Management of Locally Recurrent Chordoma of the Mobile Spine and Sacrum

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Abstract

Study Design—Systematic review.

Objective—To determine evidence-based guidelines for the management of locally recurrent spinal chordoma.

Summary of Background Data—Chordoma of the spine is a low-grade malignant tumor with a strong propensity for local recurrence. Salvage therapy is challenging due to its relentless nature

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and refractoriness to adjuvant therapies. There are currently no guidelines regarding the best management of recurrent chordoma.

Methods—We combined the results of a systematic review with expert opinion to address the following research questions: (1) For locally recurrent chordoma of the spine without systemic disease, if surgery is planned, should *en bloc* resection be attempted if technically feasible with acceptable morbidity? (2) For locally recurrent chordoma without systemic disease, in which wide *en bloc* excision is not possible, what is the treatment of choice? (2) Should adjuvant or neoadjuvant radiation therapy be used in the treatment of locally recurrent chordoma?

Results—A total of nine surgical and seven radiation therapy articles met study criteria. Evidence quality was low or very low. Recurrent disease is associated with predominantly poor outcome, regardless of treatment modality. As for primary chor-doma, resection with wide margins appears to confer an advantage with respect to local control, although this effect is attenuated in the setting of relapse. Postoperative radiation therapy likely reduces the rate of further relapse.

Conclusion—(1) For locally recurrent chordoma of the spine without systemic disease, when surgery is planned, wide *en bloc* resection should be performed if technically feasible with acceptable morbidity. Strong recommendation, Low Quality of Evidence. (2) For locally recurrent chordoma without systemic disease, in which wide *en bloc* excision is not possible, partial resection is the treatment of choice. Weak recommendation, Very Low Quality of Evidence. (3) For the treatment of locally recurrent chordoma, high-dose conformal radiation therapy should be administered postoperatively to reduce the risk of further recurrence, and may be considered as a primary therapy. Strong recommendation, Very Low Quality of Evidence.

Keywords

adjuvant; chordoma; *en bloc* resection; locally recurrent; morbidity; neoadjuvant; primary tumor; radiation therapy; recurrence; relapse; spine; surgery; systematic review

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Chordoma is a rare low-grade malignant neoplasm of the spine. The reported incidence of chordoma is 0.08 per 100,000 individuals.[1] Chordoma is most commonly found in the sacrococcygeal region followed by the skull base then the mobile spine.[2] They account for approximately 4% of primary malignant bone tumors[2] and 40% of all primary sacral tumors.[1]

Using the GRADE system, Boriani *et al*[3] combined the results of a systematic review, a multicenter cohort study and the expert opinion of the Spine Oncology Study Group to arrive at treatment recommendations for primary chordoma of the spine. They concluded that *en bloc* resection with wide or marginal margins results in decreased local recurrence (LR), longer disease-free survival, and less disease-related death. This constituted a strong recommendation based on moderate quality evidence. Conversely, they reached a strong recommendation (very low-quality evidence) against radiation therapy (RT) for the primary treatment of chordoma. Finally, they made a weak recommendation (low-quality evidence) for radiation of at least 60 to 65 Gy equivalents when incomplete resection was performed. A subsequent global consensus position paper recommended a dose of 74 GyE in the setting of macroscopic residual disease.[4] Taken together, these results support wide *en bloc*

resection as the optimal treatment of primary chordoma with adjuvant RT reserved for inadequate margins or planned incomplete resection.

Principles of surgical management for osseous tumors of the spine arose as an extension of the Enneking system of staging of appendicular tumors.[5] The Weinstein-Boriani-Biagini (WBB) staging system[6] adapts the Enneking principles of *en bloc*, wide marginal and radical resection to the unique challenges of spinal anatomy. Specifically, within the thecal sac, the spinal cord and cauda equina are encompassed by osseous structures and, with rare exceptions, cannot be resected to achieve adequate margins. In addition, longitudinal muscle compartments spanning the length of the spinal column border the outer margin of the vertebrae and precludes radical tumor excision when the tumor has invaded these compartments. As a result of these idiosyncrasies of spinal anatomy, achieving the goal of *en bloc* resection is difficult even at initial surgery.

Wide or marginal margin resection rates for sacral chordoma range from 35% to 75%[7–11] and are only 21% in the mobile spine.[12] The challenges of achieving such margins are compounded for locally recurrent or residual disease in which tissue planes are disrupted, tumor seeding may have occurred, and anatomy can be distorted. Inevitably, this leads to higher rates of LR when further surgical resection is attempted.

