Treatment and Outcome of Patients with Skull Base Chordoma: A Meta-analysis

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Abstract

Objective Chordoma is a locally aggressive tumor. The aim of this study was to assess the efficacy of different surgical approaches and adjuvant radiation modalities used to treat these patients.

Design Meta-analysis.

Main Outcome Measures Overall survival (OS), disease-specific survival (DSS), and progression-free survival (PFS).

Results The 5-year OS and PFS rates of the whole cohort ($n = 467$) were 86% and 65.7%, respectively. The 5-year DSS for patients who underwent open surgery and endoscopic surgery was 45% and 49%, respectively ($p = 0.8$); PFS was 94% and 79%, respectively ($p = 0.11$). The 5-year OS of patients treated with surgery followed by adjuvant radiotherapy was 90% compared with 70% of those treated by surgery alone ($p = 0.24$). Patients undergoing partial resection without adjuvant radiotherapy had a 5-year OS of 41% and a DSS of 45%, significantly lower than in the total-resection group ($p = 0.0002$ and $p = 0.01$, respectively). The complication rates were similar in the open and endoscopic groups.

Conclusions Patients undergoing total resection have the best outcome; adjuvant radiation therapy improves the survival of patients undergoing partial resection. In view of the advantages of minimally invasive techniques, endoscopic surgery appears an appropriate surgical approach for this disease.

Keywords

- skull base
- chordoma
- adjuvant
- meta-analysis
- endoscopic

Introduction

Chordoma is a locally aggressive tumor that arises from the embryonic notochord remnant. Population-based studies using the Surveillance, Epidemiology and End Results database suggest an incidence of chordoma of 8.4 per 10^6 population, with a median survival of 7.7 years.¹ Although chordomas of the clivus account for a third of all chordoma, they represent only 0.1% of skull base malignancies, making their study in the clinical setting very difficult.² Local recurrence is the most important predictor of mortality in these

patients; therefore total resection (TR) with or without adjuvant radiation therapy is considered the mainstay of treatment.³ Surgery for clival chordoma is challenging because infiltration to the surrounding neurovascular structures is common, and deterioration of quality of life may be considerable.^{4–6}

Chordoma have traditionally been resected by an open craniotomy or by the microscopic transsphenoidal approach. The recent development of endoscopic skull base surgery has revolutionized treatment by enabling resection of clival chordomas by minimally invasive techniques, preserving

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Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-analysis flowchart of the study selection process.

quality of life.⁷ Nevertheless, whether patients undergoing open approaches has similar outcome as those undergoing endoscopic surgery remains unknown. Furthermore, the role of adjuvant radiation therapy after endoscopic resection is undetermined, and our knowledge of its advantages is derived from a older series of patients who were operated on using open approaches.

The aim of this meta-analysis was to assess the outcome of patients undergoing resection for clival chordomas. We investigated the efficacy of different surgical approaches and adjuvant radiation modalities in this population.

Materials and Methods

Meta-analysis Search Strategy and Selection Criteria

During April 2013, we conducted a systematic electronic literature database search of articles published between January 1995 and March 2013. The search was conducted using the Medical Subject Heading (MeSH) terms (chordoma) AND (skull base OR base of skull) AND (survival) and limited to "Human." Reference lists of retrieved manuscripts were hand-searched for additional publications. Publications in a language other than English were excluded. Articles were rejected at the initial screening if their titles or abstracts showed they were clearly irrelevant. Full texts of potentially relevant articles were reviewed to assess their suitability for

inclusion in this meta-analysis. ►**Fig. 1** describes the study selection process. The meta-analysis was limited to the following study designs: randomized controlled trials, prospective and retrospective cohorts, and case series. Population eligibility criteria were histopathologic diagnosis of chordoma of the skull base, primary or recurrent, and available outcome data including survival or local control rate. When essential data were lacking, patients were excluded.

Patients

A total of 28 studies with 467 patients were identified. The patients ranged in age from 2 to 87 years (median: 43.5 years) with a male-to-female ratio of nearly 1:1. The median follow-up was 40 months. Tumor removal was categorized as TR if no residual tumor was apparent at the end of surgery and on postoperative magnetic resonance imaging; otherwise, resection was defined as partial. Patients were divided into three groups according to their therapeutic management: total surgical resection alone, partial resection with adjuvant therapy, and radiation therapy alone. When data from individual patients were available, they were compiled into a master data spreadsheet.

