Use of Salvage Surgery or Stereotactic Radiosurgery for Multiply Recurrent Skull Base Chordomas: A Single-Institution Experience and Review of the Literature

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Abstract

Introduction Chordomas are locally destructive neoplasms characterized by appreciable recurrence rates after initial multimodality treatment. We examined the outcome of salvage treatment in recurrent/progressive skull base chordomas.

Methods This is a retrospective review of recurrent/progressive skull base chordomas at a tertiary urban academic medical center. The outcomes evaluated were overall survival, progression-free survival (PFS), and incidence of new toxicity.

Results Eighteen consecutive patients who underwent $\geq$1 course of treatment (35.3% salvage surgery, 23.5% salvage radiation, and 41.2% both) were included. The median follow-up was 98.6 months (range 16–215 months). After initial treatment, the median PFS was 17.7 months (95% confidence interval [CI]: 4.9–22.6 months). Following initial therapy, age $\geq$ 40 had improved PFS on univariate analysis ($p = 0.03$). All patients had local recurrence, with 15 undergoing salvage surgical resections and 16 undergoing salvage radiation treatments (mostly stereotactic radiosurgery [SRS]). The median PFS was 59.2 months (95% CI: 4.0–99.3 months) after salvage surgery, 58.4 months (95% CI: 25.9–195 months) after salvage radiation, and 58.4 months (95% CI: 25.9.0–98.4 months) combined. Overall survival for the total cohort was 98.7% $\pm$ 1.7% at 2 years and 92.8% $\pm$ 5.5% at 5 years. Salvage treatments were well-tolerated with two patients (11%) reporting tinnitus and one patient each (6%) reporting headaches, visual field deficits, hearing loss, anosmia, dysphagia, or memory loss.

Conclusion Refractory skull base chordomas present a challenging treatment dilemma. Repeat surgical resection or SRS seems to provide adequate salvage therapy that is well-tolerated when treated at a tertiary center offering multimodality care.

Keywords
- chordoma
- skull base
- radiation therapy
- surgery
- recurrence
- Gamma Knife

Introduction

Chordomas are slowly growing tumors arising from the embryonic remnants of the notochord that are often locally destructive with high recurrence rates.[1–3] Initial treatment is usually maximally safe surgical resection with consideration of some form of adjuvant radiotherapy. Most of the current literature supports fractionated radiation with charged particles or high-energy photons with rates of local control above 70%.[4–8] A challenge in the management of skull base

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chordomas is in the recurrent setting as previous surgical resection may have altered the anatomy of the eloquent clival region or prior radiation may have approached dose tolerances for critical structures.[9] Patients may have multiple repeated recurrences requiring various modalities of salvage treatment.

Salvage treatment options may be offered with curative intent. A recent publication by the Chordoma Global Consensus Group advocates a treatment strategy for isolated skull-base local relapses to undertake high-dose re-irradiation with or without maximal tumor resection as a first-line salvage recommendation. Other approaches including observation, debulking surgery, substandard radiation with lower doses, other local therapy (radiofrequency ablation or cryotherapy), systemic therapy, or best palliative care are reserved for those cases not amenable to salvage surgery or salvage high-dose radiation.[10]

Few studies have reported outcomes with management of locally relapsed disease with either surgery or radiation.[11–21] In the recurrent setting, stereotactic radiosurgery (SRS) is an attractive option for chordomas and other skull base tumors given its high conformality, high biologically equivalent dose, and few treatments.[22–24] At our tertiary academic medical center, we have experience treating recurrent chordomas of the skull base with either salvage re-resection or radiotherapy using Gamma Knife radiosurgery (GKRS) or CyberKnife radiosurgery (CKRS). We report our experience including overall survival, progression-free survival (PFS) after initial therapy and each salvage treatment, and incidence of neurological toxicities. In addition, we provide a review of the literature pertaining to the management of recurrent skull base chordomas.

Methods

After receiving approval from the USC Institutional Review Board (IRB), we obtained a list of patients with pathology-verified chordoma from the neurosurgery and radiation oncology departments. Complementary data were obtained from the local cancer registry. All available hospital records were reviewed including patient demographics, tumor characteristics, operative reports, radiation treatment details, and follow-up visit documentation. Initial tumor location in the clivus (upper, middle, and lower) was defined by the Sekhar classification.[25] Tumor size was measured on pretreatment imaging when available with the volume calculated as an ellipsoid of revolution with the equation volume equals XYZ dimensions multiplied by (pi/6).

All patients were diagnosed via pathologic confirmation with a biopsy or initial resection. Gross total resection (GTR), subtotal resection (STR), and tumor involvement of adjacent critical structures were determined based on operative report documentation or perioperative imaging. Patients were coded as receiving *adjuvant radiation* if this treatment was administered less than 6 months after resection. Otherwise, interventions occurring after 6 months were indicated as *salvage intent* unless documented otherwise.

All patients were contacted via phone for an IRB-approved standard interview questionnaire with verbal informed consent regarding current symptomology to assess their functional outcomes. Public registries provided date of death when available.

A Swimmer's Plot was generated to visually represent each patient case's treatment history. Kaplan–Meier curves were generated for overall survival and PFS for the total population from date of diagnosis as well as from date of initial therapies. For subsequent therapies, the PFS was the main outcome examined. Univariate analyses were performed using log-rank statistics and multivariate analyses were performed using the Cox proportional hazards model, both considering $p < 0.05$ as statistically significant. All plots and statistical analyses were generated using JMP, Version 14. SAS Institute Inc., Cary, NC, 1989–2007.

Literature Review

A literature review was conducted using the PubMed database using the Boolean search terms ("skull base chordoma" OR "clival chordoma" OR "intracranial chordoma") AND ("relapse" OR "recurrent" OR "salvage") with the filters of English language and human subjects.

Results

Initial Treatment for De Novo Skull Base Chordomas

A total of 28 patients with pathologically confirmed chordoma of the skull base were treated at the Keck Hospital of the University of Southern California from 1996 to 2018. Eighteen of these patients with initial treatment performed at our institution and who had recurrent/progressive disease were included for retrospective review (►**Fig. 1**). The median age was 41 years with a range of 16 to 64. The median follow-up was 98.6 months with a range of 16 to 215 months. Patient demographics, initial tumor characteristics, and treatment details are summarized in ►**Table 1** with analysis of median PFS and 1-year PFS for each variable. Age under 40 years was statistically significant for worse PFS with a median of 7.7 months (95% CI: 1.5, 18.6) compared with 24.9 months (95% CI: 1.1, 33.2) for age over 40 years patients ($p = 0.03$). ►**Fig. 2** contains Kaplan–Meier curves from time of initial diagnosis representing the entire study. All patients in this selected cohort had locally recurrent disease with a median PFS of 17.7 months (95% CI: 4.9, 22.6). Median overall survival was not reached, but 1-year, 2-year, and 5-year estimates were all above 90%. A total of six patients died in our cohort. One patient died of local progression of tumor causing brainstem herniation. One patient died of stroke, unrelated to disease progression or treatment complication. Four patients died outside of our institution, with dates of death obtained from public records. A Swimmer's Plot shows a visual representation of all treatments received by this population in ►**Fig. 3**. A Venn Diagram shows the types of salvage therapies in ►**Fig. 4**.