Although LR is common following surgical treatment of spinal chordoma—with reports in the literature ranging from 19% to 54%[3,8–17]—there is a paucity of literature on its management. Chordoma of the spine is a rare disease for which most of the literature is of low quality and comprises small, retrospective case series. The literature on management of locally recurrent chordoma (LRC) is even more sparse. Interpretation of the limited data available is compromised by the fact that most studies fail to differentiate between primary and recurrent disease when reporting treatment outcomes. Furthermore, no studies exist that directly compare treatment modalities for LRC.

To address the knowledge gap regarding management of LRC we employed the Grading of Recommendations Development and Evaluation (GRADE) methodology to combine the results of a systematic review with expert opinion to address the following research questions:

1. For LRC of the spine without systemic disease, if surgery is planned, should *en bloc* resection be attempted if technically feasible with acceptable morbidity?

2. For LRC without systemic disease, in which wide *en bloc* excision is not possible, what is the treatment of choice?

3. Should adjuvant or neoadjuvant RT be used in the treatment of locally recurrent chordoma?

Methods

We conducted a systematic review of the English language literature by searching PubMed, Medline, and EBMR databases from 1950 to March 2016. Search terms included:

1. "Chordoma"

2. "Spine" or "Spinal"

3. "Recurrent" or "recurrence" or "relapse"

These terms were combined and articles were included if they reported on five or more cases of LRC of the mobile spine or sacrum treated with surgery and/or radiotherapy. Exclusion criteria were the following: case reports, studies with inconsistent or inadequate data collection, studies that did not report on the outcomes of LRC cases specifically, and review articles.

The GRADE system was used to combine the results of the systematic review with expert opinion to reach recommendations (Box 1).

Results

Systematic Review

The search yielded a total of 240 articles. The abstracts of the 240 articles were reviewed and those that met criteria (N=9 for surgery and N=7 for RT) were reviewed in detail. Evidence quality was determined according to previously reported guidelines.[19]

There were no controlled studies nor true cohort studies identified in the literature. There were 87 case reports that were excluded along with 20 studies that reported on fewer than five cases of LRC. Thirty-one articles involved treatments other than surgery or radiotherapy. The remainder of exclusions resulted from studies failing to adequately discriminate LRC cases in their analysis or not reporting on this subgroup's outcome separately.

Surgical Literature

Nine surgical studies were identified in our systematic review of LRC and are presented in Supplementary Table 1, http://links.lww.com/BRS/B193. All studies were retrospective case series and constituted low or very low quality of evidence.

Stacchiotti *et al*[10] reported on 130 surgical cases of chordoma, of which, 82 experienced local relapse. It should be noted that 31 of the original cohort of 130 had been previously operated on and were being treated at the authors' institution for their first local relapse. Therefore, an unspecified number of the 82 LRCs had been operated on twice. The 5- and 10-year overall survival (OS) rates were 78% and 54%, respectively, for the initial cohort as compared to only 50% and 26% after first relapse. The 5- and 10-year local relapse–free survival (LRFS) were, however, similar after surgery for the primary tumor (52% and 33%) and at first relapse (47% and 31%). For the main cohort of 130 patients, wide marginal resection was associated with improved 5- and 10-year LRFS (75% and 56% vs. 50% and 29%; *P*<0.001) as compared to marginal or intralesional margins. Conversely, for the 79 of 82 patients who had a LR and received second surgery, the type of resection (macro-scopically complete *vs.* incomplete) did not affect the likelihood of second local relapse or OS (*P*=0.41).

Xie *et al*[20] described the outcome of 30 patients with LRC from an initial group of 54. Survival was 82% at 5 years and 57% at 10 years for the overall group and 56% and 19%, respectively, after first relapse. Of the 30 patients (56%) who developed LR, 9 underwent complete resection of their lesion, 7 had incomplete resection, and 12 were treated palliatively. Twenty recurred in the sacrum, four of which developed lung metastases in addition. The remaining 10 recurred in the gluteus maximus or ischiorectal fossa. For those that had their LR completely resected, eight were alive and free of disease at last follow-up (10–65 mo after surgery); one was dead from second relapse. Six of the seven patients who had an incomplete resection were dead at last follow-up. Estimated 5- and 10-year OS for the incompletely resected LRs were 36% and 0%, respectively.

Bergh *et al*[21] reported on 10 LRC cases from a series of 39 patients with chordoma of the sacrum (n=30) or mobile spine (n = 9). These patients had all undergone intralesional resection before referral to the authors' center. Final margins after index surgery at the authors' center were wide in five cases, marginal in two, and intralesional in three. Two of five patients with wide margins experienced a second relapse as compared to all (5) patients with marginal or intralesional margins. All patients in whom wide margins were achieved were alive and disease-free at last follow-up. Of the five with marginal/intralesional margins, three died of disease, one died of other causes, and one had no evidence of disease at last follow-up.

