

# Salvage Therapy for Local Progression following Definitive Therapy for Skull Base Chordomas: Is There a Role of Stereotactic Radiosurgery?

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## Abstract

**Objective** The objective of this study was to identify factors associated with improved tumor control at individual sites of recurrence and to define the role of stereotactic radiosurgery (SRS) in the management of local or distant progression following prior radiotherapy.

**Study Design** Clinical data of patients with recurrent skull base chordoma following prior radiotherapy were retrospectively reviewed.

**Setting and Participants** This is a single-center retrospective study including 16 patients from the University of Texas MD Anderson Cancer Center Houston, Texas, United States.

**Main Outcome Measures** Each site of recurrence was considered independently, and the primary outcome was freedom from treatment site progression (FFTSP).

**Results** There were 40 episodes of either local or distant progression treated in 16 patients with skull base chordoma. Tumor recurrence was classified as either local, distant, or both local and distant involving the skull base, spinal column, or leptomeninges. Patients were treated with repeat surgical resection ( $n = 16$ ), SRS ( $n = 21$ ), or chemotherapy ( $n = 25$ ). In multivariate analysis, SRS was the only treatment modality associated with improved FFTSP ( $p = 0.006$ ). For tumors treated with SRS, there was no evidence of tumor progression or adverse radiation events. Other factors associated with worse FFTSP included the number of progressive episodes ( $>3$ ), tumor histology, and leptomeningeal disease.

**Conclusions** For local recurrence following prior radiotherapy, SRS was associated with improved FFTSP. SRS may represent an effective palliative treatment offering durable tumor control at the treated site without significant treatment-related morbidity.

## Keywords

- ▶ chordoma
- ▶ clivus
- ▶ skull base
- ▶ radiation
- ▶ stereotactic radiosurgery

## Introduction

Chordomas follow a malignant course defined by local invasiveness and destruction, a tendency to recur, and occasional distant metastases. Although a consensus approach on the

multimodal treatment of newly diagnosed skull base chordomas exists,<sup>1</sup> there is a paucity of outcomes data directing management of locally and systemically recurrent/progressive skull base chordomas. The surgical treatment of skull base chordomas has advanced with improvements in endoscopic

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and open cranial approaches, and the development of salvage reconstruction techniques has led to the consideration of repeat surgery at the time of tumor recurrence. Treatment of progressive disease, however, is currently complicated by a lack of effective systemic therapeutic options and the unknown efficacy of re-irradiation. In general, the ability to offer curative treatment at the time of recurrence is rare for skull base malignancies, and selecting an optimal therapy requires a multidisciplinary approach focused on striking a balance between local control, quality of life, and potential morbidity of further interventions.

We recently described factors affecting overall disease control and survival in patients with progressive skull base chordoma at our institution.<sup>2</sup> In this study, it was noted that disease progression after radiation therapy was more difficult to control than after surgery alone, and the presence of distant metastases or leptomeningeal disease conferred a poorer disease-specific survival and freedom from progression (subsequent progression at any local or systemic site). Moreover, repeat surgical resection followed by adjuvant radiotherapy (RT) at the time of progression significantly improved both local and systemic disease control in patients presenting after previous surgical resection alone. In the case of postradiation disease progression, no single treatment paradigm was found to be effective in reducing the risk of local or distant disease progression.

In this study, we focused on our ability to offer palliative interventions for local and distant recurrences in patients previously treated with surgery and radiation therapy. The nature of the advanced disease in these patients prevents a cure. To our knowledge, this is the only report systematically examining rates of site-specific control by treatment modality in the treatment of local or distant chordoma recurrence. The aim of this study was to identify factors influencing the ability to control individual areas of disease independent of whether or not there is progression at either local or distant sites. We hypothesized that treatment with stereotactic radiosurgery (SRS) provides effective tumor control in skull base and spine recurrences, with acceptable