Salvage Surgery for Locally Recurrent Skull Base Chordomas

Eleven patients underwent 15 salvage surgery procedures for locally recurrent disease. All failures were within the skull base. ►**Table 2** shows a summary of each salvage surgery treatment. Three operations were followed by adjuvant radiation. Only two

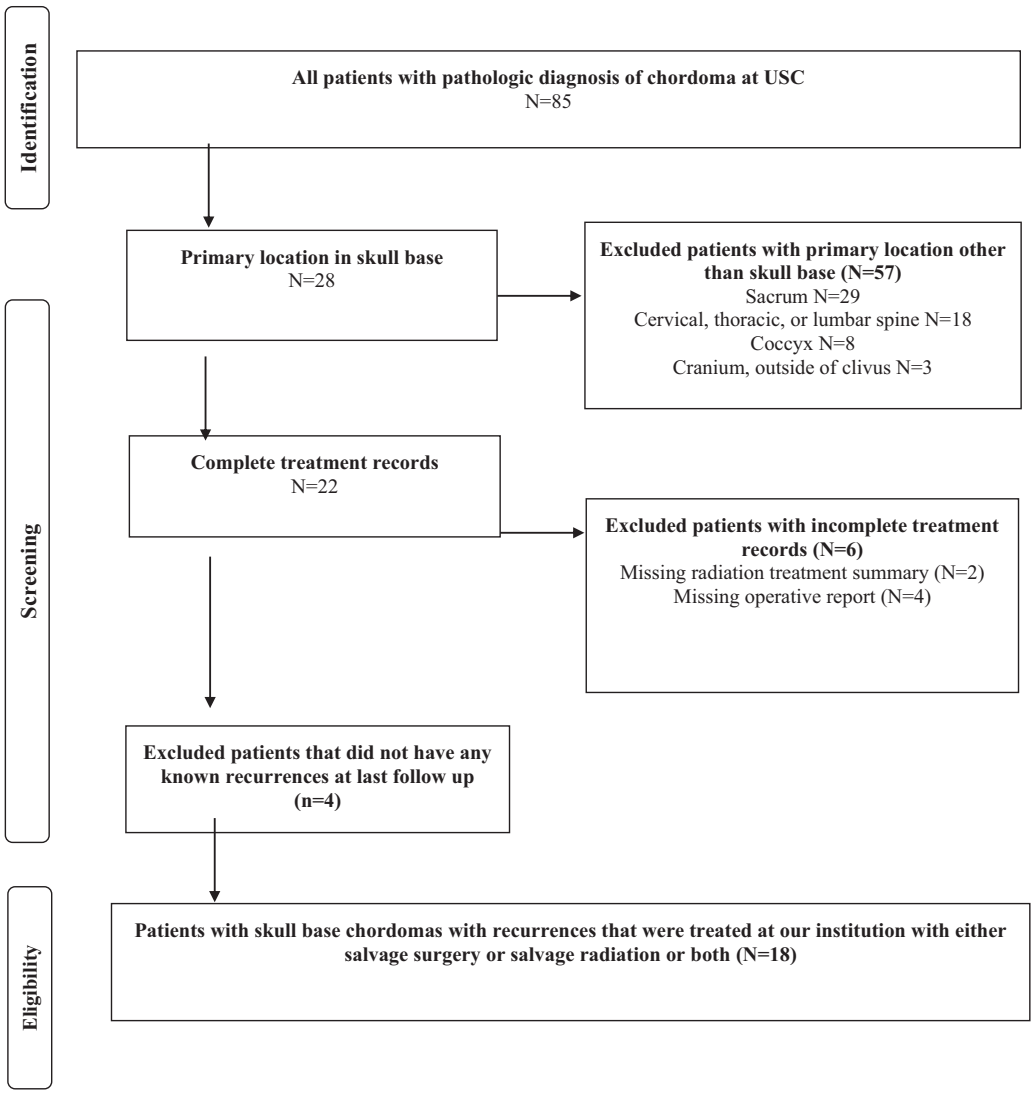


Fig. 1 Consort diagram representing selection and screening of patient cohort.

operations achieved GTR. Surgical technique included: endonasal ($N = 6$) or craniotomy ($N = 9$). Operative reports detailed abutment or invasion of critical structures during the procedure, including the cavernous sinus ($N = 3$), foramen magnum ($N = 3$), sphenoid sinus ($N = 3$), and jugular foramen ($N = 3$). Median tumor volume was 18.9 cm^3 (range 1.0–45.4). For this cohort, median PFS from time of surgical resection was 59.2 months (95% CI: 4.0, 99.3 months), 2-year PFS was 54.5% ± 10.7%, and 5-year PFS was 35.3% ± 11.2% (►**Fig. 5A**). On univariate linear regression, larger tumor volume was statistically significant for shorter PFS ($p = 0.02$), but was not significant on multivariate analysis with backward elimination when patient gender, age, surgical technique, and adjuvant radiation were included. Five patients had another recurrence after salvage surgery while seven had stable disease until death or follow-up.

Salvage Radiation Treatment for Locally Recurrent Skull Base Chordomas

►**Table 3** details the 16 radiotherapy courses underwent by 12 patients for local recurrence. All sites of failure occurred within the skull base. GKRS was the most common modality utilized ($N = 9$) followed by CKRS ($N = 5$) and intensity-modulated radiation therapy ($N = 2$). The median GKRS dose was 16 Gy (range 16–20 Gy) prescribed to the 50% isodose line (IDL). Median tumor volume was 2.9 cm^3 (range 0.48–16.1). Median PFS from time of salvage radiotherapy was 58.4 months (95% CI: 25.9–194.5 months), 2-year PFS was 93.6% ± 5.5%, and 5-year PFS was 61.2% ± 12.4% (►**Fig. 5B**). No prognostic factors, including gender, age, surgery followed by adjuvant radiation, i.e., SRT (surgery followed by adjuvant radiation) versus RT alone, tumor volume, or radiation dose were significant for PFS on univariate analysis. Six patients who underwent salvage radiotherapy ultimately developed additional recurrence, and 10 salvaged RT patients remained stable until death or follow-up. A log-rank test comparison of salvage surgery versus salvage radiotherapy was not statistically significant for PFS ($p = 0.33$). For all salvage treatments, including surgery and radiation, the median PFS was 58.4 months (95% CI: 25.9.0–98.4 months), 2-year PFS was 60.6% ± 8.1%, and 5-year PFS was 40.6% ± 9.2% (►**Fig. 5C**) from time of salvage treatment.