Seventeen of 39 patients (44%) developed LR 1.5 to 12.5 years after primary surgery at the authors' institution. LR was associated with increased risk of metastasis and tumor-related death.

Rotondo *et al*[22] reviewed 126 cases of chordoma of the mobile spine and sacrum of which 32 comprised LR disease. For all patients, the 5-year rate of local control (LC) was higher after radical *en bloc* excision (72%) than that after intralesional resection (55%) (P=0.016). The authors did not conduct a subgroup analysis on the effect of surgical margins on the patients with LR specifically. Five-year OS in patients presenting with primary and recurrent disease was 82% and 78%, respectively (P=0.34).

A retrospective case series from M.D. Anderson included 27 patients with sacral chordoma that underwent a total of 67 surgical procedures.[14] Twenty-eight of these were wide *en bloc* excisions and 39 were subtotal (marginal or intra-lesional). Twelve patients had one operation, nine had two procedures, and six underwent more than two. Analysis by procedure demonstrated LR after 47 of 67 operations. LRFS was longer after radical resection (2.3 yr) than subtotal excision (8 mo) (P<0.0001). Adjuvant RT prolonged LRFS for patients who had undergone subtotal resection (2.1 yr vs. 8 mo) with an relative risk ratio of 5.1 (P< 0.02). Although the authors did not report the results of LR disease separately, the above analysis included a majority (40/67; 60%) of recurrent disease.

Boriani *et al*[12] reported their 50-year experience treating chordoma of the mobile spine. Their series of 48 patients included 13 patients who relapsed following intralesional excision at an outside institution and 5 patients who had a laminectomy and open biopsy resulting in contamination of the epidural space. The rate of LR was considerably lower in patients who

had not received previous treatment (16/30; 53%) than in those who had (16/18; 89%). For six cases of LRC that underwent *en bloc* excision with wide or marginal margins, three were alive with no evidence of disease and three were alive with disease. The outcome for 12 cases that underwent intralesional excision with or without RT was inferior: 8 were dead of disease and 4 alive with disease.

Eight recurrent upper cervical chordomas were reported on by Wang *et al*.[23] Five of these had been operated on previously, whereas one had received RT as their primary treatment. All eight tumors underwent intralesional or marginal resection; macroscopically complete resection was achieved in six. Both patients who underwent subtotal resection experienced a second relapse and died of their disease. Of the six patients who had complete resection, one was alive with no evidence of disease and three were dead of disease.

In a series of 42 patients with sacral chordoma,[9] 12 had a resection at an outside institution and were sent to the authors' institution for management of recurrence. Prior resection was associated with a higher rate of subsequent LR (*P*<0.0001). Six of the 12 LR cases underwent wide *en bloc* resection of which, 4 developed LR. The outcome of the remaining six patients with LR was not reported separately. For the overall cohort of 42 patients, LR and survival were superior after wide as compared with intralesional resection. Ruggieri *et al*[8] similarly reported on the outcome of nine patients who underwent intralesional resection of sacral chordoma before referral to their center (overall cohort included 56 patients). Of these nine patients, seven had wide (n=5) or wide-contaminated margins (n=2), one was marginal, and one intralesional. The LR rate was 78% amongst the nine patients with previous intralesional resection compared with 32% in patients who received primary resectionat the authors' center. Ten-year survival was inferior in the relapsed cases (57%) than the primary cases (80%).

Radiation Therapy Literature

Seven RT studies were identified in our systematic review and are presented in Supplementary Table 2, http://link-s.lww.com/BRS/B193. All but one of the studies (DeLaney *et al*; prospective cohort) were retrospective case series and constituted low or very low quality of evidence.[24]

McDonald *et al*[25] investigated the outcome of treating recurrent chordoma with proton therapy. All 16 patients in this series had received at least 1 prior course of RT to the primary tumor site and all but one had at least 1 surgical resection before reirradiation. Half of the tumors were clival and the remaining eight originated from the mobile spine or sacrum. Two-year LC and OS were 85% and 80%, respectively; disease-specific survival was 88% at 2 years.

Combining spine chordomas, chondrosarcomas, and other sarcomas, DeLaney *et al*[24] identified 14 LRC out of a total of 50 patients. Chordomas comprised 29 of the total cases including 6 of the patients with local relapse. Patients received a combination of photons, intensity-modulated radiation therapy (IMRT), and 3D conformal protons. The majority received both pre- and postoperative radiation. Relapse occurred in 50% of all patients presenting with LR disease, and 11% of those with primary tumors. Five-year LC was 50%

after treatment of LR as compared with 94% for primary disease. For LRC specifically, the 5-year LC rate was 50%.