Statistical Analysis

The meta-analysis was performed in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-

analysis statement. Descriptive data were summarized and averaged. Compiled published data of individual patients were used to calculate 5-year overall survival (OS), disease-specific survival (DSS), and progression-free survival (PFS) using the Kaplan-Meier method. Differences in survival rates were assessed by the log-rank test. OS was measured from the date of surgery to the date of death or the last follow-up. The DSS for patients who died from causes other than chordoma was established as the time of death. Variables used to stratify survival included age, gender, treatment modality, surgical approach (i.e., endoscopic versus open), and surgical outcome (i.e., extent of resection). Clinical, demographic, and tumor variables were analyzed using nonparametric qualitative and

quantitative tests (JMP; SAS Institute Inc., Cary, North Carolina, United States). The Fisher exact test (StatCalc v.2.0, University of Louisiana, Lafayette, Louisiana, United States) was used when the number of events was < 10. All *p* values were two-sided, and a *p* value < 0.05 was adopted as the threshold for significance.

Results

The search resulted in 375 studies, of which 241 were excluded due to the determination of irrelevance at the initial screening. Fifteen publications were excluded due to dual publication. The remaining 119 relevant articles were

Table 1 Patients and treatment modalities of the 28 studies in the meta-analysis

Study	No. of patients	Treatment				
		Open surgery	Transsphenoidal surgery	Endoscopic surgery	RT alone	Postoperative RT
Taniguchi and Kihmura ^{a,31}	4	0	0	4	0	0
Kano et al ¹³	71	0	0	0	13	58
Eid et al ^{a,17}	7	6	0	0	1	6
Koga et al ^{a,32}	10	0	0	0	0	10
Ito et al ^{a,33}	19	17	0	2	0	4
Fraser et al ^{a,34}	7	0	0	7	0	4
Solares et al ^{a,35}	4	0	0	4	0	3
Stippler et al ³⁶	20	0	0	20	0	13
Hong Jiang et al ^{a,21}	12	0	0	12	0	10
Ares et al ²⁰	42	0	0	0	0	42
Takahashi et al ¹⁸	32	32	0	0	0	21
Dassoulas et al ^{a,37}	15	12	0	0	3	12
Fatemi et al ^{a,38}	14	0	14	0	0	9
Yoneoka et al ¹²	13	13	0	0	0	13
Cho et al ^{a,19}	19	19	0	0	0	11
Zhang et al ^{a,39}	7	0	0	7	0	0
Foweraker et al ^{a,29}	7	0	0	0	1	6
Hwang et al ^{a,40}	3	0	0	3	0	0
Hasegawa et al ¹⁴	27	0	0	0	0	27
Martin et al ⁴¹	18	0	0	0	2	16
Stüer et al ^{a,42}	11	11	0	0	0	11
Frank et al ^{a,43}	9	0	0	9	0	5
Schulz-Ertner et al ¹⁶	61	0	0	0	61	0
Igaki et al ^{a,23}	13	0	0	0	6	7
Hug et al ²²	10	0	0	0	0	10
Karci et al ^{a,44}	2	2	0	0	0	0
Nakase et al ^{a,45}	2	2	0	0	0	0
Miller et al ⁴⁶	8	0	0	0	8	0
Total	467	114	14	68	95	298

Abbreviation: RT, radiation therapy.

^aStudies with available individual data.

reviewed, of which 91 were excluded due to insufficient data or because they did not meet the inclusion criteria. The final study group consisted of 467 patients, who were extracted from 28 published studies (►Table 1).

►Table 2 summarizes the demographic characteristics, tumor characteristics, and treatment modalities for the entire cohort. Therapeutic management included surgery alone in 74 patients (15.8%), surgery and adjuvant radiation therapy in 298 (63.8%), and radiation therapy alone in 95 (20.3%). Of the 196 patients who were treated by surgery, 114 (58.1%) had open surgery, 68 (34.6%) had endoscopic surgery and 14 (7.1%) underwent microscopic transsphenoidal resection. The 5-year OS and PFS rates of the whole cohort were 86% and 65.7%, respectively. The survival rates of patients who received surgical therapy with adjuvant radiotherapy are presented in ►Fig. 2.

To further analyze the outcomes of the patients, we conducted an analysis of the compiled data from *individual patients*. This subgroup consisted of 165 cases from 18 studies that published data of individual patients. Their demographic and clinical characteristics are summarized in ►Table 3. A total of 152 patients had surgical treatment. Open surgery was performed in 72 (53.2%), 48 (35.8%) underwent endoscopic surgery, and 14 (10.4%) microscopic transsphenoidal resection. Data regarding the surgical approach were missing for 18 patients. Of the 110 patients who received adjuvant radiation treatment, 48 (43.6%) received conventional radiation therapy (CRT), 36 (32.7%) stereotactic radiation therapy (SRT), and 26 (23.6%) proton beam radiation therapy (PBRT).