Table 1 Progression-free survival after initial treatment for total population

	N	Median PFS in months (95% CI)	1-year probability of PFS	*p*-Value
Total	18 (100%)	17.7 (4.9, 22.6)	51.1% ± 8.1%	
Gender				0.36
Male	7 (38.9%)	20.7 (1.5, 33.2)	56.9% ± 12.1%	
Female	11 (61.1%)	17.1 (3.4, 22.6)	46.6% ± 10.7%	
Age at diagnosis				0.028[a]
Age < 40	8 (44.4%)	7.7 (1.5, 18.6)	31.3% ± 12.9%	
Age ≥ 40	10 (55.6%)	24.9 (1.1, 33.2)	60.6% ± 9.6%	
Tumor location in clivus				0.44
Upper	9 (50%)	17.1 (4.0, 20.8)	43.2% ± 12.1%	
Middle	3 (16.7%)	29.0 (6.3, 33.2)	59.1% ± 17.9%	
Lower	6 (33.3%)	13.0 (1.1, 52.5)	56.1% ± 13.2%	
Presenting symptoms				
Visual changes, including diplopia	6 (33.3%)	12.7 (4.0, 29.8)	46.6% ± 14.5%	0.56
Cranial neuropathy, including V, VIII, X, XII	6 (33.3%)	20.4 (1.1, 43.6)	55.5% ± 13.3%	0.71
Headaches	2 (11.1%)	35.6 (18.6, 52.5)	71.% ± 17.0%	–
Neck pain	2 (11.1%)	4.3 (1.5, 7.2)	6.5% ± 12.5%	–
Nasal obstruction	1 (5.6%)	4.9	8.7% ± 21.4%	–
Abutment or involvement of neighboring structures				
Brainstem	5 (27.8%)	4.0 (1.5, 29.8)	27.0% ± 15.8%	0.11
Cavernous sinus	3 (16.7%)	33.2 (7.2, 43.6)	65.2% ± 16.1%	0.27
Sphenoid sinus	7 (38.9%)	8.2 (4.9, 29.0)	44.4% ± 13.6%	0.45
Sella turcica	2 (11.1%)	34.8 (17.1, 52.5)	70.8% ± 17.2%	–
Initial treatment				0.97
Surgery	11 (61.1%)	18.2 (4.0, 29.0)	52.9% ± 10.2%	
Surgery with adjuvant radiation	7 (38.9%)	6.3 (1.1, 29.8)	48.1% ± 13.3%	
Initial surgery resection				0.87
GTR	3 (16.7%)	18.2 (8.2, 29.0)	52.2% ± 19.6%	
STR	15 (83.3%)	17.1 (3.3, 22.6)	50.9% ± 8.9%	
Initial radiation characteristics				
GKRS	5 (71.4%)	6.3 (1.1, 29.8)	37.3% ± 16.5%	
IMRT	1 (14.3%)	1.5	0.04% ± 0.3%	
Protons	1 (14.3%)	52.5	79.6% ± 18.2%	

Abbreviations: CI, confidence interval; GKRS, gamma knife radiosurgery; GTR, gross total resection; IMRT, intensity-modulated radiation therapy; PFS, progression-free survival.
[a]Denotes statistical significance with univariate log-rank test.

Phone Interview Follow-Up

Eight out of 12 living patients were available and provided informed consent. Their results are summarized in ►**Table 4**. Tinnitus was reported by two patients, while headaches, visual field deficits, hearing loss, anosmia, dysphagia, and memory loss had a frequency of one patient.

Representative Case of a Patient with Four Courses of Treatment

A 48-year-old woman presented with 3 weeks of acute-onset diplopia with magnetic resonance imaging of the brain revealing an erosive lesion involving the mid clivus, extending into the sphenoid sinus with abutment of the brainstem at the level of the pons. Shortly after her diagnosis, she underwent endoscopic endonasal transsphenoidal approach for STR, with microdissection and fat graft to the tumor bed. She received adjuvant radiation 4 months after her surgery with GKRS 15 Gy prescribed to the 50% IDL to a residual tumor volume of 3.1 cm^3 utilizing seven shots. She recurred after 25 months with a 1-cm suprasellar mass arising from the dorsum sellae and underwent a second course of GKRS with a dose of 16 Gy prescribed to the 50% IDL to a tumor

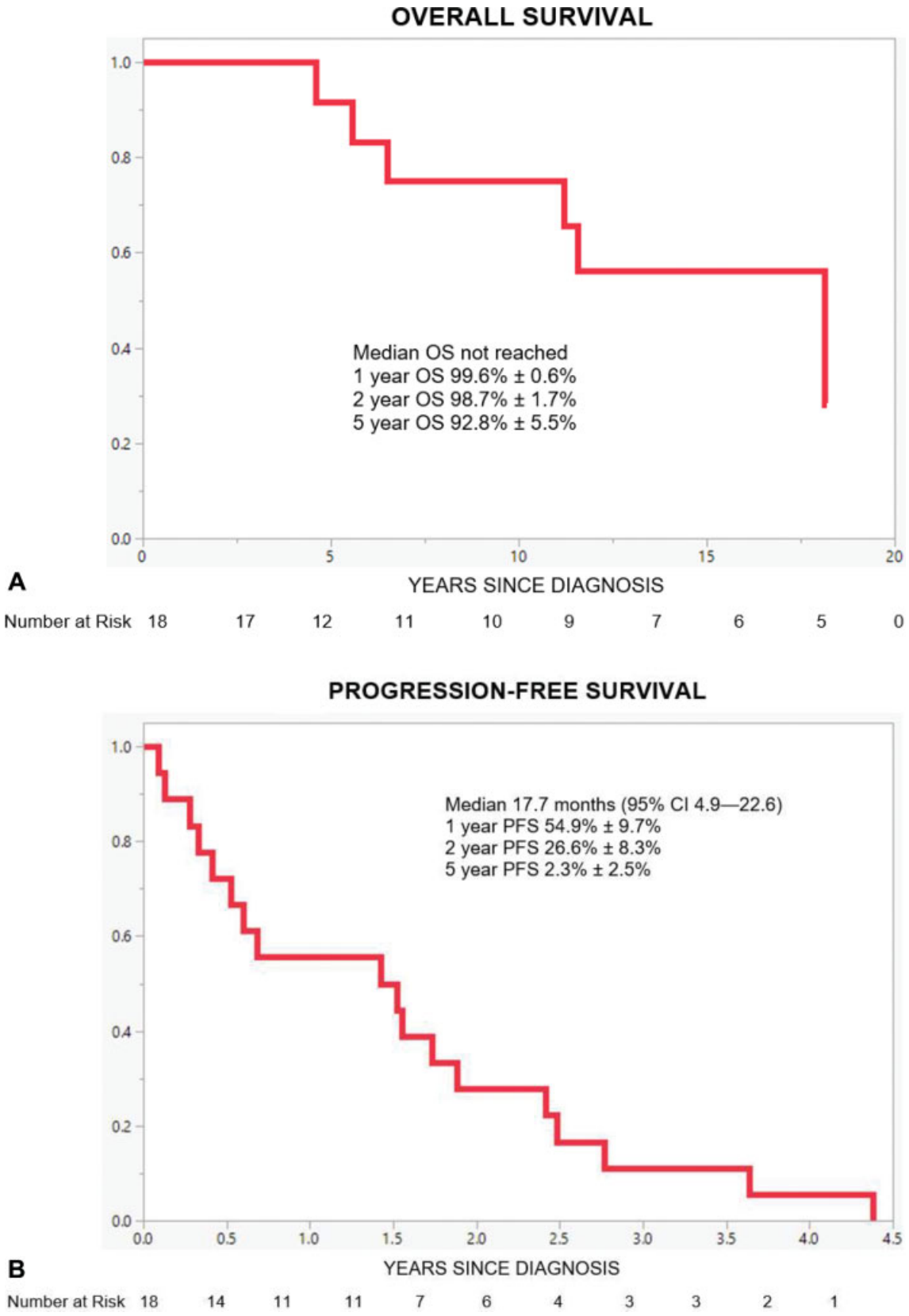
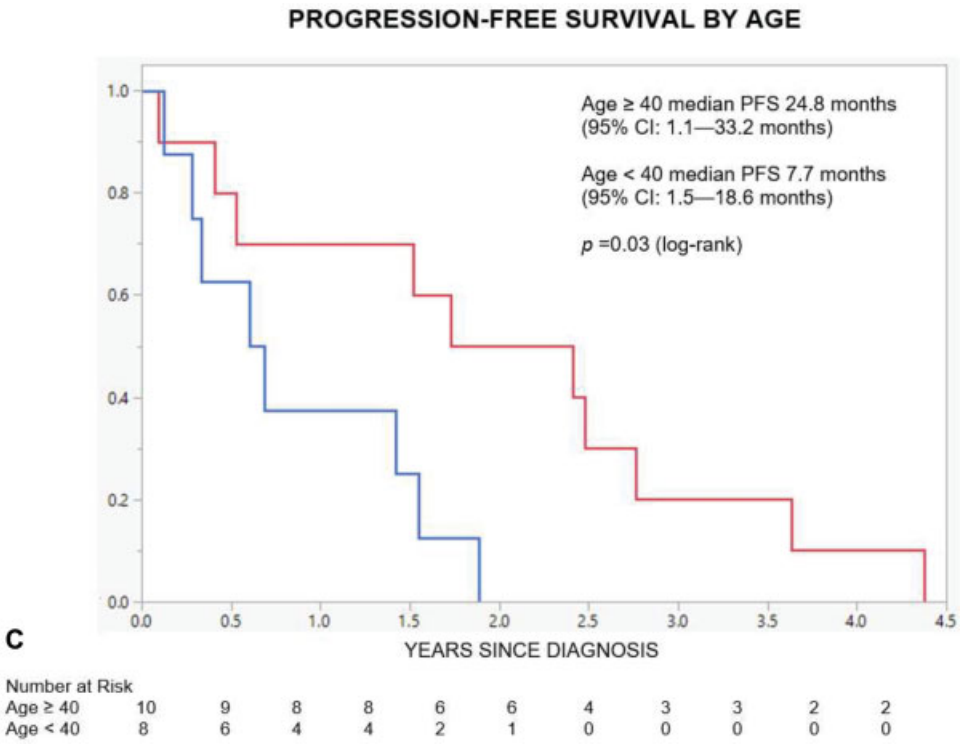


