BJR

Received: 15 December 2015 | Revised: 8 April 2016 | Accepted: 19 April 2016

http://dx.doi.org/10.1259/bjr.20151051

Cite this article as:
Hayashi Y, Mizumoto M, Akutsu H, Takano S, Matsumura A, Okumura T, et al. Hyperfractionated high-dose proton beam radiotherapy for clival chordomas after surgical removal. *Br J Radiol* 2016; **89**: 20151051.

FULL PAPER

Hyperfractionated high-dose proton beam radiotherapy for clival chordomas after surgical removal

[1]YASUTAKA HAYASHI, MD, [2]MASASHI MIZUMOTO, MD, PhD, [3]HIROYOSHI AKUTSU, MD, PhD, [3]SHINGO TAKANO, MD, PhD, [3]AKIRA MATSUMURA, MD, PhD, [2]TOSHIYUKI OKUMURA, MD, PhD, [4]TAKUYA KAWABE, MD, PhD, [2]JUNKO ZENKOH, BPharm, [2]HIDEYUKI SAKURAI, MD, PhD and [2]KOJI TSUBOI, MD, PhD

[1]Department of Radiation Oncology, Tsukuba Medical Center Hospital, Ibaraki, Japan
[2]Proton Medical Research Center, Faculty of Medicine, University of Tsukuba, Ibaraki, Japan
[3]Department of Neurosurgery, Faculty of Medicine, University of Tsukuba, Ibaraki, Japan
[4]Department of Neurosurgery, Kyoto Prefectural University of Medicine, Kyoto, Japan

Address correspondence to: Professor Koji Tsuboi
E-mail: *tsuboi-k@md.tsukuba.ac.jp*

Yasutaka Hayashi and Masashi Mizumoto contributed equally to this article.

Objective: To evaluate the hyperfractionated high-dose proton beam therapy (PBT) for patients with clival chordomas.
Methods: Records for 19 patients with pathologically verified clival chordomas treated with surgery followed by hyperfractionated PBT were retrospectively reviewed. The first 9 consecutive patients were treated with 77.44 cobalt gray equivalents (CGEs) in 64 fractions, and the latter 10 patients were treated with 78.4 CGE in 56 fractions.
Results: The median follow-up period of all 19 cases was 61.7 months with a range from 31.5 to 115.4 months. At 5 years, the local control, cause-specific and overall survival rates for all 19 cases were 75%, 94% and 83.2%, respectively. Whereas the 5-year local control, cause-specific and over all survival rates of the latter 10 cases were 100%, 100% and 88.9%, respectively, with a median follow-up period of 59.5 months. One of the first nine patients demonstrated bilateral temporal lobe radiation necrosis, who were successfully treated conservatively. In the latter cohort, two cases showed transient neurological symptoms probably due to brain stem ischaemia, but both cases recovered completely with conservative treatment.
Conclusion: The hyperfractionated high-dose scheme combined with maximum surgical removal was shown to be efficient for patients with clival chordomas.
Advances in knowledge: High-dose proton beam radiotherapy using a hyperfractionation scheme yielded a more favourable outcome than previous reports.

INTRODUCTION

Chordomas are rare, slow-growing destructive tumours arising from notochordal remnants.[1,2] Skull base chordomas often affect younger individuals and are more frequent in females than in males.[3] The clinical features of chordomas fall between benign and malignant because of their local aggressiveness.[1,2,4]

Although the surgical removal of skull base chordomas remains the mainstay of treatment, complete removal is often difficult because of the location[1,5,6] and aggressive surgical treatment has sometimes been associated with increased patient morbidity and mortality.[7–9] Patients with a skull base chordoma who underwent surgery and/or radiotherapy were reported to have a lower quality of life than normal population mainly because of neurological deficits.[10] In addition, even if gross total removal is achieved, the local recurrence rate is high because of common infiltration to the surrounding bony tissue along the lines of least resistance.[2]

Therefore, post-operative radiotherapy has been used to achieve long-term stabilization of skull base chordomas.[4,6–8] Specifically, the proton beam therapy (PBT), with its excellent dose localization properties, has been reported to be effective in achieving both local control and improved overall survival when compared with the conventional radiotherapy treatment.[4,11–19]

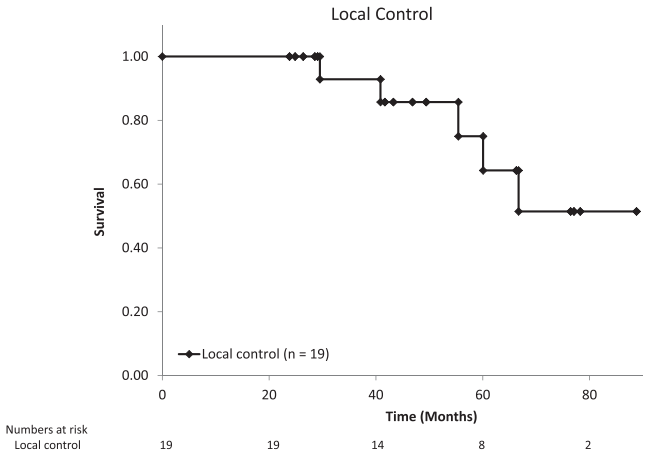
We have previously reported the early clinical results from 12 patients with clival chordomas and 1 patient with chondrosarcoma treated using PBT.[13] After treating a total of 17 patients, including these 12 patients, with the conventional dose-per-fraction scheme, we initiated hyperfractionated PBT after surgical tumour removal for minimizing complications