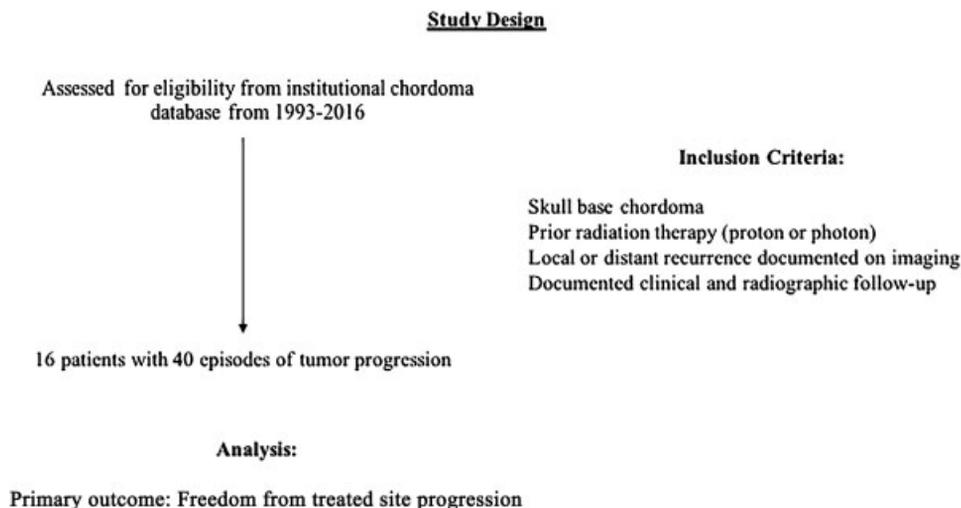
morbidity in patients with few remaining treatment options. To our knowledge, this is the first report specifically addressing the role of SRS in the management of locally progressive skull base chordomas in the post-RT setting.

## Methods

### Study Population

A retrospective review of all patients treated at our institution for skull base chordomas between 1993 and 2016 was performed. The study was performed under an Institutional Review Board approved protocol in compliance with regulations set by our institution for the study of human subjects and met all HIPAA (Health Insurance Portability and Accountability Act of 1996) standards. For this type of retrospective study, patient consent was not required. Patients were identified through a search of a prospectively collected registry. From 1993 to 2016, 91 newly diagnosed chordomas of the skull base have been treated at our institution. Based on the study design shown in ▶Fig. 1, 16 patients with 40 episodes of post-RT (proton or photon therapy) disease progression (median follow-up length: 28 months) were eligible for inclusion. Clinical charts, imaging, pathology, and treatment regimens were reviewed.

Our previous work assessed the impact of treatment in preventing further progression in the overall disease status (either local or systemic progress). This outcome was defined as the freedom from progression. The primary outcome in this study was freedom from treatment site progression (FFTSP) defined as the time between treatment for an individual site of progressive disease to subsequent progression at that treated site with radiographic demonstration of unequivocal increase in residual tumor or tumor recurrence based on the RECIST (response evaluation criteria in solid tumors) criteria (▶Fig. 2). For patients with multiple recurrences, each unique site of recurrent tumor (local or distant) was assessed as a separate event. At each time point, the overall pattern of progression was classified as local (skull base) progression only, distant metastasis only, or combined



**Fig. 1** Study flow chart.



**Fig. 2** Depiction of primary outcomes. Freedom from treatment site progression defined as the time between the treatment for an individual site of progressive disease and subsequent progression at that treated site, with radiographic demonstration of unequivocal increase in residual tumor or tumor recurrence independent of progression elsewhere locally or systemically. *Dashed square* highlights local progression independent of the original treated site.

local *and* distant disease progression. Of note, our previous work has demonstrated no impact of any particular treatment modality on disease-specific survival; hence, this was not used as a secondary outcome in the presented study.

### Histological Subtype

All tissue samples were reviewed at the time of treatment by pathologists experienced in the evaluation of bone and soft tissue sarcomas and were classified into conventional, chondroid, and dedifferentiated chordomas based on accepted histological criteria.

### Statistical Analysis

Frequency distribution and summary statistics were calculated for all variables. Kaplan–Meier estimates of FFTSP were calculated; survival curves were compared by using the log-rank test. Univariate and multivariate predictors of FFTSP were assessed using the Cox proportional hazards model. Relative risk ratios (RRs) and their 95% confidence intervals were computed. When appropriate, a two-tailed Student's *t*-test was performed to assess correlation. A *p*-value of  $<0.05$  was considered significant for all analyses. All analyses were performed using SPSS (version 2015, IBM Inc.).