Uhl *et al*[26] reported the outcome of 56 patients with sacrococcygeal chordoma treated with either carbon ion or combined IMRT and carbon ion boost radiation. This cohort included 15 patients who had undergone resection and subsequently developed LR. The 2-year LC was superior for primary (85%) than for LR tumors (47%). Similarly, Park *et al*[27] described far superior 5-year LC and OS (90.9% and 92.9%) in 14 primary sacral chordomas than in 7 recurrent chordomas (57.1% and 66.7%) treated with surgery and radiation. In the same series, three of the four patients with LRC treated with radiation alone were successfully salvaged at 2.9-, 4.9-, and 7.6-year follow-up.

The overall results of the series of Rotondo *et al*[22] are presented above in the surgical section. With respect to RT, patients received a median dose of 72.4 GyRBE (relative biological effectiveness) as a combination of photons and protons. The majority of patients received pre- and postoperative radiation. For patients with recurrent tumors who underwent combined pre- and postoperative RT, the 5-year OS and LC were 71% and 47%, respectively. The same values for patients with recurrent disease who underwent postoperative radiation alone were 83% and 44% and were not significantly different. Conversely, combined preoper-ative and postoperative radiation administered to patients with primary disease improved OS and LC from 80% and 56% to 85% and 85%, respectively. Furthermore, LC was 100% in patients with primary disease who had wide *en bloc* resection, pre- and postoperative RT.

In a series of 34 sacral chordomas, 17 patients with LR disease received salvage surgery and IMRT (n=11) or IMRT alone (n=6).[28] With this regimen, LC was 24%. For both primary and recurrent disease, treatment with a combination of surgery and radiation was associated with improved survival than RT alone.

Breteau *et al* treated 12 patients with sacral chordomas, 10 of whom were locally recurrent, with fast neutron RT. Seven of eight patients treated with curative intent were alive and locally disease-free at last at follow-up. The 4-year OS and LC rate were 61% and 54%, respectively.

Discussion

The management of recurrent chordoma of the spine is extremely challenging due to its locally aggressive behavior and its resistance to adjuvant therapies.[3,10,20,28] Given that curative salvage is rare, treatment is typically palliative in intent. As such, the aggressiveness of surgical and RT employed for LRC must take into account the effect on quality of life. Nevertheless, multimodal therapy can result in successful salvage, albeit in a minority of cases.

We systematically reviewed the surgical literature for recurrent chordoma and identified nine pertinent studies that met our criteria. The surgical literature comprised retrospective reviews of low- and very–low-quality evidence. In all studies reviewed, cases of recurrence were

included amongst cases of primary chordoma and the details of their management and outcome variably reported separately from the primary cases.

One consistent theme that emerged from the surgical literature was that the outcome of treating recurrent disease was uniformly poorer than for primary tumors.[8–10,12,14,20–23] The 5-year OS and LRFC after relapse ranged from 47% to 78% and 36% to 50%, respectively.[10,20,22] This is compared to a range of 78% to 82% and 47% to 72%, respectively, in patients with primary disease. These data further support the critical importance of obtaining a wide *en bloc* excision during the initial surgery.[3]

The data on the relation between surgical margins at resection of recurrent spinal chordoma and outcome are somewhat contradictory. The study that included the greatest number of LR tumors found no difference in rate of subsequent recurrence after incomplete versus complete resec-tion.[10] They, however, did not report the margins obtained during these procedures; they were presumably all intrale-sional, which could explain the lack of a difference in outcome. In contrast, Xie *et al*[20] reported superior outcomes for patients who underwent complete *versus* incomplete resection (intralesional margins). In the remaining studies that reported the margins achieved at surgery for relapsed disease, patients who had their recurrent tumors resected with wide margins appeared to have superior outcomes to those with marginal or intralesional margins (Supplementary Table 1, http://links.lww.com/BRS/B193).[8,9,12,14,21,22] Although in these studies meaningful statistical comparisons are precluded by small numbers, the weight of evidence supports the role for more aggressive resection when possible.