Table 1. Characterics of the 19 patients in this study

Numbers	Age (years)	Sex	PS	Surgical approach	Tumour size (cm^3)	Surgical modality	Total dose (CGE)	Fraction number	Acute reaction (grade)					Late complication (grade)	Recurrence (months)
									Blood	Sickness	Dermatitis	Mucositis	Others		
1	52	F	0	TSA	38.4	Partial	77.44	64 bid	1	0	1	0	None	None	60.1
2	60	M	1	TSA	2.5	Subtotal	77.44	64 bid	0	0	0	0	None	RN (2)	55.4
3	56	M	1	TSA	24.6	Partial	77.44	64 bid	1	0	0	0	None	None	29.5
4	55	M	2	TSA	17.8	Partial	77.44	64 bid	1	0	0	0	OM (2)	None	None
5	20	F	0	TSA × 3	1.7	Biopsy	77.44	64 bid	1	0	1	0	None	None	40.9
6	36	F	1	Posterior petrosal	14.1	Subtotal	77.44	64 bid	0	0	0	0	None	None	None
7	20	F	0	Suboccipital	3.0	Partial	77.44	64 bid	0	0	0	0	None	None	None
8	36	F	1	TOA	40.7	Partial	77.44	64 bid	0	1	1	0	OM (1)	None	41.7
9	56	M	0	TSA	48.6	Subtotal	77.44	64 bid	0	0	0	0	OM (1)	None	28.6
10	44	F	0	TOA	22.0	Biopsy	78.4	56 bid	0	1	1	0	OM (1)	None	None
11	34	M	0	TSA	8.4	Subtotal	78.4	56 bid	0	0	1	0	None	None	None
12	62	F	1	Subocciptal, subtemporal × 2	24.4	Subtotal	78.4	56 bid	1	0	2	0	None	None	None
13	44	F	1	TSA × 5, Subtemporal	19.0	Partial	78.4	56 bid	2	1	1	0	OM (2)	None	66.7
14	64	F	1	TSA	17.5	Partial	78.4	56 bid	0	0	1	2	None	TI (2)	None
15	72	F	1	TSA	20.6	Partial	78.4	56 bid	1	1	1	0	OM (2)	None	None
16	13	M	1	TSA, anterior petrosal	6.6	Subtotal	78.4	56 bid	0	1	2	0	OM (2)	None	None
17	69	M	1	TSA	32.2	Partial	78.4	56 bid	1	0	1	0	OM (2)	None	None
18	28	M	0	TSA	62.9	Subtotal	78.4	56 bid	0	0	1	1	OM (2)	TI (2)	None
19	76	F	1	TSA	14.3	Subtotal	78.4	56 bid	0	0	1	0	None	None	None

bid, twice a day; CGE, cobalt Gray equivalents; F, female; M, male; OM, otitis media; Partial, partial removal; PS, performance status, RN, radiation necrosis; Subtotal, sub (nearly) total removal; TI, transient ischaemia; TOA, transoral approach; TSA, transsphenoidal approach.

Figure 1. Local control rates of 19 patients.



while maintaining a high tumour control rate. So far we have treated 30 cases with pathologically proven clival chordomas with hyperfractionated PBT, and here we present the outcome of consecutive 19 patients who have been followed up for more than 2 years after the end of PBT.

METHODS AND MATERIALS

Patients

Between February 2006 and May 2013, 19 patients with chordoma at the clivus were treated with PBT (Table 1). Characteristics of the 19 patients are shown in Table 1. These patients have been followed up for 31.5–115.4 months with a median value of 61.7 months after the end of PBT. In this cohort, there are 8 males and 11 females with an age distribution from 13 to 76 years with a median age of 52 years. Their tumours ranged in volume from 1.7 to 62.9 cm^3 with a median value of 19.0 cm^3 at initial diagnosis. All patients were pathologically diagnosed with chordoid chordoma. Two patients (Numbers 2 and 4) were referred to our institute (Proton Medical Research Center, University of Tsukuba) after tumour recurrence. At presentation, two patients (Numbers 2 and 17) had complete abducens palsy, one (Number 4) had severe bilateral bulbar palsy and one (Number 6) had mild right bulbar palsy. At initial surgery, transsphenoidal, transoral, suboccipital, posterior petrosal and anterior petrosal approaches were utilized in 13, 2, 2, 1 and 1 patient(s), respectively. Three patients had undergone >2 surgeries prior to PBT. Among these three patients, one patient (Number 12) had multiple cranial nerve injuries resulting from their last surgery. Consequently, at the time of PBT, gross total or subtotal removal, partial removal and biopsy were performed on eight, nine and two patients, respectively (Table 1).

Proton beam therapy

In the hyperfractionation schemes, PBT using the double scattering method was performed twice daily with at least a 6-h interval between each treatment for 5 days a week. In the initial protocol, the dose per fraction, total number of fractions and total dose were set at 1.21, 64 and 77.44 cobalt gray equivalents (CGEs), respectively, based on our previous report.[13] In this first scheme, the total equivalent doses of 2.0 Gy/CGE per fraction were 62.15 and 70.64 CGE for the α/β ratio of 2.0 and 7.0 Gy, respectively. We prospectively planned and treated 10 cases with this first protocol until July 2008; however, one case was pathologically diagnosed as chondrosarcoma later and was excluded from the present analysis, resulting in nine patients in this cohort. After assessing the feasibility and early toxicity of this first protocol, we progressed to the next protocol with dose escalation, raising the fractional and total doses to 1.40 and 78.40 CGE, respectively. The total equivalent doses of 2.0 Gy/CGE per fraction were 66.64 and 73.17 CGE for the α/β ratio of 2.0 and 7.0 Gy, respectively. Between August 2008 and May 2013, 10 patients were treated with this next protocol.

