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Conventional external radiotherapy in the management of clivus chordomas with overt residual disease

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Abstract Cranial chordomas are uncommon tumors accounting for less than 1% of all intracranial neoplasms. Although they are slowly growing, rarely metastasizing tumors, cranial chordomas are challenging to treat due to their critical location, invasive nature and aggressive recurrence. The aim of this retrospective study was to evaluate the role of conventional irradiation in the treatment of clival chordomas with overt residual disease after incomplete surgery.

Between January 1979 and December 1997, 18 patients with histologically confirmed clival chordoma were treated with radiotherapy. Median age at the time of diagnosis was 32 years. The mean duration of the symptoms before diagnosis was 33.9 months. Median tumor diameter at initial presentation was 5 cm (range, 3-7 cm). The type of surgical procedure was subtotal excision in 11 patients and biopsy in 7. Radiation treatment was delivered with megavoltage units, and total doses between 50 Gy and 64 Gy (median, 60 Gy) were administered with conventional daily fractions. One patient received additional 12.50 Gy with linear accelerator-based stereotactic radiosurgery after subtotal excision and external irradiation.

The mean follow-up time was 43.2 months. Overall survival at 5 years was 35%. Eleven patients showed progression after radiotherapy. The median time to progression after radiotherapy was 40.8 months (38.4-43.2) with a 5-year progression-free survival of 23%. Five patients (29.4%) showed symptomatic relief after radiotherapy while persistent symptoms were recorded for 6 patients. Incomplete surgery and conventional external radiotherapy with a dose of around 60 Gy seem to be inadequate in the treatment of clival chordomas.

Key words Chordoma • Clivus • Radiotherapy

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Introduction

Chordomas are tumors of notochordal origin that account for approximately 1%-4% of all primary bone tumors [1, 2] and 0.1%-0.2% of all primary intracranial neoplasms [3]. One-third of the chordomas arise from the skull base [4, 5]. Intracranial chordomas rarely metastasize but are difficult to manage because of their invasive nature, critical location close to the vital neurovascular structures and aggressive recurrences after treatment [6]. Initial definitive radical surgery is the treatment of choice but it is rarely feasible for clival and parasellar region chordomas; radiotherapy plays an important role for this location [7].

In the present paper we report our experience in managing cranial chordomas using postoperative conventional radiotherapy after incomplete surgical excision in 18 patients.

Materials and methods

Between January 1979 and December 1997, 18 patients with histologically confirmed diagnosis of clival chordoma were treated at Hacettepe University Faculty of Medicine Department of Radiation Oncology.

The end points examined were local control, overall survival (OS) and progression-free survival (PFS) using the Kaplan-Meier method. Differences in progression-free survival with respect to individual baseline variables were assessed using the log rank test.

Results

We treated 18 patients, including 13 males and 4 females, with radiotherapy for clival chordoma (Table 1). Patient age at the time of the diagnosis varied from 9 to 54 years (median, 32). The most common presenting symptom was diplopia and the most common presenting sign was extraocular nerve deficit. The mean duration of the symptoms before diagnosis was 33.9 months (range, 2-180 months). Median tumor diameter at initial presentation was 5 cm (range, 3-7 cm). Four patients were considered to have tumors of less than 5 cm whereas the remaining 14 patients had tumors of more than 5 cm (Table 1). The type of surgical procedure was subtotal excision in 11 patients and biopsy in 7. All patients received megavoltage irradiation either with Cobalt 60 unit or 6 MV photons. Doses ranged from 50 Gy to 64 Gy (median, 60 Gy) with conventional daily fractionation. One patient received additional 12.50 Gy to 85% isodose line with a maximum dose of 15 Gy with linear accelerator-based stereotactic radiosurgery after subtotal excision and 60 Gy external conventional irradiation.

At the time of our analysis, the mean follow-up time was 43.2 months (range, 12-96 months). Median overall survival from diagnosis was 46 months. Overall survival at 5 years was 35% (Fig. 1). Local failure or progression was defined as evidence of progressive tumor growth on computed tomography (CT) or magnetic resonance imaging (MRI), or worsening of the symptoms and signs. Eleven patients showed progression after radiotherapy. The median time to clinical or radiological progression after radiotherapy was 40.8 months with a 5-year PFS of 23% (Fig. 2). The prognostic value of the tumor size (>5 cm vs. <5 cm, $p > 0.05$), extent of surgery (biopsy vs. subtotal excision, $p > 0.05$) and sex ($p > 0.05$) were assessed using the log rank test; none had any statistically significant prognostic value for PFS or OS.

