd; LOC: 1 T/L; 11 S	64% M; 65 yrs; NG; NG	TD med 70.4 RBE; frx NG; time NG	NG	LC: 91% 1 yr; mets: NG	NG	NG	NG	NG

EwS = Ewing sarcoma; IMRT = intensity-modulated radiation therapy; ↔ and → = change over time.
* Heidelberg Ion Beam Therapy Center.
† Japan Carbon-Ion Radiation Oncology Study Group.
‡ National Institute of Radiological Sciences, Chiba, Japan.
§ Hyogo Ion Beam Medical Center.

TABLE 4. Series describing outcomes for patients treated with a combination of proton and carbon ion radiotherapy or other hadron/charged-particle radiotherapy regimens

Authors & Year (LOE)	Neuropathology	Pt Demogr: Sex; Med Age; Med FU; Med CTV	RT Regimen	Op Outcome	LC & Mets	OS	PFS, DFS, DSS, &/or RFS	Toxicity	
								Acute	Late
Mima et al., 2014 ³⁷ (III)	23 chrd; LOC: 100% S	65% M; 72 yrs; 38 mos; 264 cm ³	TD med 70.4 RBE; frx 2.2 RBE in 9; 4.4 frx in 14; 16 CIRT; 7 prRT	17 underwent spacer place- ment	LC: 94% 3 yrs; mets: 26% LFU; LR: 17% med 45.5 mos	83% 3 yrs	PFS 68% 3 yrs	Overall: NG; skin: 35% grd ≥3	Overall: NG; skin: 22% grd ≥3; myositis: 9% grd ≥3; neurop: 17% grd ≥3
Schoen- thaler et al., 1993 ³⁸ (IV)	14 chrd; LOC: 100% S	86% M; 61 yrs; 5 yrs; 497 cm ³	TD med 75.7 RBE; frx 2–2.3 RBE; 4 days/wk x med 71 days; 5 He RT only; 5 He + phRT; 4 He + Ne RT	4 R0/R1; 8 R2; 2 biopsy only	LC: 55% 5 yrs; 23% 10 yrs; mets: 14% LFU; LR: 50% med 25 mos	85% 5 yrs; 22% 10 yrs	NG	NG	Overall: NG; chronic wound healing issues in 5; second- ary malignancy in 1
Tsugawa et al., 2020 ^{39*} (IV)	21 chrd; LOC: 100% S	48% M; 64 yrs; 50 mos; mean 497 cm ³	TD 70.4 RBE in 19 pts; 79.2 RBE in 1 pt; 80.0 RBE in 1 pt; frx 2.2–4.4 RBE; 4 days x 4–8 wks; 6 CIRT; 15 prRT	Gore-Tex spac- er implanted btwn tumor & rectum	LC: 95.2% 4 yrs; mets: 29% LFU; LR: 29% LFU	100% 5 yrs; med 54.8 mos	4-yr PFS med 60.9 mos 54%	Overall: 19% grd ≥3; skin: 19% grd ≥3	Overall: 5% grd ≥3; skin: 1 grd 4

* Hyogo Ion Beam Medical Center.

TABLE 5. Dose safety limits for radiation planning in proton and charged-particle therapy