Fig. 2 Kaplan–Meier curves for overall survival and progression-free survival for total population. (**A**) Overall survival from time of diagnosis with median not reached in this population, 1-year overall survival 99.6% ± 0.6%, 2-year overall survival 98.7% ± 1.7%, 5-year overall survival 92.8% ± 5.5%. (**B**) Progression-free survival from time of diagnosis to first progression with median of 17.7 months (95% CI: 4.9–22.6 months), 1-year PFS 54.9% ± 9.7%, 2-year local control 26.6% ± 8.3%, 5-year PFS 2.3% ± 2.5%. (**C**) Age ≥ 40 has longer PFS (median 24.8 months, 95% CI: 1.1–33.2 months) compared with age < 40 (median 7.7 months, 95% CI: 1.5–18.6 months) with $p = 0.03$. CI, confidence interval; PFS, progression-free survival.



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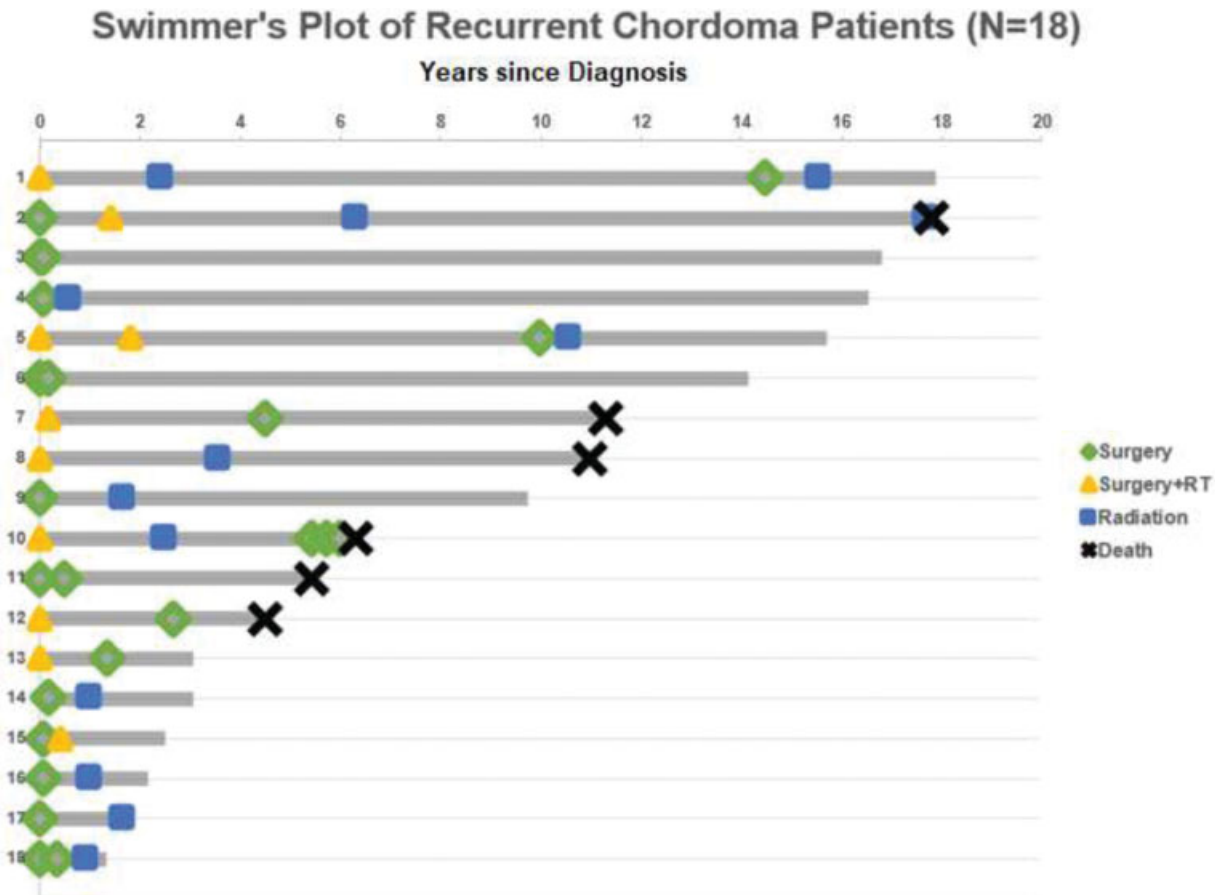

Fig. 3 Swimmer's plot of Individual chordoma patients. Bar length indicates duration of follow-up shown in months after time of initial diagnosis. X marks time point of death while others denote interventions (diamond = surgery alone, triangle = surgery followed by adjuvant radiation, square = radiation alone).