## Results

### Demographic and Descriptive Data

During the study period, 16 patients were treated for recurrence or progression of their chordoma following prior radiation therapy. Multiple recurrences were common, and each site of progression was counted as a unique event or progressive episode. In total, there were 40 instances of disease progression, with a median of 2.4 episodes (range: 1–5) per patient. The maximum number of progressive events recorded in a single patient was 5. The majority of patients received proton therapy ( $n = 11$ ) at the time of initial treatment, and the remaining 5 patients had been treated with intensity-modulated radiation therapy (–**Table 1**). Progression was classified as (1) local disease confined to the skull base, (2) distant disease, or

**Table 1** Baseline data at initial episode of disease progression postradiation therapy

Characteristic	Total number (% of cohort)
Total number of progression episodes	40 tumors (16 patients)
Sex	
Male	7
Female	9
Median age	46 y (range: 3–74)
Radiation modality at initial definitive treatment	
Proton therapy	11 patients
Intensity-modulated radiation therapy (photon)	5 patients
Histological subtype	
Chondroid	7 patients (43.7%)
Conventional	8 patients (50%)
Dedifferentiated	1 patient (6.3%)
Median number of progressions per patient	2.4

(3) both local and distant. The most frequent site of chordoma recurrence was local and was present in 78% of the episodes. Distant locations affected included the spinal column ( $n = 7$ ), leptomeninges ( $n = 7$ ), and other organ sites ( $n = 13$ ). For cases of local tumor progression, the pattern of recurrence was further classified as occurring within the prior radiation field (infield failure), at the margin (marginal failure), or entirely outside of the irradiated field (outfield failure). Nearly half of the radiation failures were infield treatment failures (–**Table 2**).

### Treatment Paradigms

At the time of local disease progression, patients were offered repeat surgical resection, chemotherapy, or SRS. The majority of local tumor recurrences were treated with

**Table 2** Baseline data regarding all episodes of disease progression

Characteristic	Total number (% of cohort)
Total number of progression episodes	40
Patterns of progression	
Local only	23 (57.5)
Distant only	9 (22.5)
Local + distant	8 (20)
Distant metastases	17 episodes total
Spinal column metastases	7 (17.5)
Leptomeningeal disease	7 (17.5)
Systemic metastases	13 (32.5)
Patterns of local progression	
Infield failure	18 (47.4)
Marginal failure	5 (13.2)
Outfield failure	15 (39.4)
Treatment paradigms	
Local progression	38 episodes
Repeat surgery	9 (24)
Chemotherapy	12 (32)
Stereotactic radiosurgery	13 (34)
Systemic metastases	17 episodes total
Surgery	7 (41)
Chemotherapy	13 (76)
Radiation therapy	8 (47)

SRS ( $n = 13$ ; 34%) and various cytotoxic or targeted chemotherapy agents ( $n = 12$ ; 32%). Additional surgical resection was less frequently used in this cohort of patients who had already undergone an extensive skull base surgical resection and adjuvant radiation therapy at the time of their initial diagnosis and treatment. Nine patients underwent repeat surgical resection followed by adjuvant SRS approximately 3 to 4 weeks postoperatively. The two most common reasons for the low rate of repeat of surgical resection were as follows: if the recurrent disease was considered low volume amenable to SRS or if it was considered unresectable (i.e., circumferential encasement of a major vascular structure despite a previous resection through a well-executed surgical approach). However, for infield or marginal failure adjacent to the radiation sensitive structures (i.e., brainstem), repeat surgery was pursued if it was felt it would help reduce the risk of radiation toxicity. In the setting of distant or systemic metastases, patients were also treated with a combination of surgical resection ( $n = 7$ ), chemotherapy ( $n = 17$ ), and/or radiation therapy ( $n = 8$ ). Ultimately, six of the spinal metastases were treated with radiation therapy.