Location	Institution					
	HbIBTC	HylBMC	Institut Curie	MGH	PSI	Shanghai Group
Nervous system						
Optic nerves	≤54 Gy	—	—	—	≤60 Gy	—
Brainstem	≤60 Gy (surface); ≤50 Gy (center)	—	—	—	<63 Gy	—
Spinal cord	≤45 Gy	≤48.0 Gy	—	—	—	≤40 Gy
Surface	—	—	≤54 Gy; ≤45 Gy (posterior edge)	≤63 Gy	≤63 Gy	—
Core	—	—	≤48 Gy	≤54 Gy	≤54 Gy	—
Cauda equina	—	—	≤57 Gy (male); ≤67 Gy (female)	—	≤64 Gy	—
Skin	—	≤90% receiving ≥63.0 Gy	≤64 Gy; ≤60 Gy (gluteal fold)	≤66 Gy	—	—
Thoracic viscera						
Heart	—	—	—	—	≤2/3 of organ (≤30 Gy); ≤1/3 of organ (≤40 Gy)	≤40 Gy
Lung	—	—	—	—	≤2/3 of organ (≤30 Gy); ≤1/3 of organ (≤40 Gy)	≤40 Gy
Abdominal viscera						
Kidney	—	—	—	—	≤20 Gy	—
Small intestine	≤50 Gy	≤52.0 Gy	—	—	—	—
Large intestine	—	≤57.0 Gy	≤60 Gy	—	—	—
Rectum	≤70 Gy; ≤30 Gy (anterior third)	≤17.0% pts w/ ≥65.0 Gy	≤60 Gy	—	—	≤66 Gy
Genitalia						
Penis	—	—	≤58 Gy	—	—	—
Testis	—	—	≤2 Gy	—	—	—
Ovaries	—	—	≤5 Gy	—	—	—

HbIBTC = Heidelberg Ion Beam Therapy Center; HylBMC = Hyogo Ion Beam Medical Center; PSI = Paul Scherrer Institute.

or OS. Investigations comparing combined proton/photon therapy to photon-only therapy have suggested that the addition of charged particles may improve LC.¹⁷ Importantly, LC and OS appear similar between patients treated with definitive charged-particle (proton or hadron-based) radiotherapy and historical multicenter surgical cohorts of chordoma (LC approximately 75%–80% and OS approximately 70%–85% at 5 years following R0 resection)⁵ and other sarcomas.^{4,50}

Timing of Radiation

Technical concerns related to the use of adjuvant radiotherapy include radiation planning and monitoring of tumor response. The first consideration is whether radiation should be given presurgery, postsurgery, or both. Based on the MGH experience,¹ LC appears superior in surgically treated patients who receive pre- and postoperative radiation versus postoperative radiation alone. Notably, this finding was independent of the total radiation dose administered. However, many investigators express concerns about the negative impact of neoadjuvant radiotherapy on surgical wound healing. To this end, a recent survey of spine oncology specialists found that the minority routinely recommend preoperative radiotherapy for either primary or recurrent chordoma.⁵¹

In light of the above findings regarding the more common preference for postoperative treatment, the prevailing inquiry remains in whether the timing of postoperative radiotherapy matters. In their series from MD Anderson, Holliday et al.¹⁸ found that better LC was achieved with early versus late adjuvant proton radiotherapy (relapse-free survival [RFS] 75% vs 45% at 2 years). In line with these results, the above survey found that most experts recommend radiotherapy within 8 weeks of surgery.⁵¹

Radiation Planning

Dosing schemas for adjuvant charged-particle therapy have been described by several centers, including the Paul Scherrer Institute,^{42,43} the Hyogo Ion Beam Medical Center in Japan,^{11,39} and the MGH.¹⁹ These schemas are based on the desire to minimize irradiation of the spinal cord, nerve roots, and adjacent healthy tissues (Table 5). In general, most groups recommend the following limits: brainstem (≤ 63 Gy) and spinal cord (surface ≤ 63 and core ≤ 48–54 Gy^{11,12,15–17,21,31,37}). Some groups³⁵ are even more conservative and recommend that doses to healthy tissues not exceed 40 Gy. These recommendations are consistent with the evidence as recently reviewed by Kirkpatrick et al.⁵² The authors found a dose-response relationship between spinal cord irradiation and injury, with doses of 54 Gy cor-

responding to a < 1% risk of injury compared with a nearly 10% risk for doses of 61 Gy.