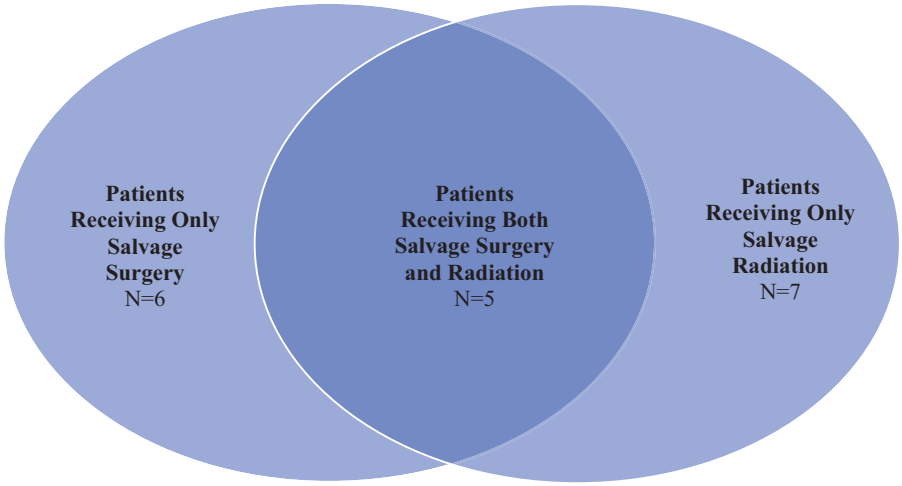

Fig. 4 Venn-diagram of salvage treatments for total cohort.

volume of 1.9 cm^3 utilizing nine shots. She recurred again after 25.9 months with a left-sided clival mass that surrounds the internal carotid artery and underwent her second surgery, achieving a GTR with an extended endoscopic endonasal transclival approach. Unfortunately, she had a third local recurrence 12.8 months after this surgery with progressive growth of a left-sided lesion in the postoperative bed (9 by 8 mm to 15 by 11 mm in 12 months) and received a third course of GKRS of 18 Gy prescribed to the 50% IDL to a tumor volume of 1.09 cm^3 utilizing 15 shots. She remained stable with surveillance imaging follow-up 147.5 months after her last GKRS (215 months after her initial diagnosis). This patient is represented as case number 1 in ►**Tables 2** and **3**.

Literature Review

Excluding review articles and abstracts, a total of 64 peer-reviewed publications were identified and examined. Of these, 29 articles only reported experience with initial management after diagnosis and 24 studies included salvage treatments without reporting outcomes for the recurrent subpopulation. The details of the remaining 11 articles regarding salvage therapy for skull base chordomas are summarized in ►**Table 5**.[11–21]

Discussion

Locally recurrent skull base chordomas present a challenging treatment dilemma due to considerations such as postoperative changes (e.g., scar tissue, adhesions, or friable anatomy) or radiation dose constraints from prior therapies. In our report, we had reasonable overall survival outcomes despite multiple recurrences due to effective salvage therapies. Median PFS after surgical re-resection or radiotherapy treatments was comparable to those reported in literature (►**Table 5**).

Our initial PFS was low in our population, but this is largely due to selection bias as we only included patients who experienced recurrences. Our median PFS of 17.7 months was in fact comparable to or longer than other reports that included only relapsed patients.[11,18] On univariate analysis, older patients had better PFS, which is incongruent with some studies which showed younger age is usually a positive prognostic factor.[20,26–28] However, some publications showed no correlation with age[11,29–31] while others showed older age had better outcomes.[32,33] In our analysis, this correlation did not stay significant on multivariate analysis and may be due to other confounding factors in our population. It is also difficult to make definitive conclusions with such small numbers.

For patients treated with salvage surgical re-resection, larger tumor volume was associated with worse PFS. Many other studies showed the same correlation.[26,28,34,35] Larger tumor sizes may lead to more complicated and difficult surgeries, more likelihood of proximity to eloquent structures, and suboptimal debulking. This correlation was not seen with radiotherapy, likely due to the selection bias for smaller tumors when delivering SRS. The sample size of our cohort is too small to make any conclusions regarding the comparison of these treatment modalities. In our multidisciplinary practice, the decision for either modality is usually informed by tumor size and location with SRS usually reserved for those smaller tumors with adequate distance from critical structures, and surgical resection recommended for more technically challenging lesions.

Our cohort experienced mild or no long-term toxicity, in line with other experiences using SRS.[13,15] More detailed treatment information such as overlapping fields, elapsed time between treatments, total biological equivalent dose, and concurrent use of systemic therapies is needed before making assumptions regarding dose response for toxicity.

The limitations of this study include its small cohort, retrospective nature, and lack of consistent long-term follow-up. Given that many patients had treatments that spanned several decades, there is heterogeneity in delivered therapies due to changing philosophies and techniques. Some older treatments had incomplete data due to inadequate electronic record keeping. Incomplete follow-up after benign diseases compared with malignant pathologies has

Table 2 Summary of salvage surgical treatments for locally recurrent skull base chordomas

Case #	Gender	Age at time of surgery	S vs. SRT	Prior Tx	Tumor volume (cm^3)	Volume comparison	GTR vs. STR	Surgery technique	Abutment of structures	Outcome	Location of recurrence	Toxicity
1	F	63	S	SRT, RT	1.7	Smaller than initial disease	STR	Endonasal	Cavernous sinus	Recurred after 12.8 mo	Within high dose region (50% IDL)	
2	F	64	SRT	S, SRT	N/A		STR	Endonasal	Sphenoid sinus	Received adjuvant radiation at 0.8 mo, then recurred at 59.2 mo	Within high dose region (50% IDL)	
3	M	31	S	S	N/A		STR	Craniotomy	Foramen magnum	Stable at last follow-up (204.1 mo)		
5a	F	35	SRT	SRT	N/A		STR	Craniotomy	Temporal lobe, cavernous sinus	Received adjuvant radiation at 4.6 mo, then recurred at 99.3 mo	Within and extending beyond high dose region (50% IDL)	Headaches
5b	F	43	S	SRT, SRT	23.6	Larger than previous disease	GTR	Craniotomy	Temporal lobe	Recurred after 5.7 mo	Within high dose region (50% IDL)	Headaches
6	F	42	S	S	17.0	Smaller than initial disease	GTR	Endonasal	Foramen magnum	Stable at last follow-up (170.3 mo)		Tinnitus, anosmia
7	M	46	S	S	7.9	Smaller than initial disease	STR	Craniotomy	Foramen ovale	Death after 83.7 mo		
10a	M	49	S	SRT, RT	18.0	Smaller than initial disease	STR	Craniotomy	Sphenoid sinus, facial nerve	Recurred after 4.0 mo	Within and extending beyond high dose region (50% IDL)	
10b	M	49	S	SRT, RT, S	24.3	Larger than previous disease	STR	Endonasal	Jugular foramen	Recurred after 2.2 mo	Within high dose region (50% IDL)	
10c	M	49	S	SRT, RT, S, S	19.5	Smaller than previous disease	STR	Craniotomy	Jugular foramen, internal auditory canal	Recurred after 2.2 mo	Within high dose region (50% IDL)	
11	F	59	S	S	N/A		STR	Craniotomy	Optic chiasm, left optic canal	Death after 4.2 mo		
12	M	67	S	S	20.9	Larger than initial disease	STR	Endonasal	Sphenoid sinus, cavernous sinus	Death after 60.3 mo		
13	F	34	S	SRT	3.2	Smaller than initial disease	STR	Craniotomy	Sella turcica	Death after 22.2 mo		
15	M	30	SRT	S	1.0	Smaller than initial disease	STR	Endonasal	None	Received adjuvant radiation at 3.8 mo and stable at last follow-up (25.3 mo)		
18	F	36	S	S	45.0	Larger than initial disease	STR	Craniotomy	Foramen magnum, jugular foramen	Recurred after 2.2 mo	Within and extending beyond initial area of disease	Tinnitus, dysphagia

Abbreviations: F, female; GTR, gross total resection; M, male; N/A, not available; RT, radiation; S, surgery; SRT, surgery and adjuvant radiation; STR, subtotal resection.

