Midterm Prognosis and Surgical Implication of Clival Chordoma after an Extended Transsphenoidal Tumor Removal and Gamma Knife Radiosurgery

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Research article

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Abstract

**Background:** Treatment for chordoma by surgery alone is often ineffective, so surgery and irradiation is often performed with a reported 5-year survival rate of 60-75%. The clinical course varies; however, disease rarity has prevented large number clinical investigations.

**Methods:** Nineteen patients suffering from clival chordomas were retrospectively investigated. They were initially treated with maximal tumor removals by extended transsphenoidal approach. When total removal was achieved prophylactic irradiation was not performed. If tumor remnants or recurrence was confirmed, gamma knife (GK) was performed. Follow-up periods ranged from 9 to 224 months (mean 85.4 months).

**Results:** Total removal was achieved in 10 patients; however, 4 patients suffered recurrence and required GK. Overall progression free intervals were 9 to 151 months (mean 59.9 months). GK was applied for 11 patients with a 50 % isodose of 13 to 18 Gy (mean 15.4 Gy). Eight patients remained progression free, but 3 patients suffered repeated local recurrence and died from tumor related complications. Overall survival was 9 to 224 months (mean 90.9 months). Eighteen patients survived more than 5 years with the exception of one male patient, who died of lung cancer 36 months after the initial treatment (5-year survival rate 94.7 %). The results indicated that sex (males), those given more than 15 Gy of a 50% isodose by GK, and prophylactic brain scanning were significant favorable prognostic factors.

**Conclusions:** The favorable outcomes in this investigation may indicate value for early detection and early treatment. The role of surgery may be adequate conditioning for enough dose of GK.

Background

Chordomas arise from the prenatal remnants of the notochord and are frequently located at the midline of the skull base, cervical vertebrae and sacrum [3]. The frequency of occurrence is only 0.5% among all the intracranial tumors, and 1–4% among skeletal tumors [1, 16, 20–21]. This disease rarity has prevented large number clinical investigations and the results lead to a great discrepancy between the indolent pathological features and the malignant clinical course [5, 7–10, 12–15], with a reported 5-year survival is 60–75%. Although the tumor doubling time is rather long for chordomas, repeated local recurrence and dissemination are not unusual due to invasive growth along bone marrow [2, 5]. Tumor control by surgery alone is thought to be difficult, and therefore, the majority of the patients are treated by combined therapy with irradiation [6–9, 14, 17]. Because this tumor usually resists against conventional radiation therapy and evidence for effective chemotherapy has not yet been established, ion beam therapy including proton or heavy ion beam therapy has been expected to provide good tumor control [6, 8, 17]. However once again disease rarity has prevented large number clinical experiences and insurance is barely but partially adapted in Japan for ion beam therapy.

We present a single-center experience of maximal tumor removal of clival chordomas by the extended transsphenoidal approach following gamma knife radiosurgery for visualized remnants or tumor recurrence. The role and the implications of surgery are also discussed.
Methods

In this report 14 males and 5 females aged from 41 to 85 years (mean age 60.4 years) suffering from clival chordomas were included with histological confirmation at the Department of Neurosurgery, Kohnan Hospital between March 2006 and July 2019. The most common initial symptom was diplopia in 6 patients owing to cranial nerve palsy, but 2 patients owing to optic nerve dysfunction and 1 patient owing to spontaneous cerebrospinal fluid leakage (clival erosion with no visible tumor). Overall 8 patients were asymptomatic and the tumors were detected by prophylactic brain scans at each checkup. Initial treatments were applied for 17 patients; however, the remaining 2 patients had suffered from re-growth after pleural tumor removal and radiation therapy (Table 1). All of the tumors extended along the clivus; 8 patients experienced extra-arachnoidal localization, and the remaining 11 experienced tumor extension into the subarachnoid spaces. The patients were initially treated with maximal tumor removal by the extended transsphenoidal approach with simultaneous removal of the surrounding bone cortex and bone marrow as far as possible within the technical range of skull base repair. When gross total removal was achieved prophylactic irradiation was not performed, and patients were simply observed at 6-months intervals. If tumor remnants were visualized, the gamma knife was stood by until the skull base regeneration was accomplished (3 months after the operation) and applied. When tumor recurrence was confirmed, gamma knife surgery was subsequently applied to the visualized tumor bulk; this occurred in all patients except for one female patient (case 16), who was treated with postoperative fractionated irradiation because of her older age (85 years old). All the patients were followed up through out their clinical course with 9 to 224 months of follow up (mean 85.4 months).
Table 1
Preoperative clinical profile