Skin doses are also minimized to reduce the rates of radiation-induced dermatitis, though this complication occurs in up to 100% of patients in the acute setting.¹² These skin toxicities are likely of increased importance in postoperative patients, as irradiation is a known risk factor for wound infection in spine oncology patients.⁵³ However, given that some recent evidence suggests that radiation may more strongly dictate LC than surgical margins,⁹ many spinal oncologists recommend its use.⁵¹ As alluded to by the aforementioned survey, there is no high-quality evidence on what radiotherapy time frame provides the best LC while minimizing results. Yet, based on a recent review of level III/IV data in the spinal metastasis population, 2 weeks postoperatively may be an ideal time point,⁵³ in line with the results of the Dea et al. survey.⁵¹ Additionally, using smaller fractions may help reduce skin toxicities, a finding that the Hyogo group³⁹ cited as a primary reason for shifting from fractions of 4.4 to 2.2 RBE. Nevertheless, some groups continue with 4.4–4.6 RBE fractions because they feel it may offer superior LC.²⁶

The guidelines for isodose line contouring are beyond the scope of this study, as is the best timing of radiographic follow-up. However, the included studies suggested leaving a minimum margin around the spinal cord of 3–5 mm²¹ or, in most cases, 5–10 mm.^{11,35,39,42,43} Experts at the MGH have recommended even larger margins, 1–1.5 cm around the spinal cord and 3.5 cm along neurovascular bundles.¹⁹ These large margins may negatively impact the ability to treat the entire tumor penumbra, however, and so the surgeon should discuss with the patient the relative benefits of greater tumor bed coverage relative to the increased risk of postradiation neuropathy. The group from the Chiba Heavy Ion Medical Accelerator Center report that the risk of neural injury may only be significant for high doses, as evidenced by their finding that postradiation sciatic nerve injury was only a significant risk for those receiving > 70 Gy to > 10 cm of the sciatic nerve.

Theoretical Advantages of Charged-Particle Therapy Over Photon Radiotherapy

The primary theoretical advantage of using charged particles is the ability to deliver high-dose radiation to target tissues while minimizing doses to normal tissues. This property derives from the higher mass of the charged particles and is described by the Bragg peak displayed by charged-particle therapies (Fig. 2).⁵⁴ Some clinical studies have supported the superiority of charged-particle therapies. In a series of 41 patients with sacral chordoma undergoing definitive or adjuvant radiotherapy, Beddok et al.¹² showed that those treated with combined proton/photon tomotherapy had 75% lower doses to the bladder than those treated with photons alone.

Other evidence, however, has failed to demonstrate the superiority of charged particles. In a multicenter study by the Sacral Tumor Society working group,⁵⁵ the use of proton versus photon radiotherapy was not associated with differences in OS, DFS, DSS, or rates of metastasis. Yet patients treated with protons versus photons suffered higher rates of wound complication and stress fracture, in-

FIG. 2. Plot illustrating dose delivery as a function of depth of tissue penetrated for three radiation modalities. Charged-particle therapies, such as protons and carbon ions, demonstrate a Bragg peak, where there is a steep rise in the delivered dose at the beam's focus point and a commensurately steep decline in dose delivered to those tissues past the tissue target. This behavior theoretically enables charged particles to deliver high doses to target tissue with relatively little radiation delivered to the surrounding healthy tissues. The overall tissue penetration of charged particles is determined by their initial energy (in megaelectron volts, MeV), the material/tissue through which they are passing, and the type of particles used (e.g., carbon ions).

dependent of the radiotherapy dose, tumor size, and use of high versus low sacral resection. Snider et al.⁴² similarly found no difference in LC, PFS, or OS between patients treated with proton radiotherapy and those treated with combined proton/focused photon radiotherapy. Only 12% of the patients received combination therapy, however. Beddok et al.¹² likewise saw no difference in OS between tomotherapy-treated and combined proton/tomotherapy-treated patients. Locoregional recurrence appeared to be lower in the combined proton/photon treatment group, but the difference was not significant. Indelicato et al.⁴⁰ similarly found a nonsignificant trend toward better LC in the proton/photon group. Beddok et al.¹² found that proctitis and acute cauda equina syndrome were more common in the tomotherapy group, but dermatitis was more common in the proton/tomotherapy combination group, as was posttreatment pain (acute phase).