Patients were assessed for their symptoms at the last follow-up. Of 18 patients, 11 (61%) were recorded to have either improved or persistent symptoms. A complete or partial improvement in the presenting signs or symptoms was recorded for 5 (28%) of the symptomatic patients after radiotherapy, whereas 6 (33%) patients showed persistent symptoms.

Four patients were reoperated for local progression after radiotherapy and the median follow-up time after retreatment was 6 months (range, 4-24 months). All the reoperated patients showed symptomatic relief without any progression at the time of the analysis.

Table 1 Patient characteristics

Patient	Age at diagnosis (years)	Sex	Symptom duration before diagnosis (months)	Tumor diameter (cm)	Surgery	Radiation dose (Gy)	Current status	Follow-up (years)
1	12	M	2	6	Subtotal	60	Deceased	4.4
2	34	M	4	4	Subtotal	64	Deceased	4.0
3	27	M	4	5	Biopsy	60	AWD	3.6
4	45	M	6	6	Biopsy	54	Deceased	1.3
5	28	M	6	3	Subtotal	60	ANED	2.2
6	38	M	120	5	Subtotal	60	AWD	2.2
7[a]	32	F	8	3	Subtotal	60+S	ANED	3.1
8	29	F	9	7	Biopsy	60	ANED	1.0
9	27	M	12	7	Subtotal	53	Deceased	2.4
10	9	F	6	5	Biopsy	50	Deceased	3.6
11	38	M	10	5	Biopsy	60	ANED	8.0
12	33	F	2	5	Subtotal	56	AWD	4.0
13	32	M	12	5.5	Subtotal	60	ANED	6.3
14	42	M	72	5	Subtotal	50	Deceased	4.0
15	44	F	120	4	Biopsy	60	Deceased	2.1
16	54	M	3	7	Biopsy	60	Deceased	2.3
17	47	M	180	7	Subtotal	60	ANED	6.7
18	32	M	34	5	Subtotal	60	AWD	3.7

[a] This patient received stereotactic radiosurgery after 60 Gy external radiotherapy.
ANED, alive with no evidence of disease progression; *AWD*, alive with progressive disease; *S*, Stereotactic radiosurgery

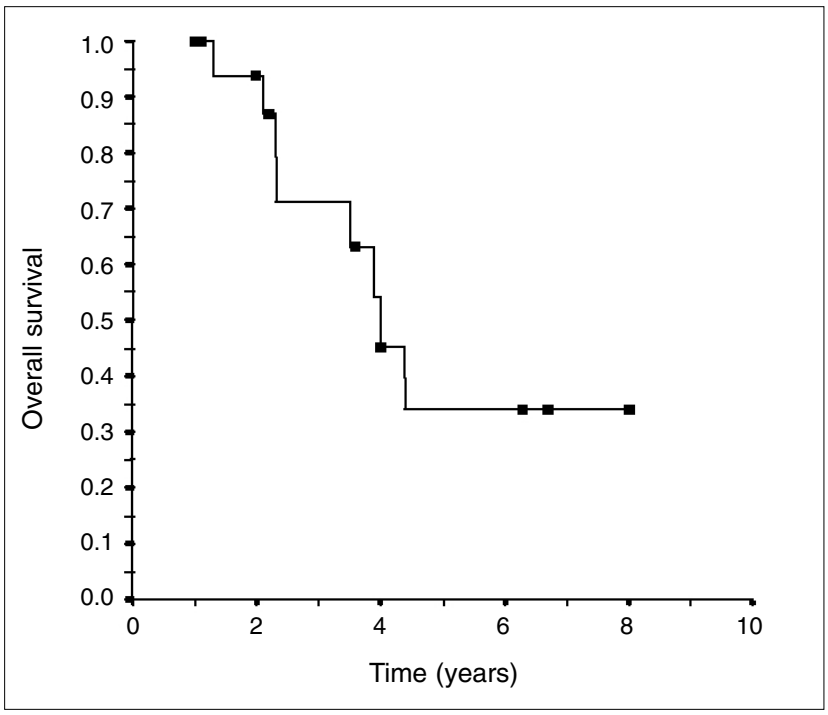
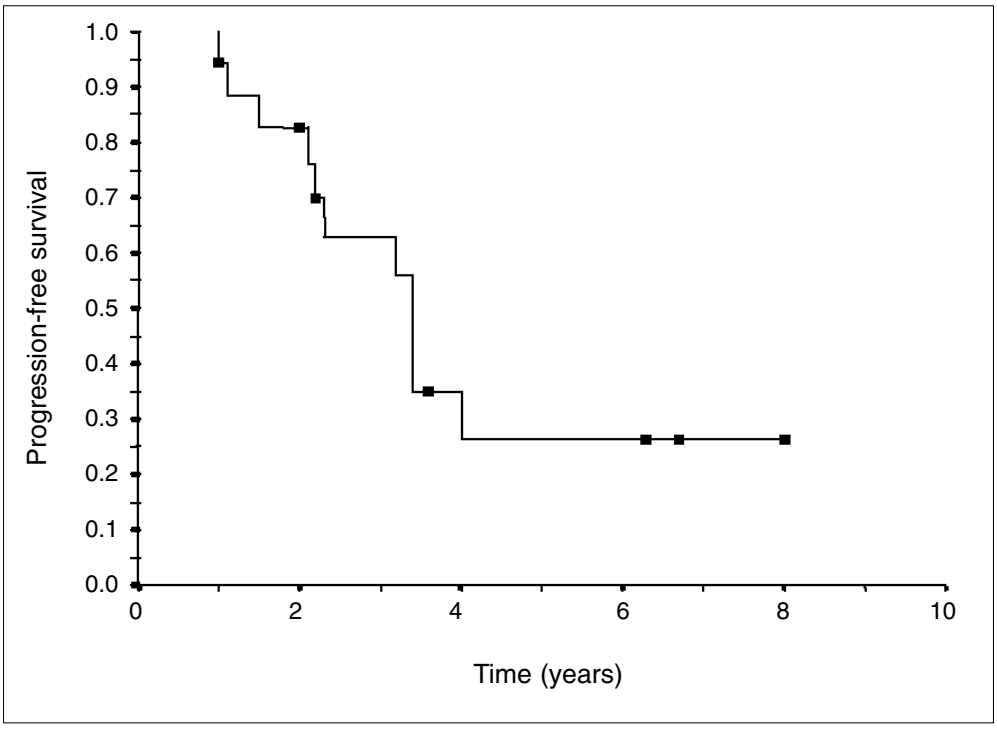