The 13 locally progressive tumors treated with re-irradiation were treated with gamma knife SRS (GKSRS). The

**Table 3** Re-irradiation for local skull base progression: treatment parameters and outcomes

Variable	Total number (13 treated tumors)
GKSRS parameters	
Median radiation volume (range), cm <sup>3</sup>	23.7 (14–73)
Margin dose, Gy	
Median (range)	15 (12–20)
Maximum dose, Gy	
Median (range)	28 (17–32)
Tumor response	
Regression	6
Stable	7
Progression	0
Radiation-induced changes	
AREs	0
Radiation necrosis	0

Abbreviations: AREs, adverse radiation events; GKSRS, gamma knife stereotactic radiosurgery.

median treatment volume was 23.7 cm<sup>3</sup>, with a range of 14 to 73 cm<sup>3</sup>. The median margin and maximum doses were 15 and 28 Gy, respectively (►Table 3). Following SRS, seven of the tumors remained stable in size and six exhibited evidence of tumor regression. Re-irradiation with SRS was not associated with any adverse radiation events (AREs) or radiation necrosis, and there were no instances of tumor progression seen during the median follow-up of 28 months.

### Main Results: Factors Affecting Freedom from Treatment Site Progression

The primary outcome measured was FFTSP after salvage therapy. For the entire cohort, the mean FFTSP was 47.2 months (range: 1–65 months) (►Table 4). The median disease-specific survival was 36 months (range: 2–114 months). Analysis of histological subtype revealed a relationship between histology and FFTSP. Patients treated for the recurrence of chondroid chordoma had significantly longer mean FFTSP (71.2 months) than conventional (29.8 months) or dedifferentiated subtypes (20 months). This was significant ( $p = 0.018$ ) in multivariate analysis (►Fig. 3A). The pattern of overall disease progression and distant metastases was associated with FFTSP in multivariate analysis. Patients presenting with simultaneous local and distant disease progression had significantly shorter durations of FFTSP (7.1 months) versus those with either local recurrence only (56.3 months) or distant metastases only (51.2 months) disease (►Fig. 3B). In the case of distant disease, spinal column metastases were not associated with worse FFTSP. The presence of leptomeningeal disease, however, was found to correlate with shorter FFTSP (10.4 vs. 43.5 months;  $p = 0.022$ ). Other factors at presentation that were not found to have a significant association with FFTSP in multivariate analysis included the presence or

**Table 4** Factors affecting FFTSP

	Mean FFTSP (months)	p-Value	Univariate Cox regression analysis (95% CI)	p-Value	Multivariate Cox regression analysis (95% CI)	p-Value
Overall cohort 47.2						
Factors at presentation						
Progression episode number						
1	54.9	<b>0.036</b>				
2	54.5					
3	19.3		2.8 (1.2–8.1) <sup>a</sup>	<b>0.047</b>	10.9 (2–58.8)	<b>0.006</b>
4	15.6					
5	5.5					
Histological subtype						
Chondroid	71.2	0.06				
Conventional	29.8		3.2 (1.1–9.3) <sup>b</sup>	<b>0.029</b>	5.4 (1.3–21.7) <sup>b</sup>	<b>0.018</b>
Dedifferentiated	20					
Radiation modality received at initial treatment						
Proton therapy	53.5	<b>0.006</b>				
Photon therapy	14.7		3.8 (1.3–10.8)	0.012	2.6 (0.26–27.6)	0.407
Radiation dose received at initial treatment						
73 Gy or Less	24.5					
74 Gy or More	57.7	<b>0.021</b>	3.8 (1.1–14.1)	0.041	2.8 (0.49–16.1)	0.288
Presence of distant metastasis						
No	55.6	0.06				
Yes	31.9		2.5 (0.9–6.9)	0.076		
Pattern of overall disease progression						
Local only	56.3	<b>&lt;0.005</b>				
Distant only	51.2		10 (3.14–31.3)	<b>&lt;0.005</b>	5.4 (1.1–28.6)	<b>0.045</b>
Local + distant	7.1		10 (2.5–62.5)	<b>&lt;0.005</b>	9.1 (1.2–66.6)	<b>0.029</b>
Pattern of local failure						
Infield failure						
Yes	36.7	0.124				
No	43.4		2.65 (0.76–9.7)	0.141	1.068 (0.226–5.040)	0.934
Marginal failure						
Yes	26.8	0.902				
No	47.3		1.09 (0.24–5.02)	0.903		
Outfield failure						
Yes	34.6	0.697				
No	47.4		1.24 (0.41–3.7)	0.699		
Pattern of distant metastases						
Spinal column metastases						
Yes	47.6	<b>0.05</b>				
No	15.5		3.4 (0.8–18.9)	0.082		

(Continued)