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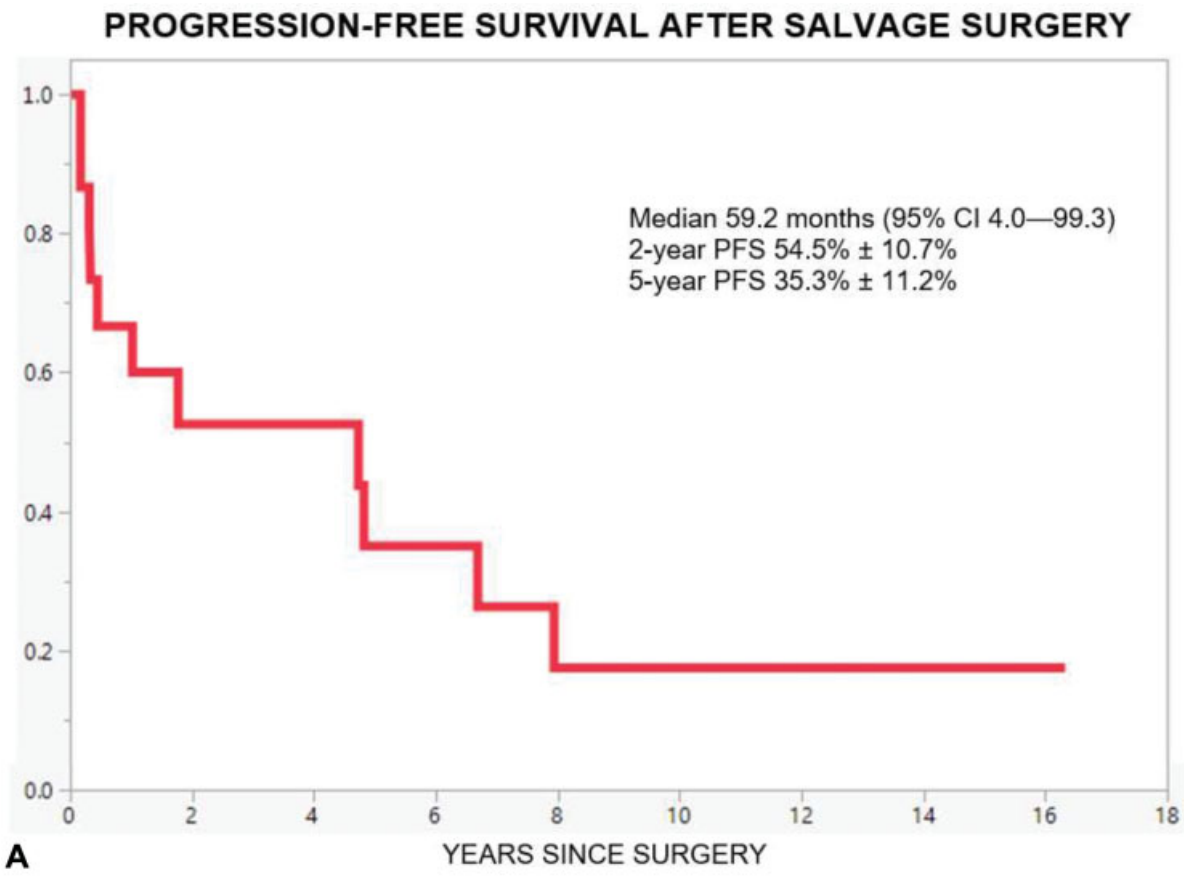

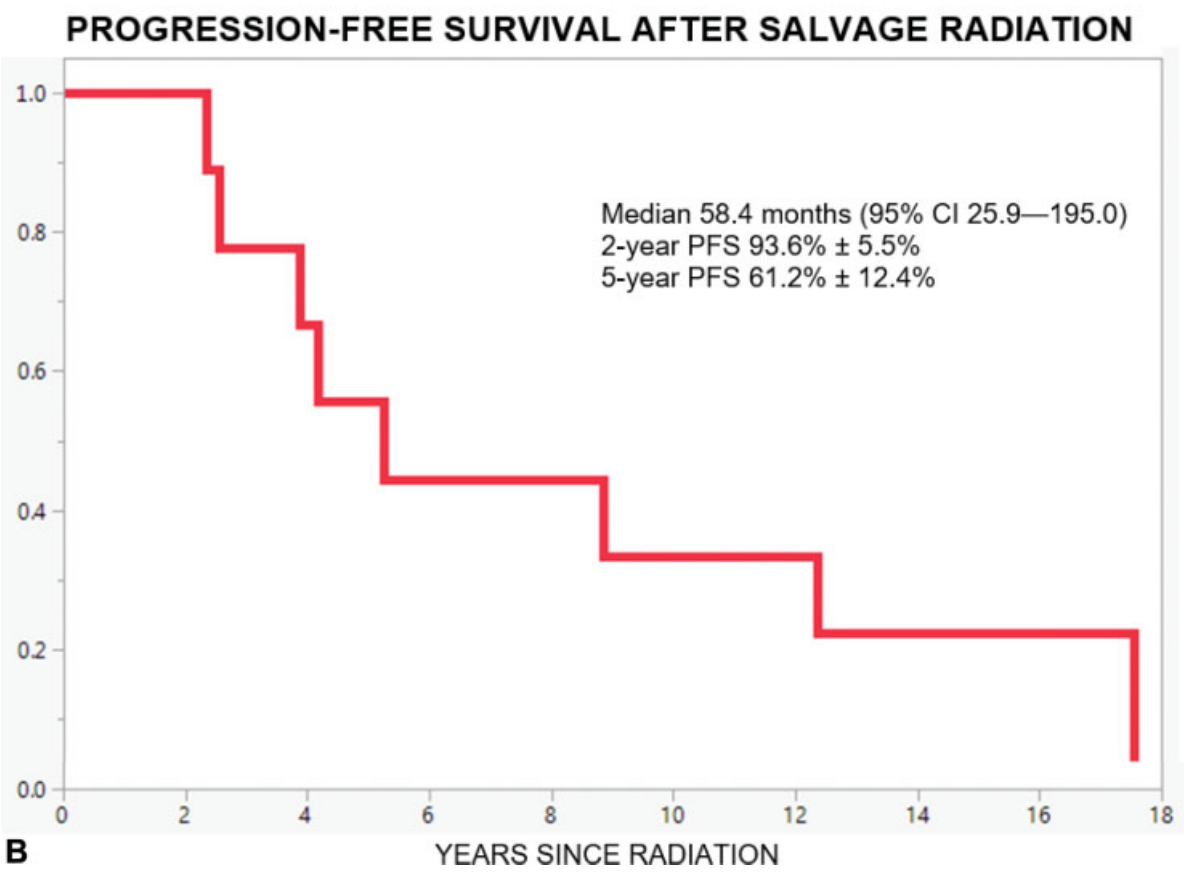

Fig. 5 Kaplan–Meier plots for salvage treatments for locally recurrent skull base chordomas. (**A**) PFS for Salvage Surgery Treatments. (**B**) PFS for salvage radiation treatments. (**C**) Combined PFS. PFS, progression-free survival.