Fig. 1 Overall survival

Fig. 2 Progression-free survival



Discussion

Clival chordomas are among the most challenging tumors to treat despite their indolent growth and low tendency for metastasis. Radical tumor removal plays a definitive role in the treatment [3, 8-10]. In a study by Gay et al. [10], the recurrence-free survival rates at 5 years were 84% for the patients who underwent total or near total removal and 64% for the cases in which there was partial or subtotal resection. Al-Mefty and Borba [8] reported that 71.4% of patients with skull base chordomas were alive and without any evidence of disease with a mean follow-up of 25.4 months. The surgical procedure in that study was in the form of radical surgical removal with resection of the soft tumor tissue and extensive drilling of adjacent bone structures beyond the

limits of involved bone. In that study, however, 17 of 23 patients were also referred for adjuvant photon-proton beam therapy and 60-72 Gy equivalent dose of irradiation was applied. The surgical resection type did not have any prognostic value in our series, which is not in accordance with the literature. Although statistically insignificant prognostic value of the tumor size and extent of surgery might be due to the relatively small number of cases, as the majority of our patients had tumors greater than 5 cm and biopsy or subtotal excision instead of radical surgical removal, it seems reasonable why extent of surgery did not have any prognostic value.

The role of radiotherapy in the management of cranial chordomas is well documented [11-14]. Catton et al. [14] reported a median survival of 62 months without any difference between clival and non-clival presentations. In that study, 44 of 48 patients were referred with overt disease after a biopsy or incomplete resection; a median dose of 50 Gy in conventional fractions was applied. The median time to clinical or radiological progression for those treated for overt disease in Catton's series was 35 months. Retrospective evaluation of postoperative MRI or CT scans of 18 patients in our series revealed overt residual disease in all patients. The median time to progression after radiotherapy in our series was 40.8 months which is consistent with Catton et al's. The progression-free and overall survival at 5 years in our series were found to be 23% and 35%, respectively. Progression-free survival and overall survival rates in our series seem to be lower than most series in the literature [6, 12, 15, 16]. In these series, however, either charged particles [6, 12, 15] or stereotactic radiosurgery [16] were used alone or in combination with conventional radiotherapy. Our results on the other hand are comparable to Fuller and Bloom's [17], who reported 15% of local control rate among 13 patients with chordoma treated by radiotherapy after partial excision or biopsy with a median follow-up time of 5 years.