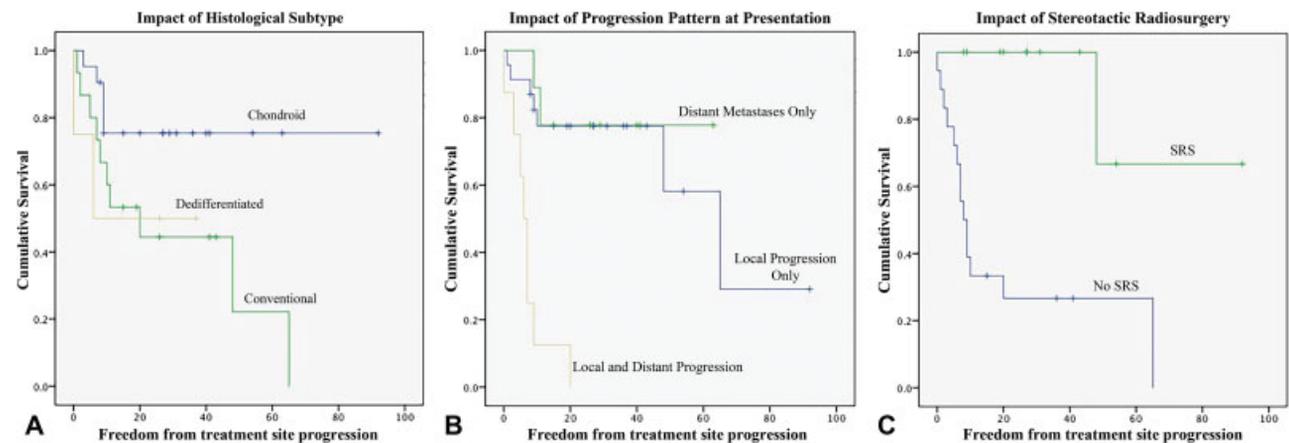
**Table 4** (Continued)

	Mean FFTSP (months)	p-Value	Univariate Cox regression analysis (95% CI)	p-Value	Multivariate Cox regression analysis (95% CI)	p-Value
Leptomeningeal disease						
Yes	10.4	0.012	4.6 (1.2–16.9)	0.022		
No	43.5					
Local progression treatment						
Surgery						
Yes	40.8	0.552	1.4 (0.41–5.4)	0.6	1.021 (0.220–4.731)	0.98
No	37.8					
Chemotherapy						
Yes	20.8	0.008	4.2 (1.3–13.3)	0.015	2.4 (0.32–18.7)	0.39
No	70.8					
Radiation therapy						
Yes	77.3	<0.005	6.1 (1.7–21.7)	0.006	11.9 (1.3–109.1)	0.029
No	22.4					

Abbreviations: CI, confidence interval; FFTSP, freedom from treatment site progression.

<sup>a</sup>First/second progression versus third or higher progression.

<sup>b</sup>Chondroid versus conventional and dedifferentiated histological subtype.



**Fig. 3** (A) Kaplan–Meier curve demonstrating the impact of histology on freedom from treatment site progression (FFTSP). (B) Kaplan–Meier curve demonstrating the impact of pattern of recurrence on FFTSP. (C) Impact of re-irradiation with stereotactic radiosurgery on FFTSP.

absence of distant metastasis and if the local treatment failure was in-field, marginal, or out-field (► **Table 4**). Of note, radiation modality at initial treatment (proton or photon therapy) was initially found to be significant in univariate analysis but, ultimately, not in multivariate analysis. Of the factors at presentation that were included in the analysis, only third or higher recurrence, histological subtype, and local and distant disease progression had a meaningful influence on FFTSP. Lastly, while a previous radiation dose of >74 Gy was significantly indicative of improved site control in univariate analysis (24.5 vs. 57.7 months,  $p < 0.05$ ; RR: 3.8;  $p < 0.05$ ), this was not deemed to be significant in further multivariate analysis.