For treatment planning, CT was performed in 3- to 5-mm slices in the treatment position. The gross tumour volume was determined as the enhanced area or tumour cavity on enhanced CT and/or MRI. The clinical target volume encompassed the gross tumour volume plus a 5- to 10-mm margin. The planned target volume encompassed the clinical target volume plus a 5-mm margin.

Analysis

Acute reactions were evaluated according to the Common Terminology Criteria for Adverse Events v. 3.0 from the National Cancer Institute (Rockville, MD).[20] Late normal tissue complications were evaluated according to the late effects in normal tissues subjective, objective, management and analytic scoring system.[21] Survival rates were calculated by the Kaplan–Meier method.

RESULTS

All patients underwent PBT without suspension. No patient was lost to follow-up. The median follow-up period was 61.7 months with a range from 31.5 to 115.4 months.

At this point in the analysis, 13 patients were alive and 6 patients were dead. Four patients died from tumour recurrence, one patient from aspiration pneumonia due to bulbar palsy (Number 4) and one patient from subarachnoid haemorrhage (Number 12). Seven patients showed tumour recurrence after PBT. Of the seven patients, three (Numbers 1, 2 and 3) had marginal zone recurrences and two (Numbers 5 and 13) had in-field recurrences, one (Number 8) had cervical lymph node metastases and one

Figure 2. Overall and cause-specific survival rates of 19 patients.

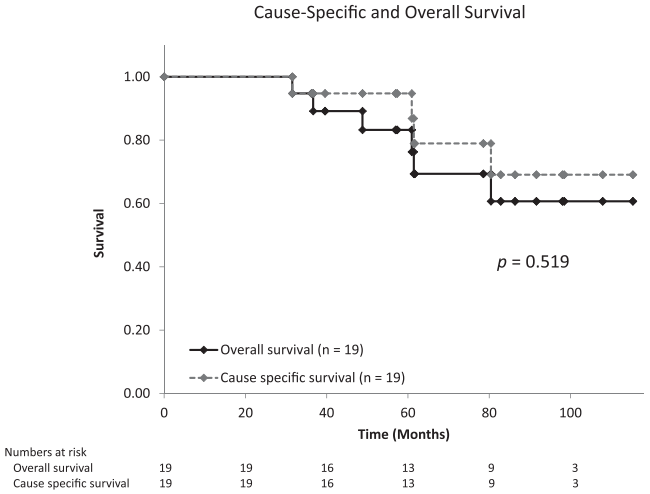
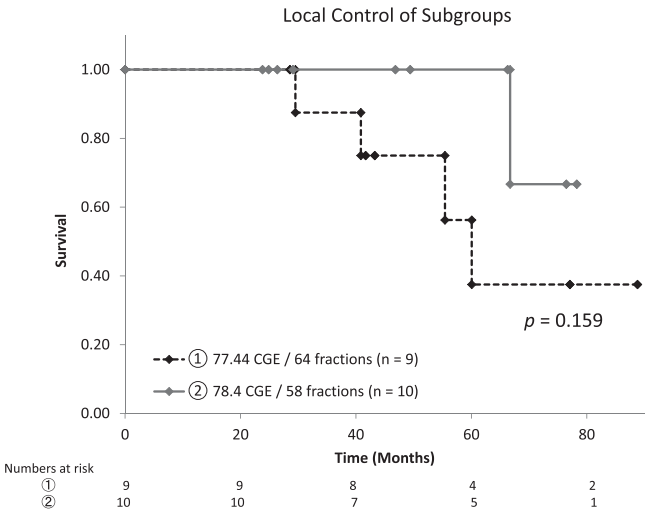


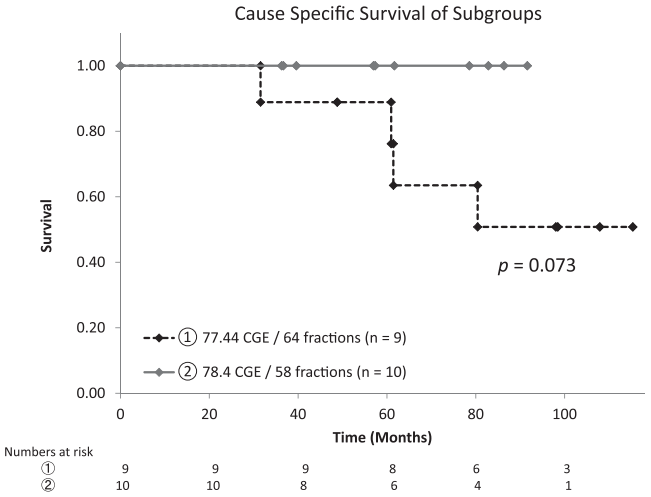
Figure 3. Local control rates of 9 cases with 77.44 cobalt Gray equivalents (CGE) in 64 fractions and 10 cases with 78.4 CGE in 56 fractions.



(Number 9) showed surgical path drop metastasis and meningeal dissemination. Consequently, at 3 and 5 years, local control rates were 92.9% and 75.0%, respectively (Figure 1). In addition, the cause-specific and overall survival rates at 3 and 5 years were 94.7%, 94.7%, and 94.7%, 83.2%, respectively (Figure 2).

In the subgroup analyses comparing the 9 patients treated with 77.44 CGE in 64 fractions and the 10 patients treated with 78.4 CGE in 56 fractions, the former cohort showed 3- and 5-year local control rates of 87.5 and 56.3%, respectively, with a median observation period of 80.4 months. In the latter cohort, 3- and 5-year local control rates were both 100% with a median observation period of 59.5 months (Figure 3), but one patient showed tumour regrowth at 66.7 months. Also, the cause-specific survival rates of the patients with 77.44 CGE in 64 fractions were 88.9% at both 3 and 5 years, whereas the rates of patients with 78.4 CGE in 56 fractions were both 100% (Figures 4 and 5).