First we compared the survival outcomes of patients according to the surgical approach. Five-year OS was 96% for patients who underwent open surgery compared with 76% for those who underwent endoscopic surgery ($p = 0.07$). The 5-year DSS for patients who underwent open surgery and

endoscopic surgery was 45% and 49%, respectively ($p = 0.8$). PFS was 94% and 79%, respectively ($p = 0.11$).

Next, we analyzed the impact of adjuvant treatment on outcome. The 5-year OS of patients treated with surgery followed by adjuvant radiotherapy was 87% compared with 69% of those treated by surgery alone ($p = 0.12$). The 5-year OS rates of patients treated with the adjuvant radiotherapy including PBRT, CRT, and SRT, were 74%, 88% and 92%, respectively ($p = 0.48$). Five-year DSS was 74%, 97% and 96% for PBRT, CRT, and SRT, respectively ($p = 0.3$).

A subgroup analysis was performed to investigate the utility of adjuvant therapy in case of total or partial resection (►Fig. 3). For patients undergoing *total-resection* without radiotherapy, the 5-year OS and DFS were 92% and 94%, respectively, and for those receiving adjuvant radiotherapy, the 5-year OS and DFS were 100% and 89%, respectively. In patients undergoing *partial resection* without adjuvant radiotherapy, the 5-year OS was 41% and the DSS was 45%. In contrast, in those receiving adjuvant radiotherapy after partial resection, the 5-year OS and DSS rates were 84% and 85%, respectively, significantly higher than without adjuvant treatment group ($p < 0.001$ and $p = 0.01$, respectively).

Finally, we assessed perioperative complications according to the surgical approach (►Table 4). Cerebrospinal fluid (CSF) leak was reported in 11.6% (7/60) of patients after open surgery and in 11.1% (3/27) after endoscopic surgery ($p = 0.6$). Postoperative endocrine disorders (i.e., diabetes insipidus, hypopituitarism) were reported in 6.6% (4/60) of patients after open surgery, in 7.1% (1/14) after the microscopic transsphenoidal approach, and in zero of 27 of those operated on by the endoscopic approach ($p = 0.3$). The incidence of cranial nerve injury was 20% in the open surgery group (12/60) compared with 3.7% in the endoscopic surgery group (1/27). These differences were not statistically different ($p = 0.07$).

Table 2 Demographic and clinical characteristics of the entire cohort

Variable		No. of patients	%
Median age, y (range)	43.5 (2–87)	467	100
Gender (n = 364)	Male	191	52.4
	Female	173	47.5
Treatment modality	Surgery	74	15.8
	Surgery and RT	298	63.8
	RT	95	20.3
Surgical approach (n = 196)	Open	114	58.1
	Transsphenoidal	14	7.1
	Endoscopic	68	34.6
Radiation therapy (n = 383)	CRT	127	33.1
	SRS (GKS,CKS)	157	40.9
	PBRT	84	21.9
	Combined	15	3.9
Median follow-up, mo	40	438	100

Abbreviations: CKS, cyber knife surgery; CRT, conventional radiation radiotherapy; GKS, gamma knife surgery; PBRT, proton beam radiotherapy; RT, radiotherapy; SRS, stereotactic radiosurgery.

Fig. 2 Survival rates of patients who received surgical therapy followed by adjuvant radiotherapy. (A) Five-year overall survival. (B) Five-year progression-free survival (PFS). *The low PFS here was apparently due to a low dose of radiation therapy.

Discussion

Chordomas are characterized by progressive local growth with a tendency for local recurrence. The commonly accepted

treatment for chordomas of the skull base is resection followed by adjuvant radiation therapy, aimed to eradicate residual disease. Although the comprehensiveness of surgery is a major factor affecting prognosis, controversy still remains

Table 3 Demographic and clinical characteristics of the individual patient groups

Variable		No. of patients	%
Median age, y (range)	45 (3–87)	165	100
Gender (n = 161)	Male	79	49.1
	Female	82	50.9
Treatment modality ^a	Surgery	55	33.3
	Surgery and RT	97	58.7
	RT alone	13	7.8
Surgical approach (n = 134)	Open	72	53.7
	Transsphenoidal	14	10.4
	Endoscopic	48	35.8
Radiation therapy (n = 110)	CRT	48	43.6
	SRS (GKS,CKS)	36	32.7
	PBRT	26	23.6
Follow-up, mo, median (range)	30 (1–167)	165	100

Abbreviations: CKS, cyber knife surgery; CRT, conventional radiation therapy; GKS, gamma knife surgery; PBRT, proton beam radiotherapy; RT, radiotherapy; SRS, stereotactic radiosurgery.
^aAll patients who did not receive adjuvant RT underwent total resection. Three patients who underwent total resection received adjuvant RT.