The type of treatment modality used in treating progressive disease had an impact on local control or FFTSP. There was no

improvement in primary outcome measures for patients offered repeat surgical resection of their local recurrence. The mean FFTSP for patients undergoing surgery versus non-operative management was 40.8 and 37.8 months, respectively ( $p = 0.98$ ). Patients treated with chemotherapy received either targeted therapies or other cytotoxic medications. Surprisingly, the mean FFTSP was actually shorter for patients receiving chemotherapy (20.8 months) compared with those who did not receive chemotherapy (70.8 months). This difference was significant in univariate analysis ( $p = 0.015$ ) but did not reach significant in multivariate analysis ( $p = 0.39$ ). Patients receiving re-irradiation for their local skull base recurrence or spinal disease experienced significantly longer mean times of freedom from progression (77.3 months) compared with those treated with nonradiation-based modalities (22.4 months)

(► **Fig. 3C**). This correlation was significant in multivariate analysis ( $p = 0.029$ ). Of the treatments offered to patients in this series, SRS was the only paradigm providing a significant improvement in local control of advanced or recurrent chordoma. As previously described, radiation treatments were well tolerated with no reported adverse radiation outcomes including radiation necrosis.

## Discussion

Although there is consensus regarding the use of multimodal treatment in the definitive management of chordomas at diagnosis, there is a paucity of data related to the management of advanced disease. The management of tumor recurrence after previous radiation clearly poses several management challenges; the ability to achieve a gross total resection from surgery is often limited,<sup>3-6</sup> and surgical intervention alone without any adjuvant therapy is unlikely to provide any durable tumor response. Previous radiation, with either photon- or proton-based modalities, has previously been considered a contraindication to repeat radiation; studies on other skull base malignancies is now demonstrating a role of SRS as a re-irradiation modality.<sup>7-9</sup> Determining the optimal therapy for local or distant recurrence is complex and requires consideration of tumor location, functional status, histology, disease burden, and prior interventions.

Our study demonstrates that SRS was the only treatment modality associated with improved site-specific control in patients presenting with locally recurrent disease after previous surgical resection and radiation. During the follow-up period, there were no instances of tumor progression following radiosurgery; the treated areas remained stable or decreased in size. Interestingly, location of the treated recurrence relative to the prior radiation field did not limit delivery of an effective and safe radiation dose, with median maximum and marginal doses of 28 and 15 Gy, respectively; these dosing schemes are similar to those reported by other GKSRS series in the literature.<sup>10-15</sup> As discussed in the following, it is likely that the judicious use of surgery helped radiation outcomes for patients with infield/marginal recurrences adjacent to the brainstem. The largest radiosurgery series to date reported outcomes for 71 patients, 20 of whom were treated for recurrence following prior radiation.<sup>14</sup> In all patients, regardless of previous treatment status, the authors demonstrated that a margin dose of  $\geq 15$  Gy significantly improved tumor control and survival compared with a dose of  $< 15$  Gy. Tumor control following radiosurgery in the prior RT cohort was 98% at 1 year and decreased to 65% at 7 years. In our series, we observed effective site-specific tumor control across relatively large treatment volumes (14–73 mL). The role of SRS in the overall management of skull base chordomas— independent of previous treatments—has certainly been demonstrated in numerous other publications. Other centers have reported high rates of local control using radiosurgery to treat local residual or recurrent disease.<sup>10-15</sup> However, these studies do not exclusively address the management of recurrent disease after a previous charged particle therapy. Most recently, Förander et al demonstrated the role of GKSRS in the management of residual disease after no previous

radiation and management of progression after previous SRS.<sup>11</sup> With dosing parameters similar to that in our study, a tumor control rate of 50% at 15 years for first time GKSRS patients was noted in the setting of an ARE rate of 18%; notably, a majority of the recurrences were considered out of field. In the repeat SRS subcohort of six patients, a prominent effect on tumor control was also noted.

The primary concern with re-irradiation of infield or marginal recurrences, regardless of modality, is the risk of radiation-associated injury to critical structures including the brainstem, cranial nerves, pituitary gland, and mesial temporal lobes. The North American Gamma Knife Consortium observed AREs following SRS in 6 of their 71 patients.<sup>14</sup> The reported morbidities were related to worsened cranial nerve or pituitary dysfunction and occurred exclusively in patients with prior RT. The incidence of grade 2/3 ARE (i.e., neurologic toxicities requiring management with either steroids or hospitalization) in the previous RT group was approximately 30%. In our series, there were no AREs, as per the Radiation Therapy Oncology Group and the European Organization for Research and Treatment of Cancer criteria, or radiation necrosis; this is particularly notable for the infield recurrences treated with SRS. The difference in reported outcomes between our study and prior publications could be related to several factors. The site of local recurrence and proximity to critical structures may differ between the two groups, as well as baseline cranial nerve function. Furthermore, we hypothesize that judicious use of repeat surgical resection to clear disease away from radiation sensitive structures, such as the brainstem, helped reduce the risk of radiation toxicity in our cohort. In our experience, however, radiosurgery for local recurrence is an effective palliative treatment in patients who cannot expect a cure, offering local tumor control without imposing significant morbidity.