| Case | Age Ranges | Sex | Tumor volume (ml) | Maximum diameter (mm) | Initial symptom          |
|------|------------|-----|-------------------|-----------------------|--------------------------|
| 1    | 61–70      | F   | 15.1              | 39                    | 6 nerve palsy            |
| 2    | 41–50      | M   | 0.73              | 12                    | brain checkup            |
| 3    | 51–60      | M   | 36                | 50                    | 1 TO, 3GK                |
| 4    | 61–70      | M   | 12.7              | 40                    | 6 nerve palsy            |
| 5    | 51–60      | M   | 14.4              | 32                    | incidental               |
| 6    | 41–50      | M   | 9.8               | 39                    | 1 removal, 1 FR          |
| 7    | 61–70      | M   | 26.4              | 50                    | nasal congestion         |
| 8    | 41–50      | M   | 0.98              | 15                    | incidental               |
| 9    | 51–60      | M   | Not visible       | Not visible           | CSF leakage              |
| 10   | 41–50      | M   | 11.7              | 30                    | brain checkup            |
| 11   | 71–80      | M   | 2.52              | 28                    | 3,4 nerve palsy          |
| 12   | 71–80      | M   | 5.13              | 27                    | 6 nerve palsy            |
| 13   | 61–70      | M   | 3.4               | 20                    | brain checkup            |
| 14   | 61–70      | F   | 12.8              | 41                    | 6 nerve palsy            |
| 15   | 51–60      | F   | 2.76              | 23                    | brain checkup            |
| 16   | 81–90      | F   | 17.9              | 42                    | unilateral blindness     |
| 17   | 51–60      | M   | 68.5              | 52                    | bitemporal hemianopsia   |
| 18   | 51–60      | F   | 66.5              | 63                    | 3,6 nerve palsy          |
| 19   | 51–60      | M   | 0.17              | 8                     | brain checkup            |

All patients underwent axial, coronal and sagittal T1 and T2-weighted magnetic resonance (MR) imaging with and without contrast medium (Signa Horizon, General Electric, Milwaukee, WI; 3.0 T system) and bone image computed tomography (CT) (Discovery CT 750 HD, General Electric) preoperatively, just after the operation. Follow-up MR imaging was performed at 6-month intervals after the operation (1.5 T system; Magnetom, Siemens AG, Erlangen, Germany). Gross total removal was defined as an absence of visible tumor bulk on both intraoperative findings and postoperative MR imaging.

The surgical specimens were immediately fixed for histological and immunohistochemical examinations with 10% buffered formalin, then embedded in paraffin, and serial sections were cut to 3-µm thickness.
Hematoxylin and eosin, and periodic acid-Schiff staining were performed in all cases. The avidin-biotin-peroxidase complex method was applied for immunohistochemical staining and cell proliferation was assessed for Ki-67 (MIB-1, Dako, 1:100). Immunohistochemical positive cells were counted within at least 1000 background cells in three high power visual fields including the hot spot and other fields, and then indicated as a percentage. Positive controls used normal lymph nodes for Ki-67. Statistical comparisons were made using Statmate 5 software (ATMS Co., Ltd., Tokyo, Japan), and \( P \) values of less than 0.05 were regarded as significant.