Figure 4. Overall survival rates of 9 cases with 77.44 cobalt Gray equivalents (CGE) in 64 fractions and 10 cases with 78.4 CGE in 56 fractions.



Although the differences between the two groups were not statistically significant ($p = 0.162$ in local control, $p = 0.074$ in cause specific survival), the 78.6 CGE in 56 fractions scheme tended to be more efficient than the 77.44 CGE in 64 fractions scheme.

None of the 19 patients experienced acute reactions over grade 2 (Table 1). In late complications, one patient (Number 2) showed mild cognitive and memory dysfunction 3 years after the end of PBT. As MR images demonstrated bilateral medial temporal lobe radiation necrosis (RN), he was treated with oral steroids, vitamin E and hyperbaric oxygen therapy, resulting in partial resolution of the symptoms in approximately 1 year. He was able to take care of himself and could take a short walk at the last follow-up. In addition, two patients (Numbers 14 and 18) showed mild neurological symptoms with slight high-intensity changes on T_2 weighted MRI in the medulla. One patient (Number 14) complained of numbness in the left leg 9.5 months after the end of PBT. The other patient (Number 18) complained of slight weakness of left extremities associated with numbness 13 months after the end of PBT. Both of them were treated with oral anticoagulants, and they recovered completely both clinically and on MRIs. Retrospectively, they were diagnosed as transient brain stem ischaemia probably due to peripheral blood flow insufficiency in the structures around the brain stem.

A representative case (Number 18) treated with the present scheme after maximum surgical removal is shown in Figures 6 and 7.

DISCUSSION

Chordomas grow slowly; however, Fagundes et al[22] reported a recurrence rate of 31% and an overall local relapse rate of 29% in an analysis of 204 patients with skull base or cervical chordomas treated by surgery and radiotherapy. In this analysis, the patterns of recurrence included local (78%), surgical pathway seeding (5%), regional nodal (3%) and/or metastases (20%). Total or near-total resection is accepted as being an important factor for local control of chordomas; however, the aggressive

Figure 5. Cause-specific survival rates of 9 cases with 77.44 cobalt Gray equivalents (CGE) in 64 fractions and 10 cases with 78.4 CGE in 56 fractions.

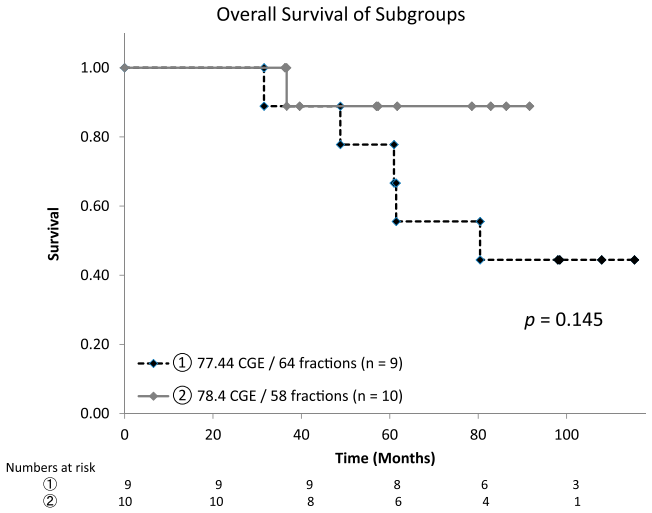
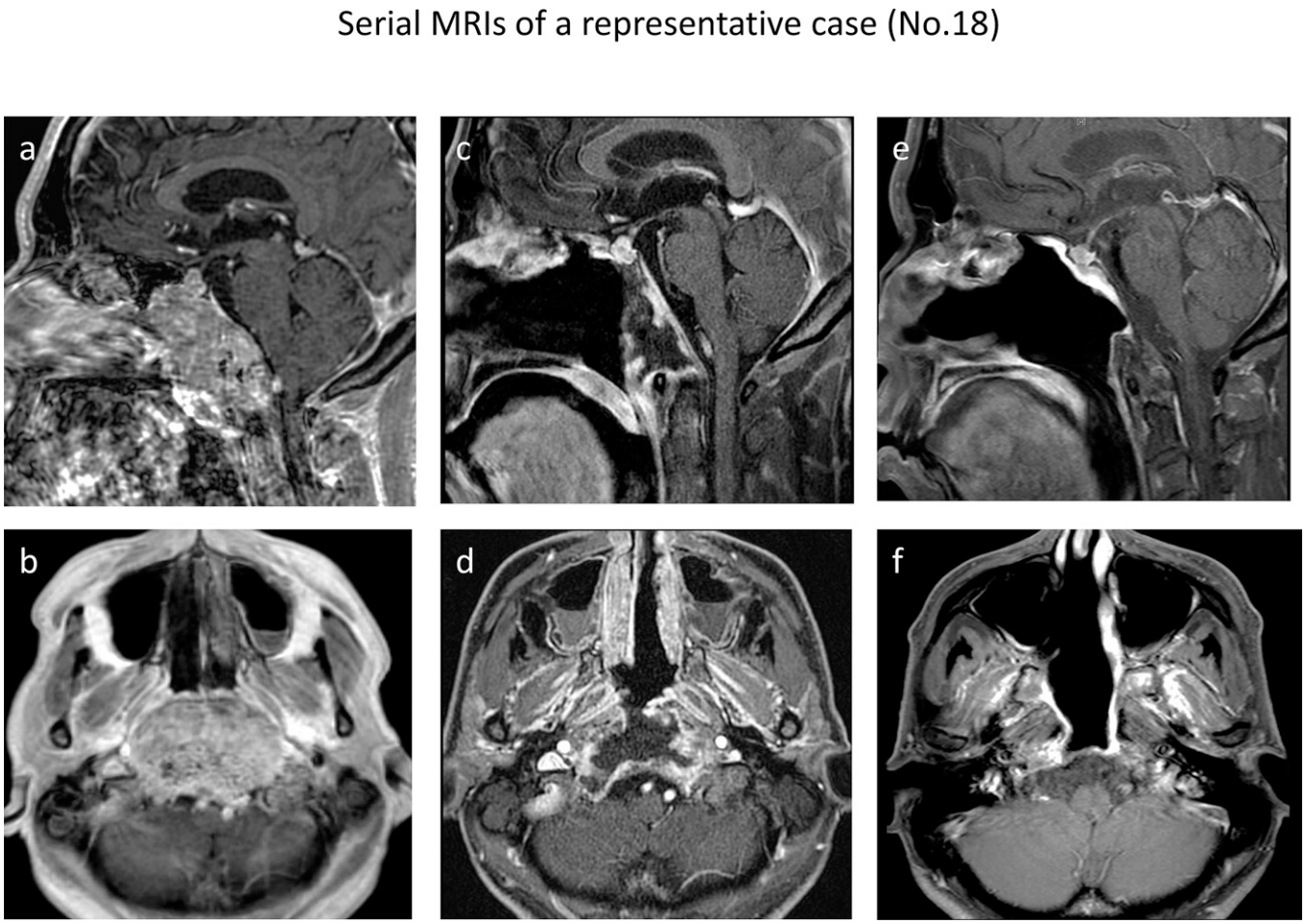