Similar to our prior study, we found that repeat surgical resection as the sole treatment modality of post-RT local recurrence did not improve FFTSP. This is consistent with previous publications reporting statistically and significantly reduced local control rates with posttreatment surgical intervention. Numerous other studies have indicated a significantly higher risk of subtotal resection in the setting of previous treatments (either radiation or surgery alone).<sup>3-6</sup> Presumably, radiation-induced arachnoid and extradural soft tissue scarring limit the ability to identify appropriate resection margins, further increasing the risk of a subtotal resection. As with other malignancies, the role of repeat surgical resection needs to be considered within the context of advancements in surgical technique and the ability to resect disease previously considered unresectable. It is important to acknowledge that our cohort may have skewed analysis. Generally, these were patients who received their initial surgical treatment at our institution and had already undergone a maximal skull base resection. Hence, the residual disease was typically adherent to critical neurovascular structures and not due to an inadequate surgical exposure.

The refinement of expanded endoscopic approaches now allows us to consider repeat surgery for residual disease in areas (i.e., petroclival synchondrosis, clivus) where the

alternative or traditional strategy would have been associated with more soft tissue morbidity and a lower likelihood of achieving a gross total resection. Hence, we do still consider repeat surgery in select patients where the area of progressive disease is amenable to a gross total resection using a well-designed surgical approach. In particular, this may be an effective strategy to help salvage patients with high volume marginal field recurrences where there is room for additional higher doses of radiation therapy. Furthermore, neurologic symptoms related to compression of cranial nerves or brainstem may warrant conservative surgical resection. Most importantly, within the context of this study, we hypothesize that the low observed rate of AREs was a result of employing surgical resection to clear disease away from radiation-sensitive structures. This was likely an important reason why radiation complications were not seen with recurrences considered infield relative to previous radiation fields despite their proximity to the brainstem and other critical neurovascular structures.

Several patients received cytotoxic or targeted therapies for salvage therapy. There was no improvement in FFTSP in trials of chemotherapy. In fact, tumor control was worse for patients treated with chemotherapy. This likely reflects the severity and aggressiveness of disease in patients who were allocated to medical therapy rather than a result of the treatment itself. In general, these patients are enrolled in clinical trials due to the limited remaining options for treatment. Related to this observation is also a finding in our study, indicating that tumor histology, pattern of recurrence, and number of recurrences impact local control. Our report also identified that chondroid histology was associated with significantly increased FFTSP in patients treated for recurrence compared with conventional and dedifferentiated chordoma. The ability to control local recurrences was notably shorter for patients on their third or higher episode of recurrence anywhere locally or systemically. At the time of the first recurrence, FFTSP was 54 months compared with 5.5 months at the fifth recurrence. Likely indicative of the aggressive biology of some tumors, factors such as history and patterns of recurrence are typically considered in salvage management strategies for other solid malignancies. However, this has yet to happen with chordomas due to the lack of efficacious systemic therapy options. The suboptimal outcomes associated with commonly employed receptor tyrosine kinase inhibitors emphasize the need for the development of effective therapies tailored to molecular or histological subtype and, perhaps, consideration for systemic therapy earlier in the treatment paradigm for high-risk tumors.

## Study Limitations

Despite the fact that this report draws on the experience of a multidisciplinary team at a large referral center, it is a relatively small series composed of heterogeneous patients. The analysis included both local and distant recurrences treated with different modalities, limiting the statistical power of the study. The decision of salvage therapy was not standardized, and allocation to different treatments was

potentially biased, affecting analysis of each treatment's efficacy. Specifically, the nature in which surgical resection was applied introduced a selection bias that may have skewed analyses regarding the role of surgery and the risk of AREs. Additionally, our outcome was FFTSP. In this patient population, future efforts should include measures of patient-reported quality of life.