Pearlman and Friedman [18] defined a clear dose-response effect with conventional radiotherapy with 80% local control rate in patients receiving more than 80 Gy and 20% in patients receiving 40-60 Gy. These authors strongly recommended a dose of higher than 70 Gy. Following their review of the literature prior to 1969, Pearlman and Friedman [18] came to a conclusion that doses in the range of 60-80 Gy are successful in approximately one-fourth of patients and may achieve significant palliation in another one-third. In a study by Cummings et al. [19], symtomatic improvement for at least five years was no more likely at doses above 50 Gy than at lower doses. A complete or partial improvement in the presenting signs or symptoms was recorded for 29.4% of the symptomatic patients in our series after radiotherapy whereas 35.3% patients showed persistent symptoms. Since all patients in our series received more than 50 Gy (median, 60 Gy), we could not estimate a dose-response relationship in this regard. The low survival rates in our series and similar series from the literature lead us to conclude that 50-60 Gy conventional external radiotherapy in the management of clival chordomas with overt residual disease after surgery can produce good palliation without any long-term PFS.

Chordomas have high mortality and morbidity rates due to local growth with compression and invasion when inadequately treated and to the proximity of the brainstem so close behind the clivus. Therefore, radiotherapy either with stereotactic radiosurgery [16, 20] or charged particles [6,12,15] has gained a great clinical interest in the management of cranial chordomas. Stereotactic radiosurgery in combination with conventional radiotherapy produce high control rates [16, 20]. However, radiosurgery can only be used for the treatment of small residual tumors after microsurgery, or to deliver a focused radiation boost to recurrent tumors after previous radiation therapy [21]. Only one patient in our series received stereotactic radiosurgery boost after subtotal excision with a residual disease of less than 2 cm and 60 Gy conventional radiotherapy. This patient is without any tumor progression or treatment complication 37 months after radiotherapy.

In conclusion, incomplete surgery and conventional radiotherapy seem to be inadequate in obtaining high cure rates in the management of chordomas, although some benefit can be achieved in palliation of the symptoms. Aggressive surgical approach with the aim of complete resection and stereotactic radiosurgery or particle beam therapy should be the treatment choice whenever possible. Although there is not enough supporting data in the literature, conformal radiotherapy to total doses higher than 70 Gy with meticulous treatment planning or intensity-modulated radiotherapy may be the right option when external radiotherapy is planned.

Sommario *I cordomi craniali sono tumori rari riscontrabili con frequenza inferiore all'1% tra i tumori cerebrali. Benché siano tumori a lento accrescimento e raramente metastatizzanti, il loro trattamento pone problemi importanti a causa della localizzazione critica, della natura invasiva e della marcata tendenza a recidivare. Scopo di questo studio retrospettivo è la valutazione del ruolo della terapia radiante convenzionale nel trattamento dei cordomi del clivus asportati incompletamente. Tra il gennaio 1979 e il dicembre 1997, 18 pazienti portatori di cordomi del clivus confermati istologicamente furono trattati con radioterapia. L'età mediana al momento della diagnosi era di 32 anni. La durata media della sintomatologia prima della diagnosi era 33,9 mesi. Il diametro del tumore alla prima diagnosi era compreso tra 3 e 7 cm (mediana 5 cm). L'asportazione fu subtotale in 11 pazienti, limitata alla biopsia in 7. Il trattamento radiante venne somministrato con apparecchiatura ad alta energia ad una dose totale compresa tra 50 e 64 Gy (mediana 60 Gy) con frazionamento quotidiano convenzionale. Un paziente ricevette in più 12.50 Gy attraverso radiochirurgia stereotassica con*

acceleratore lineare dopo exeresi subtotale e irradiazione esterna. Il follow-up medio fu di 43.2 mesi. La sopravvivenza a 5 anni fu del 35%. In undici pazienti si verificò progressione dopo la radioterapia. Il tempo alla progressione dopo radioterapia risultò compreso tra 38.4 e 43.2 mesi (mediana 40.8 mesi), il 23% dei pazienti ebbe una sopravvivenza di 5 anni libera da progressione. Cinque (29.4%) pazienti ebbero un miglioramento della sintomatologia dopo radioterapia mentre in altri 6 la sintomatologia persistette immodificata. La combinazione di un trattamento chirurgico non radicale con una radioterapia a dosi dell'ordine dei 60 Gy appare inadeguata per la terapia del cordome del clivus.

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