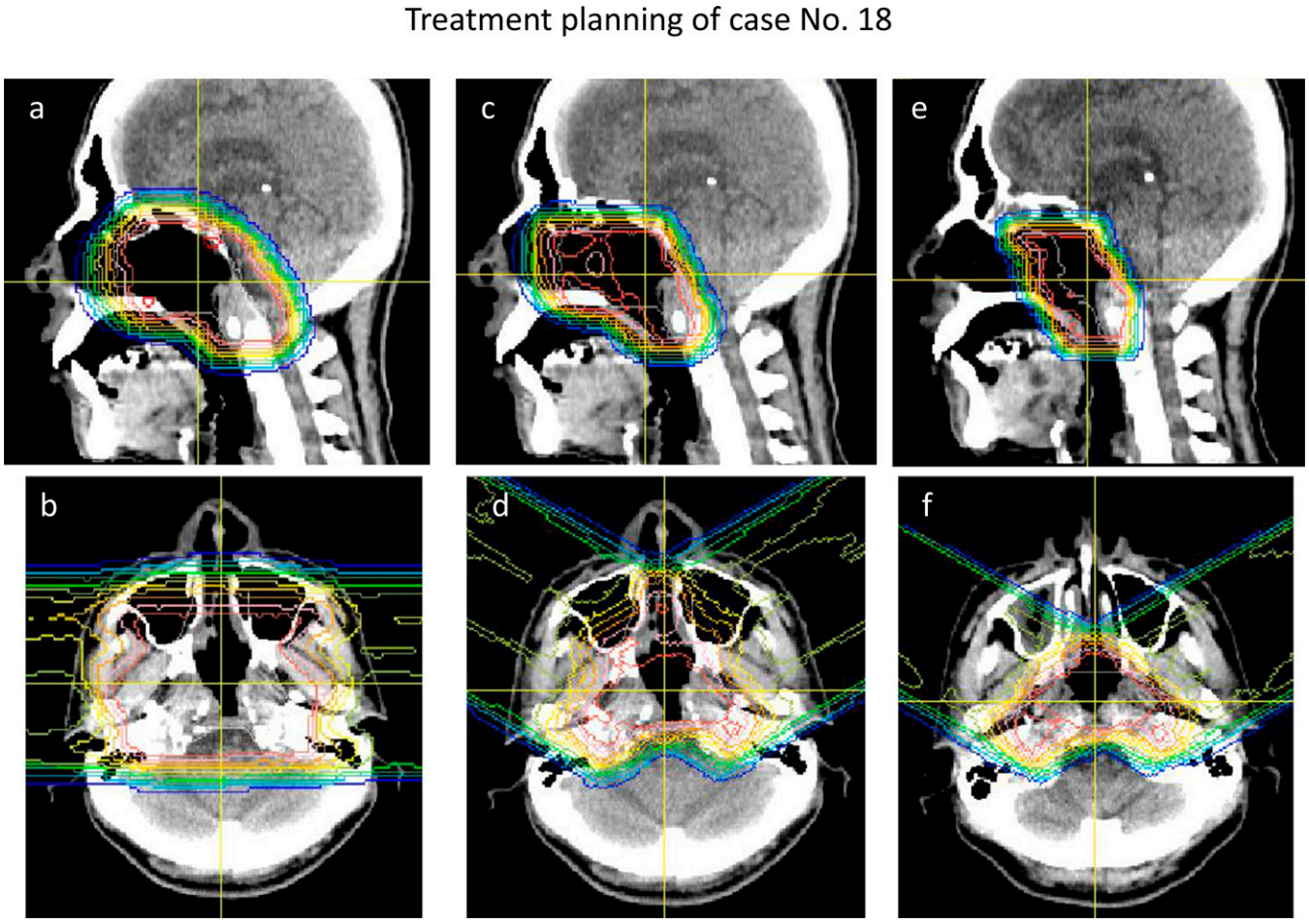
Figure 6. The serial images of patient number 18; (a, b) pre-surgical images, (c, d) after endoscopic transnasal surgery. Note that nearly total removal of the tumour was achieved resulting in a space between the brain stem and the clival dura mater. (e, f) 24 months after proton beam therapy. Note that the tumour is stabilized without evidence of adverse effects in the surrounding normal structures.



surgical treatment has sometimes been associated with increased patient morbidity and mortality rates[7–9] resulting in lower quality of life for survivors.[10] Therefore, the combination of maximal surgical resection within a safe range and optimal post-operative radiotherapy is very important for preventing local tumour recurrence and maintaining patients' performance status (Figure 7).