## Conclusions

Treatment of recurrent chordomas is a complex and challenging task. Patients frequently present with multiple recurrences and have undergone several prior procedures including surgical resection and radiation therapy. The focus of therapy is different than that at the time of initial diagnosis as an oncological or complete resection is unlikely. Thus, treatment should maximize local control with minimal morbidity. We advocate that surgical resection for local recurrence in the setting of prior radiation should be limited to situations where a gross total resection is considered possible, such as for decompression of neural structures and for optimization of radiation fields to decrease AREs. SRS provides patients with local or distant disease progression improved local control without significant morbidity or complications.

### Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (name of institute/committee) and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

### Conflict of Interest

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent/licensing arrangements) or nonfinancial interest (such as personal or professional relationships, affiliations, knowledge, or beliefs) in the subject matter or materials discussed in this study.

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## References

- 1 Stacchiotti S, Sommer J; Chordoma Global Consensus Group. Building a global consensus approach to chordoma: a position paper from the medical and patient community. *Lancet Oncol* 2015;16(02):e71–e83
- 2 Raza SM, Bell D, Freeman JL, Grosshans DR, Fuller GN, DeMonte F. Multimodality management of recurrent skull base chordomas: factors impacting tumor control and disease specific survival. *Operative Neurosurgery*. 2018;15(02):131–143

- 3 Koutourousiou M, Gardner PA, Tormenti MJ, et al. Endoscopic endonasal approach for resection of cranial base chordomas: outcomes and learning curve. *Neurosurgery* 2012;71(03):614–624, discussion 624–625
- 4 Sen C, Triana AI, Berglind N, Godbold J, Shrivastava RK. Clival chordomas: clinical management, results, and complications in 71 patients. *J Neurosurg* 2010;113(05):1059–1071
- 5 Wang L, Tian K, Wang K, et al. Factors for tumor progression in patients with skull base chordoma. *Cancer Med* 2016;5(09):2368–2377
- 6 Wu Z, Zhang J, Zhang L, et al. Prognostic factors for long-term outcome of patients with surgical resection of skull base chordomas-106 cases review in one institution. *Neurosurg Rev* 2010;33(04):451–456
- 7 Ho JC, Phan J. Reirradiation of skull base tumors with advanced highly conformal techniques. *Curr Oncol Rep* 2017;19(12):82
- 8 Phan J, Sio TT, Nguyen TP, et al. Reirradiation of head and neck cancers with proton therapy: outcomes and analyses. *Int J Radiat Oncol Biol Phys* 2016;96(01):30–41
- 9 Takiar V, Garden AS, Ma D, et al. Reirradiation of head and neck cancers with intensity modulated radiation therapy: outcomes and analyses. *Int J Radiat Oncol Biol Phys* 2016;95(04):1117–1131
- 10 Chang SD, Martin DP, Lee E, Adler JR Jr. Stereotactic radiosurgery and hypofractionated stereotactic radiotherapy for residual or recurrent cranial base and cervical chordomas. *Neurosurg Focus* 2001;10(03):E5
- 11 Förander P, Bartek J Jr, Fagerlund M, et al. Multidisciplinary management of clival chordomas; long-term clinical outcome in a single-institution consecutive series. *Acta Neurochir (Wien)* 2017;159(10):1857–1868
- 12 Hasegawa T, Ishii D, Kida Y, Yoshimoto M, Koike J, Iizuka H. Gamma Knife surgery for skull base chordomas and chondrosarcomas. *J Neurosurg* 2007;107(04):752–757
- 13 Ito E, Saito K, Okada T, Nagatani T, Nagasaka T. Long-term control of clival chordoma with initial aggressive surgical resection and gamma knife radiosurgery for recurrence. *Acta Neurochir (Wien)* 2010;152(01):57–67, discussion 67
- 14 Kano H, Iqbal FO, Sheehan J, et al. Stereotactic radiosurgery for chordoma: a report from the North American Gamma Knife Consortium. *Neurosurgery* 2011;68(02):379–389
- 15 Martin JJ, Niranjan A, Kondziolka D, Flickinger JC, Lozanne KA, Lunsford LD. Radiosurgery for chordomas and chondrosarcomas of the skull base. *J Neurosurg* 2007;107(04):758–764