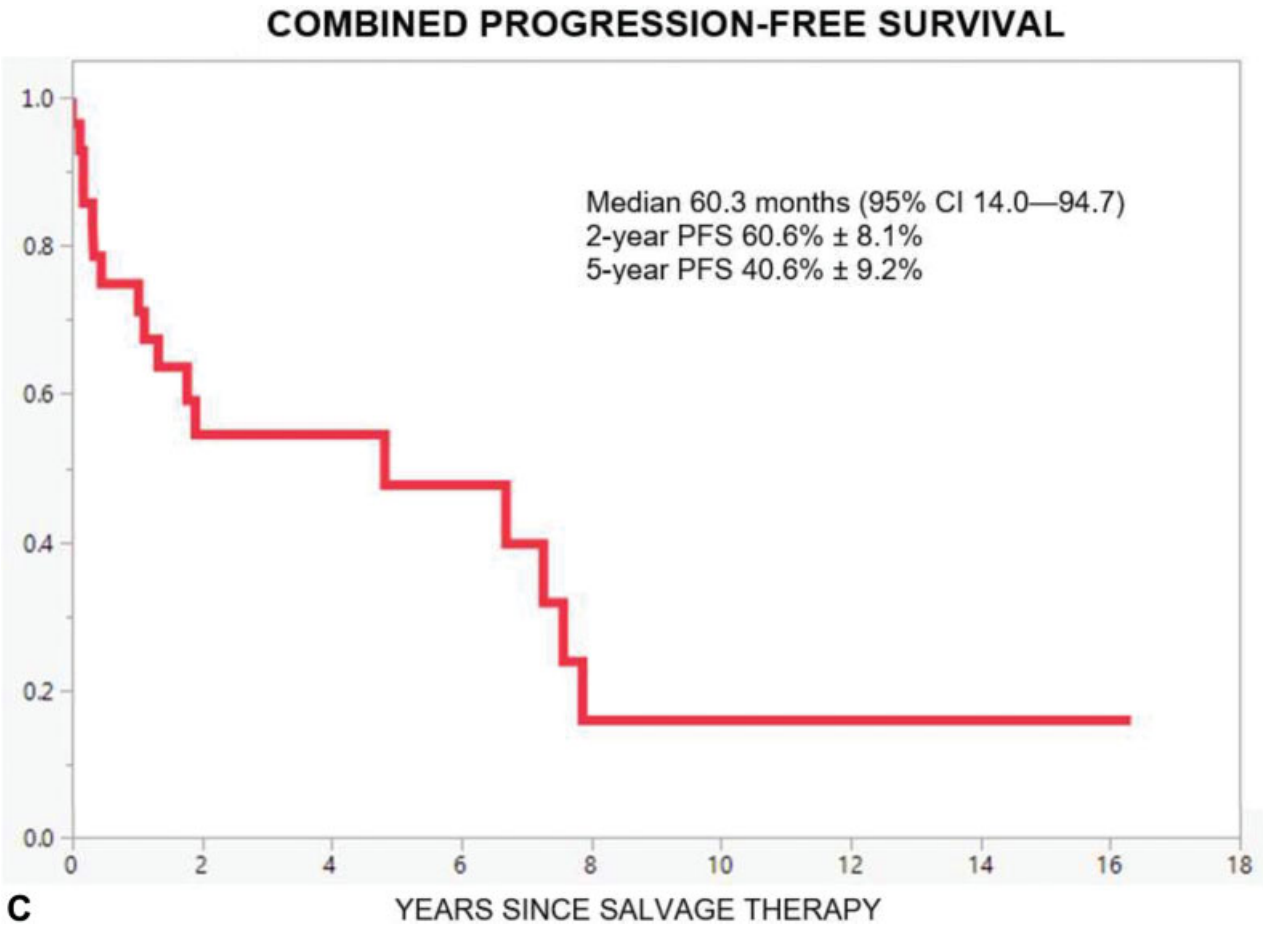

Fig. 5 (*Continued*)

previously been documented and proved true in our study.[36] The phone interviews were conducted to compensate for lack of clinic visits, but most patients were unavailable or had expired, and those who answered may be affected by some degree of recall bias. Four patients died outside of our institution, and data on their survival were obtained from public registries, which do not provide the cause of death. Whether the deaths were due to tumor progression or treatment complications would have provided useful insight into our experience with salvage therapies. Due to the benign nature of this disease, there was a general lack of consistent follow-up among patients, and perhaps suggests a need for better patient education regarding the high recurrence rates of chordomas and potential need for additional salvage therapies.

In our review of the current literature on recurrent skull base chordomas, we found reports of other institutions using a wide array of surgical or radiation treatment strategies. Fagundes et al from Harvard University published the earliest report of a large cohort of 45 patients with recurrent skull base chordomas, of which the majority received surgical salvage with GTR only achieved in two patients and a short median interval to progression of 7 months.[11] Of note, none of these patients received reirradiation. Other reports of primarily surgical salvage using a variety of techniques, including micro-surgical, midline anterior, lateral, and endoscopic approaches, had recurrence rates ranging from 39 to 81%.[12,14,19] Radiation techniques for salvage therapies included GKRS, CKRS, proton therapy, carbon ion therapy, and LINAC-based SRS with recurrence rates ranging from 36 to 85%.[13,15,17,18,20] Bugoci et al from Kaiser, Los Angeles described novel therapy using molecular targets, including agents such as Gleevec and Dasatinib, with two out of three patients alive with stable disease after at least 30 months of therapy.[16] Attempts for meaningful comparisons between these different treatment algorithms are limited due to differences in patient population, tumor characteristics, and reported outcome measures. In general, these cases are challenging and require a multidisciplinary approach with careful and realistic consideration of the limitations of each available modality.

Conclusion

Our report provides detailed information on salvage surgical or radiation treatment for recurrent/progressive skull base chordomas. This experience, combined with a rigorous literature review, supports the use of salvage therapies with re-resection or high-dose radiation, particularly SRS, as feasible strategies with reasonable outcomes and minimal toxicities when treated at tertiary academic centers.

Table 3 Summary of radiation treatments for locally recurrent skull base chordomas

Case #	Gender	Age at time of RT	Salvage SRT vs. RT	Prior Tx	Tumor volume (cm^3)	Volume comparison	Modality	Salvage prescription	Outcome	Location of recurrence	Toxicity
1a	F	51	RT	SRT	1.9	Smaller than initial disease	GKRS	16 Gy to 50% IDL	Recurred after 25.9 mo	Within high dose region (50% IDL)	Visual field deficits, hearing loss
1b	F	64	RT	SRT, RT, S	1.1	Smaller than previous disease	GKRS	18 Gy to 50% IDL	Stable at last follow-up (147.5 mo)		
2a	F	65	SRT	S	3.2	Smaller than previous disease	GKRS	18 Gy to 50% IDL	Recurred after 28.3 mo	Within and extending beyond high dose region (50% IDL)	
2b	F	69	RT	S, SRT	9	Larger than previous disease	GKRS	16 Gy to 50% IDL	Recurred at 58.4 mo	Within high dose region (50% IDL)	
2c	F	81	RT	S, SRT, RT	9.2	Larger than previous disease	GKRS	16 Gy to 50% IDL	Death after 137.4 mo		
4	F	16	RT	S	8.3	Smaller than initial disease	GKRS	16 Gy to 50% IDL	Stable at last follow-up (1.5 mo)		
5a	F	36	SRT	SRT	11.5	Larger than initial disease	CKRS	24 Gy in 3fx	Recurred after 18.9 mo	Within high dose region (50% IDL)	Headaches
5b	F	44	RT	SRT, SRT, S	0.82	Smaller than previous disease	GKRS	16 Gy to 50% IDL	Stable at last follow-up (94.7 mo)		Headaches
8	F	49	RT	SRT	16.1	Larger than previous disease	CKRS	27 Gy in 5fx to 80% IDL	Death after 42.9 mo		
9	F	34	RT	S	15.0	Smaller than previous disease	IMRT	54 Gy in 30fx	Recurred after 90.9 mo	Adjacent to 70% IDL volume	
10	M	46	RT	SRT	N/A		CKRS	N/A	Recurred after 23.8 mo	Within high dose region (50% IDL)	
14	M	36	RT	S	0.47	Smaller than initial disease	CKRS	35 Gy in 5fx to 88% IDL	Stable at last follow-up (16.6 mo)		
15	M	30	SRT	S	1.2	Smaller than initial disease	GKRS	16 Gy to 50% IDL	Stable at last follow-up (25.4 mo)		
16	F	46	RT	S	2.7	Smaller than initial disease	CKRS	18 Gy in 3fx to 80% IDL	Stable at last follow-up (21.5 mo)		
17	M	42	RT	S	1.6	Larger than initial disease	GKRS	20 Gy to 50% IDL	Stable at last follow-up (14.0 mo)		
18	F	36	RT	S	6.0	Smaller than initial disease	IMRT	50 Gy in 25fx followed by 25 Gy in 5fx SBRT boost	Stable at last follow-up (1 mo)		Tinnitus, dysphagia