In a review article reported by Amichetti et al,[4] the mean 5-year survival and local control rates for the 191 reported patients treated with conventional photon radiotherapy were 53.5% and 33.5%, respectively. The total doses applied were from 22.93 to 69.36 Gy with an average value of 52.7 Gy. As for proton radiotherapy, we extracted data specifically on skull base chordomas treated by proton beams, and they are listed in Table 2. Munzenrider and Liebsch[14] reported 169 patients of skull base chordoma treated with protons and photons, with a median observation period of 41 months. They reported 5- and 10-year local control rates of 73% and 54%, respectively, and overall survival rates of 80% and 54%, respectively. However, there were 3 patients who died of brain stem injury and 3 patients who underwent temporal lobe resection due to RN. Also, Hug et al[12] reported 33 patients with skull base chordomas treated by proton and photon therapy, with a mean dose of 70.7 CGE and a mean follow-up time of 33.2 months. They reported a 5-year local control rate of 59% and an overall survival rate of 79%. In their study, grade 3 or 4 toxicities included one patient with asymptomatic RN, one patient with focal seizure (single episode) and two patients with severe hearing loss. The result of our very early phase trial was reported by Igaki et al[13] in 2004. In this study, since dose and fraction sizes varied from 63 to 95 CGE and 2.0–3.5 CGE, respectively, 5-year local control and overall survival rates were 46% and 66.7%, respectively, with two cases resulting in grade 4 late toxicity. Later, Noël et al[18] reported 100 cases of skull base and upper cervical spine chordomas treated using proton and photon therapy, with a median follow-up of 31 months. The 5- and 10-year survival rates were 86.3% and 53.8%, respectively; however, 42 patients experienced 1 or more late complications. More recently, Ares et al[11] reported 42 patients with skull base chordomas treated with PBT using spot scanning technology with a dose of 73.5 CGE. The mean follow-up period was 38 months. Although the 5-year local control and disease-specific survival rates were both 81%, there were one patient with grade 3 and one patient with grade 4 unilateral optic neuropathy and two patients with grade 3 temporal lobe RN.

Figure 7. The treatment planning of patient number 18. (a, b) The initial plan encompasses not only the tumour but also the surgical path with 5- to 10-mm margins. With this plan, 0–39.2 cobalt Gray equivalents (CGE) in 28 fractions were delivered. (c, d) The second plan that designs the dose to the brain stem and the optic chiasma to be <50% of the maximum dose. With this plan, 40.4–58.5 CGE in 13 fractions was delivered. (e, f) The third plan that covers only the tumour bed, designing the dose to the brain stem and the optic chiasma to be <20% of the maximum dose. With this plan, 60.2–78.4 CGE in 13 fractions was delivered.



In the present study evaluating 19 patients, the median observation period of 61.4 months was longer than that in most of the previous studies using PBT, and the obtained survival data were compatible or superior to others. Particularly, in the 10 patients given 78.4 CGE in 56 fractions, the 5-year local control, cause-specific survival and overall survival rates were 100%, 100% and 88.9%, respectively, with a median follow-up period of 59.5 months. Although the number of patients in this study is small, these outcomes are favourable compared with previous ones. To further improve the reliability of data with this hyperfractionation scheme and to be accepted as a choice of therapeutic protocol, longer follow up and greater patient numbers are greatly desired.

One of the limitations of radiotherapy treatments, including PBT, is the unavoidable dose deficit areas that occur because of adjacent dose-limiting normal tissue structures, such as the optic nerves or the brain stem. It is inevitable to make plans to reduce the dose to as low as 54 Gy to these risky structures. Consequently, local recurrence rates in these areas become relatively high;[14] however, salvage therapy for recurrence after radiation therapy is extremely difficult.[8] Fagundes et al[22] reported that the 3- and 5-year overall survival rates after local relapse were 44% and 5%, respectively. Therefore, maximum reduction of tumour burden should be performed to improve the geometry of interface of the tumour and normal tissue, and to maintain an adequate distance from these dose-limiting structures.[23] These are critical factors to reduce dose deficit areas in the following PBT planning.

The risk of RN is reported to be significantly higher when the fraction size is >2.2–2.5 Gy.[24] It is also important to remember that RN can occur when the total dose is <60 Gy.[15] Furthermore, the risk of RN can be higher when the structures are located at the distal end of the proton beams, as the relative biological effectiveness of proton beams is reported to be >1.1 at the distal end of the Bragg peak.[25] Although we experienced one case of temporal lobe RN, the lesion was fortunately stabilized with conservative medical treatment. Temporal lobe RN is a well-known late complication of PBT for skull base chordomas because of the anatomical vicinity and that dose is usually delivered using opposed lateral fields. Santoni et al[26] reported that among 96 patients of chordomas/chondrosarcomas treated with proton and photon irradiation, 10 patients (10.4%) developed temporal lobe RN. Of these 10 cases, 6 cases received 72 CGE and 4 cases received