Fig. 3 Kaplan-Meier survival analysis of 5-year overall survival (OS), disease-specific survival (DSS), and disease-free survival (DFS) according to the extent of surgical resection. Comparison of gross total resection (GTR [red line]) versus partial resection (PR [green line]) and PR and radiation therapy (RT [blue line]).

regarding the preferred surgical approach and the role of adjuvant treatment in this population.^{8,9}

Recent advancements in endoscopic techniques now allow improved access to the middle skull base and have reduced the rates of complications associated with endonasal

surgery.^{10,11} These advancements, together with modern protocols for the delivery of radiation therapy, warrant a reappraisal of the outcomes of patients with chordoma. In this meta-analysis we assessed the safety and effectiveness of the contemporary regimes for skull base chordoma. We found similar outcome measures in patients undergoing endoscopic resections and those undergoing open surgery. Rates of complications in the open and endoscopic groups were also similar.

Results were superior in patients who had TR compared with those undergoing partial resection. In those who had partial resection, adjuvant treatment offered improved outcome. For example, the recurrence rate was 2.6-fold higher in patients who underwent partial resection without adjuvant treatment compared with those who underwent TR alone. The overall 5-year PFS after surgery and adjuvant radiation (65.7%) is comparable with previously published data.^{12–14}

In the last decade, improvements in the planning and delivery of radiation including proton beam therapy, intensity-modulated radiation therapy, and carbon-ion radiotherapy were suggested for skull base chordoma.¹⁵ Older series that used a moderate dose on the order of 50 Gy in 25 fractions had very low complication rates but also poor local control.^{16–19} More recent series that used modern technology such as intensity modulated radiotherapy (IMRT) or proton beam radiotherapy (PBRT) have used doses in the range of 70 to 75 Gy with better local control and a relatively modest risk of complications.²⁰ In contrast to IMRT, where a conformal dose distribution is achieved by treating the tumor with multiple intersecting beams, proton beams have no exit dose due to the Bragg peak so that fewer beams are necessary and a tighter dose distribution is achieved.^{20–23}

Despite theoretical advantages, the superiority of one modality over another has not been clearly demonstrated.^{24–27} This meta-analysis did not identify a specific advantage of a particular radiation technique. Similarly, in their 10-year meta-analysis, Di Maio et al did not find a difference in OS among types of adjuvant radiation therapy, nor a difference in PFS between PBRT, stereotactic fractionated radiotherapy, or conventional radiation therapy.²⁸ Their results were limited by the fact that most patients who received adjuvant radiation therapy had subtotal resections.²⁸ We suggest that delivery techniques for any modality should be

Table 4 Postoperative complications according to the surgical approach

Complication	Open surgery n (%)	Transsphenoidal surgery n (%)	Endoscopic surgery n (%)	p value
CSF leak	7 (11.6)	0	3 (11.1)	0.6
Hydrocephalus	0	0	1 (3.7)	0.5
Meningitis	6 (10)	1 (7.1)	0	0.12
Cranial nerve palsy	12 (20)	0	1 (3.7)	0.07
Endocrine disorder	4 (6.6)	1 (7.1)	0	0.3
Total	60 (100)	14 (100)	27 (100)	

Abbreviations: CSF, cerebrospinal fluid.

based on local availability and experience of the treating physician. Although we clearly showed the advantage of adjuvant radiotherapy in patients undergoing partial resection, whether radiotherapy improves the outcome of patients undergoing total resection is still controversial.^{12,19,21,29}

This meta-analysis is limited due to the incomplete data presented across the studies. Although data heterogeneity might better reflect overall global population trends and enable generalization of our findings, many of the included studies have relatively small populations, which subject the analysis to publication bias. This may result in an over or under estimation of treatment effect. Also, the surgical approaches used cannot be directly compared without controlling for the extent of disease. Hence the endoscopic approach can be appropriate in selected patients.

In conclusion, our findings show that complete resection is associated with the best outcome and that adjuvant radiotherapy improves the survival of patients undergoing partial resection. We found similar efficacy and complication rates in the open and endoscopic groups. We did not identify a significant advantage of any radiation delivery method. Randomized controlled trials are needed to further evaluate the benefit of adjuvant radiation therapy after complete resection. In view of the benefit of minimally invasive surgery to the quality of life of patients with skull base tumors, we believe that endoscopic techniques should be considered appropriate for patients with clival chordoma.^{4,30}

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Conflict of Interest/Disclaimer

This work had no specific funding. The authors have nothing to disclose.

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