The patients were informed preoperatively of the salvage treatment protocol and the study design was approved by the Ethical Committee of Kohnan Hospital 2020.

**Results**

Gross total removal was achieved in 10 patients and 9 patients had tumor remnants with a removal rate that ranged from 73 to 100 (mean 92.8%). Four of 10 patients with gross total removal developed tumor recurrence and required gamma knife treatment thereafter. The remaining 6 patients were observed only and all of them were asymptomatic preoperatively. Overall progression free intervals were 9 to 151 months (mean 59.9 months), and overall survival was 9 to 224 months (mean 90.9 months), with the exception of one male patient, who died of lung cancer 36 months after the initial treatment (case 12). The other 18 patients survived more than 5 years (5-year survival rate 94.7%).

Preoperative tumor volume ranged from 0.17 to 68.4 ml (mean 16.2 ml) and the maximum tumor diameter ranged from 8 to 63 mm (mean 32.2 mm). Postoperative residual tumor volume ranged from 0 to 6.17 ml (mean 1.61 ml). Gamma knife surgery was applied for 11 patients with a 50% isodose of 13 to 18 Gy (mean 15.4 Gy). Eight of 11 patients remained progression free, but 3 patients suffered repeated local recurrence and died of tumor related complications. Ki-67 labeling index ranged from less than 1 to 25.1% (mean 8.91%). The clinical data are shown in Table 2.
| Case | Removal rate (%) | Residual volume (ml) | 50% isodose (Gy) | PF period (months) | After GK | Overall survival (months) |
|------|------------------|----------------------|------------------|-------------------|---------|--------------------------|
| 1    | 100              | 0                    | 14               | 12                | 4 GK    | 168                      |
| 2    | 100              | 0                    | N/A              | 151               | N/A     | 151                      |
| 3    | 75               | 9                    | 14               | 51                | 1 TC, 1 CK | 224                      |
|      |                  |                      |                  |                   |         | 65 months: dead from disease progression to sarcoma |
| 4    | 100              | 0                    | 14               | 48                | 2 removal, 1 GK | 62                      |
|      |                  |                      |                  |                   |         | 62 months: dead from epistaxis |
| 5    | 90               | 1.44                 | 16               | 147               | 139 months progression free | 147                      |
| 6    | 70               | 2.94                 | 13               | 31                | 2 removal, 1 GK | 69                      |
|      |                  |                      |                  |                   |         | 69 months: dead from brain stem invasion |
| 7    | 100              | 0                    | N/A              | 69                | N/A     | 132                      |
| 8    | 100              | 0                    | N/A              | 134               | N/A     | 134                      |
| 9    | 100              | 0                    | N/A              | 120               | N/A     | 120                      |
| 10   | 100              | 0                    | 18               | 95                | 17 months progression free | 112                      |
| 11   | 100              | 0                    | 16               | 30                | 79 months progression free | 109                      |
| 12   | 95               | 0.26                 | 17               | 38                | stable but died from lung cancer | 38                      |
| 13   | 100              | 0                    | N/A              | 97                | N/A     | 97                       |
| 14   | 80               | 2.56                 | 16               | 21                | 23 months progression free | 44                      |
| 15   | 95               | 0.14                 | 16               | 24                | 18 months progression free | 42                      |
| 16   | 73               | 4.83                 | N/A              | 15                | 18 months progression free | 33                      |
| 17   | 91               | 6.17                 | 15               | 19                | 8 months progression free | 27                      |
| 18   | 95               | 3.33                 | N/A              | 9                 | prepare | 9                       |
| 19   | 100              | 0                    | N/A              | 9                 | N/A     | 9                        |
### Table

| Case Removal rate (%) | Residual volume (ml) | 50% isodose (Gy) | PF period (months) | After GK | Overall survival (months) |
|-----------------------|----------------------|------------------|-------------------|----------|--------------------------|
|                       |                      |                  |                   |          |                          |

PF = progression free, GK = gamma knife, FR = fractionated irradiation, N/A = not applicable