Table 2. Studies of skull base chordomas treated with proton beams

Authors (years)	Number of points	Follow-up (month)	Dose (CGE)	Dose/ fraction	LC (%)				OS (%)				Toxicity
					2-year	3-year	4-year	5-year	2-year	3-year	4-year	5-year	
Munzenrider and Liebsch (1999)[14]	169	41 (1–254)	66–83	1.8–1.92	–	–	–	73	–	–	–	80	Brain stem toxicity: 8% at 5 years Temporal lobe injury: 13% at 5 years Optic neuropathy: 4.4%
Hug et al (1999)[12]	33	33.2	64.8–79.2 (mean: 70.7)	1.8	–	67	–	59	–	87	–	79	Grades 3 and 4 toxicity: 7%
Igaki et al (2004)[13]	13 (1 CS)[a]	69.3 (14.6–123.4)	72 (63–95)	2.0–3.5	–	67.1	–	46	–	84.6	–	66.7	Grade 4 temporal lobe necrosis: 1 case Grade 4 oral ulceration and grade 5 brain necrosis: 1 case
Noël et al (2005)[18]	100	31 (0–87)	67 (60–71)	1.8	86.3	–	53.8	–	94.3	–	–	80.5	Visual disorder: 8 cases Neuropsychological disorder: 11 cases Bilateral temporal lobe necrosis: 1 case Hearing loss: unilateral 16, and 5 bilateral: 5 cases Pituitary dysfunction: 16 cases
Ares et al (2009)[11]	42	38 (14–92)	73.5	1.8–2.0	–	87	–	81	–	–	–	62	Grade 3 or 4 optic neuropathy: 2 cases Central nervous system necrosis: 2 cases
This study	19	61.4 (31.5–115.4)	77.44 or 78.4	1.21 or 1.4	–	92.9	–	75	–	94.7	–	83.2	Temporal lobe necrosis: 1 case
This study (subgroups)	9	80.4 (31.5–115.4)	77.44	1.21	–	87.5	–	56.3	–	88.9	–	77.8	Temporal lobe necrosis: 1 case
	10	59.5 (36.3–91.6)	78.4	1.4	–	100	–	100	–	100	–	88.9	None

CGE, cobal Gray equivalents; CS, chondrosarcoma; LC, local control; OS, overall survival.
[a]A case of CS was included.

66.6 CGE with conventional fractionation (1.8 CGE/day, 5 fractions/week). Our results may indicate that even with the hyperfractionation scheme, it is difficult to entirely prevent temporal lobe RN when the total dose is >77.44 CGE. We also experienced two cases of late onset transient ischaemia of the brain stem. Although the aetiology has not been clarified yet, this probably occurred due to small vessel vasculopathy in the structures around the brain stem. Although arterial damage may occur after doses of 50–70 Gy are delivered in conventional fraction patterns,[27] the mechanism of late onset such as in our cases is not very clear. We consider that treatment plans which surround more than half of the brain stem may have some risks, making it difficult to maintain long-term peripheral blood flow around the brain stem even if the brain stem itself was spared. Close observation is highly recommended in cases treated with similar treatment planning.

One drawback to this procedure is the long period of time necessary for completion. Since 78.4 CGE in a 56-fraction scheme takes 28 treatment days to complete, the individual patient's performance status may have to meet this requirement, and patients with extremely aggressive tumours may not be suited for this treatment.

In conclusion, our analyses of the relatively long-term outcomes of patients with clival chordomas indicate that the hyperfractionated scheme reported here is worthy of consideration as one therapeutic approach, which delivers sufficient doses to the tumours with maximum preservation of neurological function. Particularly, PBT administered with 78.4 CGE in a 56-fraction scheme may be efficient. In addition, surgical resection should include not only debulking but also maintaining an adequate distance from nearby dose-limiting normal tissue structures to improve the long-term outcomes of patients with clival chordomas.