Reviewing the literature on RT for LRC of the spine yielded seven studies after applying exclusion criteria. These studies employed a variety of RT modalities and dose regimens in treating a heterogeneous group of patients with locally recurrent disease. Six of the seven studies did not compare outcome for patients who received RT with those that did not. Rotondo *et al*,[22] on the contrary, demonstrated improved LC with the addition of preoperative RT for primary but not recurrent tumors. For the remainder of the studies, rates of LC were quite high at 2 years (85%– 88% in two studies)[25,26] and satisfactory at 4 to 5 years (range 47%–68% in five studies).[22,24,27,29,30]

Determining the benefit attributable to adjuvant RT in the setting of recurrent disease from the existing literature is beset by challenges. The surgical and radiation literature cross over in terms of patient population. These studies include a heterogeneous mix of patients, with primary and recurrent disease, treated with similarly varied treatment regimens that typically including surgery and/or RT. Nevertheless, given the poor ratesofLCwith surgery alone,[10,14,20] and the suggestion of improved LC in RT studies,[22,24–27,29,30] it seems reasonable to offer postoperative RT (with a neoadjuvant component based on institutional practice) after resection in most cases of LRC.

The dominant mode of recurrence for chordoma of the mobile spine or sacrum is local.[3,28] Depending on the location of the primary tumor, recurrence may be asymptomatic, for example in the gluteal muscle after resection of a sacral chordoma. Unlike for primary disease in which oncologic principles and current guidelines[3] strongly recommend wide

marginal excision when it is technically feasible, the management of an asymptomatic recurrent lesion is unclear. The literature reviewed herein provides scant guidance for this scenario. Xie *et al* found no difference in 5-year OS comparing patients who underwent incomplete resection with or without RT to those who were treated palliatively. Similarly, in a series of eight clival and eight spinal recurrent chordoma patients, salvage surgery (n= 8) did not improve 2-year LC compared with RT alone (n=8).[25] Conversely, Zabel-du Bois *et al*[29] reported higher rates of LC when surgery was combined with RT as opposed to RT alone. It is also interesting to note that Uhl *et al* reported a fairly low 2-year LC rate (47%) using carbon ion therapy alone for LR sacrococ-cygeal chordoma. Acknowledging important limitations in comparing these fairly disparate retrospective data sets, the best disease control appears to result from multimodality therapy with surgery and high-dose RT.

There were several limitations to the present study. All included articles were of low or very low quality. The majority of these studies focused on groups of patients with spinal chordoma which included a subgroup of patients with locally recurrent disease. Hence, the details regarding this subgroup's baseline characteristics, treatment and outcome were sparsely reported. Surgical and radiation treatment regimens reported in the literature varied widely, precluding direct comparison of outcomes. Selection bias likely featured heavily in these articles because the decision to treat and the modalities employed were at the discretion of the treating physician. Similarly, confounding by indication may have occurred, for example, if patients with more aggressive disease did poorly despite more aggressive local therapy. Moreover, none of the studies reviewed directly compared the outcomes of surgery, radiation, combined therapy, or observation. Finally, there was some variation in the definition of locally recurrent disease amongst the studies reviewed. Some articles defined LR as any operation done at an outside center before their definitive surgery. This included a spectrum of procedures ranging from laminectomy with open biopsy to an intralesional resection of a substantial portion of the tumor. This may well have increased the heterogeneity of the study population reviewed herein.

Conclusion

Recommendations

1. For LRC of the spine without systemic disease, when surgery is planned, wide *en bloc* resection should be performed if technically feasible with acceptable morbidity. Strong recommendation, Low Quality of Evidence.

2. For LRC without systemic disease, in which wide *en bloc* excision is not possible, partial resection is the treatment of choice. Weak recommendation, Very Low Quality of Evidence.

3. For the treatment of locally recurrent chordoma, high-dose conformal RT should be administered post-operatively to reduce the risk of further recurrence, and may be considered as a primary therapy. Strong recommendation, Very Low Quality of Evidence.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Box 1

How to Use and Interpret GRADE Recommendations[18]

Strength of Recommendation	Interpretation
Strong	Can be confidently applied to all or almost all patients.
	Clinicians apply an intervention in all or almost all circumstances without a thorough review of the evidence and factors, and with an informing, but not necessarily detailed discussion with the patient.
Weak	Can be applied to most patients, but not all patients.
	Clinicians consider fundamental variables such as the quality of evidence, risk and benefit of the intervention, their experience, cost-effectiveness, and most importantly, patient preferences, thus, often resulting in a shared decision-making process with the patient.

Key Points

- Treatment of LRC of the mobile spine or sacrum represents a significant management challenge and is associated with uniformly poorer outcomes relative to primary disease, regardless of treatment modality.

- As for primary chordoma, wide en bloc excision appears to confer an advantage for LC, although the effect is attenuated in this setting.

- After incomplete resection of locally recurrent chordoma, RT improves LC, although not as reliably as in the setting of primary chordoma.