In light of these findings, it is unclear that charged particles are superior to modern photon-based modalities. To this end, Jin et al.⁵⁶ recently reported LC rates of 96.3% and 89.9% at 3 and 5 years, respectively, in patients with chordoma of the mobile spine or sacrum treated with 24-Gy single-fraction radiosurgery delivered as either adjuvant or definitive treatment. These rates are comparable or superior to the rates reported here and in historical cohorts, suggesting that charged particles may not be superior to modern focused radiation modalities. Additional studies directly comparing the outcomes of these two modalities are necessary.

Instrumentation and Radiotherapy

Many patients treated for primary spinal or sacral sar-

comas require instrumentation to correct iatrogenic instability, which is most common in patients treated with high sacrectomy or en bloc spondylectomy. However, in reviewing the series here, we note that postradiation sacral and vertebral fracture occur in up to 49% of patients, with as many as 16% having fractures severe enough to require intervention.^{11,13,19,21,28,42} This may be due to the trabecular bone loss that is linked to the use of high-dose radiation.⁵⁷ Consequently, many additional patients may require instrumentation.

Postoperative radiotherapy and follow-up are complicated by placement of metallic instrumentation, which may generate image artifacts that decrease the accuracy with which isodose lines can be drawn and cause local radiation scattering that often forces radiation oncologists to use lower prescribed doses.⁴⁰ Consistent with these findings, data from the Paul Scherrer Institute^{41–43} indicate that LC, PFS, and OS were all much poorer for patients receiving instrumentation. According to an analysis by Snider et al.,⁴² the influence of instrumentation remained significant for LC and PFS on multivariable analysis, and in a study by Murray et al.⁴¹ the influence of instrumentation remained significant for OS and LC; it was of borderline significance for PFS. At the MGH, DeLaney et al.¹⁶ similarly found a more than 2.5-fold higher rate of local recurrence in spine sarcoma patients with instrumentation. However, the difference did not meet the threshold for significance, perhaps due to the relatively small sample size. Of note, Staab et al.⁴³ found that the negative effects of instrumentation on radiotherapy were greatest for those in most need of adjuvant radiotherapy; the decrements in LC were greatest for patients with gross residual disease at the time of radiotherapy.

These difficulties with radiotherapy planning along with the difficulty that instrumentation creates in executing effective radiographic follow-up have led some centers to consider the use of carbon fiber–reinforced polyetheretherketone (CFR-PEEK) instrumentation.^{58,59} CFR-PEEK rods, unlike titanium rods, are radiolucent and so create minimal artifact on the CT scans employed for radiation planning.^{60,61} Additionally, CFR-PEEK rods better approximate the elastic modulus of cortical bone.⁶² However, they have been found in cadaveric models to produce less-rigid constructs.⁶³ No differences in hardware complications have been noted in early clinical series;⁵⁹ however, follow-up is extremely limited at present and further investigation is merited.

Study Limitations

The present study has inherent limitations, several of which have potential implications for its interpretation. The most notable limitation is that all included studies are level III or IV data. No studies directly compared follow-up between photon- and charged-particle–treated patients. Additionally, the majority of reports are based on limited experiences reported by a half dozen centers, so it is unclear whether the present results are generalizable to all patients with chordomas and sarcomas of the spine and sacrum. To this end, a quantitative meta-analysis could not be performed because of the significant overlap in study samples and the limited study quality. A further limita-