REFERENCES

1. Colli B, Al-Mefty O. Chordomas of craniocervical junction: follow-up review and prognostic factors. *J Neurosurg* 2001; **95**: 933–43. doi: http://dx.doi.org/10.3171/jns.2001.95.6.0933
2. Heffelfinger MJ, Dahlin DC, MacCarty CS, Beabout JW. Chordomas and cartilaginous tumors at the skull base. *Cancer* 1973; **32**: 410–20. doi: http://dx.doi.org/10.1002/1097-0142(197308)32:2<410::AID-CNCR2820320219>3.0.CO;2-S
3. McMaster ML, Goldstein AM, Bromley CM, Ishibe N, Parry DM. Chordoma: incidence and survival patterns in the United States, 1973–1995. *Cancer Causes Control* 2001; **12**: 1–11. doi: http://dx.doi.org/10.1023/A:1008947301735
4. Amichetti M, Cianchetti M, Amelio D, Enrici RM, Minniti G. Proton therapy in chordoma of the base of the skull: a systematic review. *Neurosurg Rev* 2009; **32**: 403–16. doi: http://dx.doi.org/10.1007/s10143-009-0194-4
5. Guinto G, Guinto-Nishimura Y. Clivus chordomas: role of surgery. *World Neurosurg* 2014; **81**: 688–9. doi: http://dx.doi.org/10.1016/j.wneu.2013.01.123
6. Tai PT, Craighead P, Bagdon F. Optimization of radiotherapy for patients with cranial chordoma. A review of dose-response ratios for photon techniques. *Cancer* 1995; **75**: 749–56. doi: http://dx.doi.org/10.1002/1097-0142(19950201)75:3<749::AID-CNCR2820750302>3.0.CO;2-D
7. al-Mefty O, Borba LA. Skull base chordomas: a management challenge. *J Neurosurg* 1997; **86**: 182–9. doi: http://dx.doi.org/10.3171/jns.1997.86.2.0182
8. Gay E, Sekhar LN, Rubinstein E, Wright DC, Sen C, Janecka IP, et al. Chordomas and chondrosarcomas of the cranial base: results and follow-up of 60 patients. *Neurosurgery* 1995; **36**: 887–97. doi: http://dx.doi.org/10.1227/00006123-199505000-00001
9. Monfared A, Agrawal S, Jackler RK. Cranial base approaches to inaccessible intracranial tumors. *Curr Opin Neurol* 2007; **20**: 726–31.
10. Diaz RJ, Maggacis N, Zhang S, Cusimano MD. Determinants of quality of life in patients with skull base chordoma. *J Neurosurg* 2014; **120**: 528–37. doi: http://dx.doi.org/10.3171/2013.9.JNS13671
11. Ares C, Hug EB, Lomax AJ, Bolsi A, Timmermann B, Rutz HP, et al. Effectiveness and safety of spot scanning proton radiation therapy for chordomas and chondrosarcomas of the skull base: first long-term report. *Int J Radiat Oncol Biol Phys* 2009; **75**: 1111–8. doi: http://dx.doi.org/10.1016/j.ijrobp.2008.12.055
12. Hug EB, Loredo LN, Slater JD, DeVries A, Grove RI, Schaefer RA, et al. Proton radiation therapy for chordomas and chondrosarcomas of the skull base. *J Neurosurg* 1999; **91**: 432–9. doi: http://dx.doi.org/10.3171/jns.1999.91.3.0432
13. Igaki H, Tokuuye K, Okumura T, Sugahara S, Kagei K, Hata M, et al. Clinical results of proton beam therapy for skull base chordoma. *Int J Radiat Oncol Biol Phys* 2004; **60**: 1120–6. doi: http://dx.doi.org/10.1016/j.ijrobp.2004.05.064
14. Munzenrider JE, Liebsch NJ. Proton therapy for tumors of the skull base. *Strahlenther Onkol* 1999; **175**: 57–63. doi: http://dx.doi.org/10.1007/BF03038890
15. Noël G, Habrand JL, Mammar H, Pontvert D, Haie-Méder C, Hasboun D, et al. Combination of photon and proton radiation therapy for chordomas and chondrosarcomas of the skull base: the Centre de Protonthérapie D'Orsay experience. *Int J Radiat Oncol Biol Phys* 2001; **51**: 392–8.
16. Noël G, Habrand JL, Jauffret E, de Crevoisier R, Dederke S, Mammar H, et al. Radiation therapy for chordoma and chondrosarcoma of the skull base and the cervical spine. Prognostic factors and patterns of failure. *Strahlenther Onkol* 2003; **179**: 241–8.
17. Noël G, Feuvret L, Ferrand R, Boisserie G, Mazeron JJ, Habrand JL. Radiotherapeutic factors in the management of cervical-basal chordomas and chondrosarcomas. *Neurosurgery* 2004; **55**: 1252–60.
18. Noël G, Feuvret L, Calugaru V, Dhermain F, Mammar H, Haie-Méder C, et al. Chordomas of the base of the skull and upper cervical spine. One hundred patients irradiated by a 3D conformal technique combining photon and proton beams. *Acta Oncol* 2005; **44**: 700–8. doi: http://dx.doi.org/10.1080/02841860500326257
19. Weber DC, Rutz HP, Pedroni ES, Bolsi A, Timmermann B, Verwey J, et al. Results of spot-scanning proton radiation therapy for chordoma and chondrosarcoma of the skull base: the Paul Sherrer Institute experience. *Int J Radiat Oncol Biol Phys* 2005; **63**: 401–9. doi: http://dx.doi.org/10.1016/j.ijrobp.2005.02.023
20. National Cancer Institute. Common terminology criteria for adverse events version 3.0. [Cited 2 May 2016.] Available from: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_30
21. Pavy JJ, Denekamp J, Letschert J, Littbrand B, Mornex F, Bernier J, et al. EORTC Late

Effects Working Group. Late effects toxicity scoring: the SOMA scale. *Radiother Oncol* 1995; **35**: 11–15. doi: http://dx.doi.org/10.1016/0167-8140(95)97448-M

22. Fagundes MA, Hug EB, Liebsch NJ, Daly W, Efird J, Munzenrider JE. Radiation therapy for chordomas of the base of skull and cervical spine: patterns of failure and outcome after relapse. *Int J Radiat Oncol Biol Phys* 1995; **33**: 579–84. doi: http://dx.doi.org/10.1016/0360-3016(95)02014-3
23. Menezes AH. Clival and craniovertebral junction chordomas. *World Neurosurg* 2014; **81**: 690–2. doi: http://dx.doi.org/10.1016/j.wneu.2013.03.050
24. Schultheiss TE, Kun LE, Ang KK, Stephens LC. Radiation response of the central nervous system. *Int J Radiat Oncol Biol Phys* 1995; **31**: 1093–112. doi: http://dx.doi.org/10.1016/0360-3016(94)00655-5
25. Paganetti H. Relative biological effectiveness (RBE) values for proton beam therapy. Variations as a function of biological endpoint, dose, and linear energy transfer. *Phys Med Biol* 2014; **59**: 419–72. doi: http://dx.doi.org/10.1088/0031-9155/59/22/R419
26. Santoni R, Liebsch N, Finkelstein DM, Hug E, Hanssens P, Goitein M, et al. Temporal lobe (TL) damage following surgery and high-dose photon and proton irradiation in 96 patients affected by chordomas and chondrosarcomas of the base of the skull. *Int J Radiat Oncol Biol Phys* 1998; **41**: 59–68. doi: http://dx.doi.org/10.1016/S0360-3016(98)00031-5
27. Hall EJ. Clinical response of normal tissue. In: Hall EJ, ed. *Radiobiology for the radiologist*. 5th edn. Philadelphia, PA: Lippincott Williams & Wilkins; 2000. pp. 355–6.