Abbreviations: CKRS, cyber knife radiosurgery; F, female; GKRS, gamma knife radiosurgery; IDL, isodose line; IMRT, intensity-modulated radiation therapy; M, male; RT, radiation; S, surgery; SBRT, stereotactic body radiotherapy; SRT, surgery followed by adjuvant radiation.

Table 4 Summary of phone interviews

Symptom	*N*	%
Headaches	1	12.5
Visual field deficits	1	12.5
Blurry vision	0	0
Hearing loss	1	12.5
Tinnitus	2	25
Anosmia	1	12.5
Dysgeusia	0	0
Dysphasia	0	0
Dysphagia	1	12.5
Ambulatory difficulty	0	0
Seizures	0	0
Episodes of loss of consciousness	0	0
Memory loss	1	12.5
Total available for phone interview	*8*	

Note: A total of 8 out of 12 living patients were available for phone interview. After giving informed consent, the patients answered questions regarding their current symptoms.

Table 5 Literature review of reported outcomes on locally recurrent skull base chordomas

Reference	*N*	Initial treatment modality	Salvage treatment modality	Salvage treatment details	Outcomes specific to recurrent population	Toxicity
Fagundes et al, IJROBP (Harvard)	$N = 45$ (Skull base) $N = 18$ (Cervical spine)	S + RT (PBRT)	Mostly S	STR ($N = 44$) GTR ($N = 2$) RT alone ($N = 1$) Chemotherapy alone ($N = 1$) CRT ($N = 1$)	Median interval to progression = 7 mo (range 4–50) 2-y OS 63% 5-y OS 6%	Not reported for the subset of recurrent population
Tzortzidis et al, Neurosurgery (University of Washington)	$N = 27$	S ± RT	S	Aggressive microsurgical resection	3-y RFS 41%, 5-y RFS 39%, 10-y RFS 26%	Not reported for the subset of recurrent population
Ito et al, Acta Neurochir (Japan)	$N = 11$	S + RT (GKRS)	S or RT	S ($N = 5$) GKRS ($N = 21$) with mean marginal dose 17.8 Gy Novalis ($N = 1$)	All tumors well-controlled during follow-up mean of 71.2 mo, range 25–148 mo	None
Sen et al, J Neurosurg (Mount Sinai)	$N = 23$	S ± RT	S	Midline anterior approach ($N = 5$), lateral approach ($N = 13$), combined ($N = 5$)	5-y recurrence rate 81%	Not reported for the subset of recurrent population
Jiang et al, J Clin Neurosci (Stanford)	$N = 9$	S + RT (PBRT or IMRT)	RT	CKRS ($N = 9$) with mean marginal dose 32.5 Gy	28.6% had stable or improved outcomes	None
Bugoci et al AJCO (Kaiser, Los Angeles)	$N = 5$	S + RT (FSRT)	S or molecular targeted therapy	SRS 18 Gy, surgery 9 mo after ($N = 1$) Surgery ($N = 1$) Gleevec ($N = 2$) Dasatinib ($N = 1$)	3 alive with stable disease, 1 alive with disease progression after RT, 1 died of disease Overall survival range 32–90.3 mo after initial RT	Not reported for the subset of recurrent population
McDonald et al, IJROBP, (Indiana University)	$N = 16$	S + RT	RT	Proton therapy with mean dose 75.6 Gy RBE (range 71.2–79.2 Gy)	2-y LC 85%, 2-y OS 80%	G3 bitemporal lobe radionecrosis ($N = 1$) G4 CSF leak ($N = 1$) G4 brainstem stroke ($N = 1$)

Table 5 (*Continued*)

Reference	*N*	Initial treatment modality	Salvage treatment modality	Salvage treatment details	Outcomes specific to recurrent population	Toxicity
Uhl et al (University of Heidelberg, Germany)	$N = 20$ (chordoma) $N = 5$ (chondrosarcoma)	S + RT	RT	Carbon ion therapy, median dose 51 GyE (range 45–60 GyE)	2-y LPFS 79.3% 1 relapse for chondrosarcoma, 5 relapses for chordomas	G1 temporal lobe reaction ($N = 5$) G2 mucositis ($N = 1$) G2 hypacusis ($N = 3$) G3 osteoradionecrosis ($N = 1$)
Chibbaro et al, Neurosurg Rev (France)	$N = 22$	S ± RT	S	Endoscopic endonasal approach with GTR ($N = 7$) or STR (15)	4 (11%) had recurrence, 4 (11%) had progression with mean follow-up of 32 mo	Death due to bleeding aneurysm ($N = 1$) Moderate CSF leakage ($N = 4$) Meningitis ($N = 8$)
Choy et al, J of Neurosurg (UCLA)	$N = 26$	N/A	S ± RT	Adjuvant SRS or SRT using 6-MV Novalis LINAC	1-y PFS 72.9% with adjuvant RT, 74% without adjuvant RT 5-y PFS 36.5% with adjuvant RT and 23.5% without adjuvant RT	Not reported for the subset of recurrent population
Vasudevan et al, Front Surg (UCSF)	$N = 5$	S + RT (PBRT, FSRT)	RT	FSRT ($N = 5$) with median dose 37.5 Gy in 5 fractions Surgery ($N = 1$)	All significant events occurred within 1 y following FSRT	Not reported for the subset of recurrent population

Abbreviations: CKRS, cyber knife radiosurgery; CRT, chemotherapy and radiation; CSF, cerebrospinal fluid; FSRT, fractionated stereotactic radiation therapy; GKRS, gamma knife radiosurgery; GTR, gross total resection; IMRT, intensity-modulated radiation therapy; LC, local control; LINAC, linear accelerator; LPFS, local progression-free survival; OS, overall survival; PBRT, proton beam radiotherapy; PFS, progression-free survival; RBE, relative biological effectiveness; RFS, recurrence free survival; RT, radiation; S, surgical resection; SRS, stereotactic radiosurgery; SRT, surgery followed by adjuvant radiation; STR, subtotal resection; USC, University of Southern California.

Conflict of Interest
E.L.C. reports other from Brainlab, outside the submitted work.

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