The results showed that male patients (p < 0.01), those who received more than 15 Gy of a 50% isodose at the time of gamma knife radiosurgery (p < 0.05), and those who received regular brain scans (p < 0.05) had a significantly favorable prognosis. Gross total removal and tumor volume less than 1 ml before gamma knife surgery did not appear to have a significant effect on prognosis. Age older than 60, a tumor volume more than 10 ml or a tumor maximum diameter more than 30 mm was not adverse prognostic factors. A comparison of patients with a Ki-67 labeling index between more or less than 10% did not show statistical significance in the present investigation (Table 3).

### Discussion

According to one meta-analysis for chordomas, the 5-year survival of patients was reported to be 60 to 75% and thus far, treatment results have shown little improvement even with modern surgical procedures [12]. Although the 5-year survival in this investigation was 95% and therefore a little higher than previously reported with no postoperative acquired neurological deficits, total removal had not become prognostic factor. So adjuvant irradiation to this tumor is confirmed to be essential once again. On the contrary preoperative tumor volume, maximum tumor diameter and residual tumor volume before irradiation were not identified as significant prognostic factors, but delivering a dose higher than 15 Gy of a 50% isodose had a significant effect as previous report had suggested [11]. Although objective surgical goals are varied between the reports and the ideal relationship between surgery and postoperative gamma knife irradiation is unclear [7, 9, 13, 23], the results in this investigation may suggest an importance of reducing maximal tumor volume, provide an adequate condition for sufficient irradiation, of which maximal reduction of tumor volume and to secure a distance from the optic pathway. Along this principal we tried to remove the tumor bulk together with the surrounding bone cortex and bone marrow as far as possible within the technical range of skull base repair. This expansion of removal could contribute dose escalation of irradiation and/or localization of the radiation field.

Performing regular prophylactic brain scans was also identified as another prognostic factor, which was applied as prophylactic medicine mainly targeted to un-ruptured cerebral aneurysm or asymptomatic arterial stenosis. Because efficacy for larger population and the necessary social expense are greatly varied between the nations this system has not become popular in many countries except for Japan. However, the favorable outcomes in this investigation may indicate some value for early detection and early treatment of this malignant disease. If the tumor is detected, a wait and see approach should not be adopted, and instead, early surgery should be implemented even for asymptomatic lesions. The extended transsphenoidal approach is thought to be less invasive and therefore a better approach for treatment.
Pathophysiological investigations revealed a possible influence of Ki-67 labeling index, overexpression of p53 and receptor tyrosine kinase expression [4, 19, 22]. Another report presumed the prognostic difference between chondroid chordoma and chordoma [18]. Although no significant difference was found between these parameters in this investigation (data not shown), study volume and/or the difference in treatment protocols may inadvertently cover up that significance.

The limitation of this investigation was the low patient number, which is consistent with previous reports. These reports have been compared the prognosis by conducting meta-analyses of different treatment protocols and different disease backgrounds. To establish classified treatment guideline, larger multi-institutional investigation is strongly encouraged.

Declarations

Ethics approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent to participates

The surgical policy was explained preoperatively to the patients and written informed consents were obtained.

Consent for publication

This is a retrospective investigation, and overall study design was approved by the Ethical Committee of Kohnan Hospital 2020.

Availability of data and material

All the data using in this investigation can be disclosed after the request from editor in chief.

Competing interests

The authors declare that they have no conflict of interest.

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No funding was received for this research.

Authors’ contributions

All authors contributed to the study conception and design. YO was a major contributor in writing the manuscript and performed tumor removal all through the investigated period. HJ performed all the gamma knife radiosurgery all through the investigated period. And TT gave an essential suggestion and supervised this manuscript. The first draft of the manuscript was written by YO and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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**Table**

Due to technical limitations, table 3 is only available as a download in the Supplemental Files section.

**Supplementary Files**
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- TABLE3.docx