tion was the overlap in the discussed pathologies, as the outcomes for chordomas, chondrosarcomas, and other sarcomas were grouped in most series, whereas previous work has indicated that prognoses differ for these pathologies.^{4,5,50,64,65} Similarly, for chondrosarcomas⁶⁶ and osteosarcomas,⁶⁷ tumor grade and subtype have a significant impact on both OS and DSS and the radiation responsiveness of the lesion. Additionally, research published in the past year has suggested that tumor grade has a significant impact on radiation responsiveness in chondrosarcoma.⁶⁸ To better appreciate the relative influence of charged-particle therapies on LC and OS, it will be necessary to incorporate these factors. Last, from a practical standpoint, proton treatment is offered in relatively few centers in the US, which may limit the feasibility of this treatment for patients from some geographic regions. Carbon ion treatment is even rarer, and no centers in the US currently offer this treatment. Consequently, it is unclear as to whether the present results can be incorporated into treatment protocols for all centers.

Conclusions

This review of the literature demonstrated that the current data evidence for proton and carbon ion radiotherapy for chordoma and sarcomas of the mobile spine and sacrum is quite limited and derived from a small number of centers. Given the quality of data, this systematic review does not demonstrate the superiority of one specific charged-particle approach in the definitive or adjuvant setting. In the adjuvant setting, charged-particle therapy likely offers similar LC to modern photon therapy regimens. Likewise, comparing reports of definitive charged-particle therapy for nonsurgical patients to historical surgical cohorts suggests that PFS may be similar for those treated with proton and carbon ion therapy. Additional investigations based on experiences from a larger number of centers are required.

Appendix

Search Queries for the PubMed, Embase, OVID Medline, and Web of Science Databases

PubMed Query: (“chordoma” OR “chondrosarcoma” OR “osteosarcoma” OR “osteogenic sarcoma” OR “Ewing sarcoma” OR “Ewing’s sarcoma” OR “Ewings sarcoma” OR “primary bone tumor” OR “primary vertebral tumor” OR “primary spine tumor”) AND (spine OR spinal OR vertebral OR vertebra OR vertebrae OR sacrum OR sacral) AND (“carbon ion” OR “hadron” OR “proton” OR “proton therapy” OR “carbon ion therapy” OR “hadron therapy” OR “charged ion” OR “charged ion therapy”)

Embase Query: (‘chordoma’ OR ‘chondrosarcoma’ OR ‘osteosarcoma’ OR ‘osteogenic sarcoma’ OR ‘ewing sarcoma’ OR ‘ewings sarcoma’ OR ‘primary bone tumor’ OR ‘primary vertebral tumor’ OR ‘primary spine tumor’) AND (spine OR spinal OR vertebral OR vertebra OR vertebrae OR sacrum OR sacral) AND (‘carbon ion’ OR ‘hadron’ OR ‘proton’ OR ‘proton therapy’ OR ‘carbon ion therapy’ OR ‘hadron therapy’ OR ‘charged ion’ OR ‘charged ion therapy’)

OVID Medline Query: ((“chordoma” or “chondrosarcoma” or “osteosarcoma” or “osteogenic sarcoma” or “Ewing sarcoma” or “Ewing’s sarcoma” or “Ewings sarcoma” or “primary bone tumor” or “primary vertebral tumor” or “primary spine tumor”) and (spine or spinal or vertebral or vertebra or vertebrae or

sacrum or sacral) and (“carbon ion” or “hadron” or “proton” or “proton therapy” or “carbon ion therapy” or “hadron therapy” or “charged ion” or “charged ion therapy”)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

Web of Science Query: ALL=(“chordoma” OR “chondrosarcoma” OR “osteosarcoma” OR “osteogenic sarcoma” OR “Ewing sarcoma” OR “Ewing’s sarcoma” OR “Ewing’s sarcoma” OR “primary bone tumor” OR “primary vertebral tumor” OR “primary spine tumor”) AND ALL=(spine OR spinal OR vertebral OR vertebra OR vertebrae OR sacrum OR sacral) AND ALL=(“carbon ion” OR “hadron” OR “proton” OR “proton therapy” OR “carbon ion therapy” OR “hadron therapy” OR “charged ion” OR “charged ion therapy”)

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