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Original article

Proton beam therapy for skull base chordomas in 106 patients: A dose adaptive radiation protocol

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ABSTRACT

Background and purpose: To evaluate clinical results and safety of a dose adaptive protocol based on tumor volume coverage and critical structure constraints, for the treatment of skull base chordomas.

Material and methods: Between May 2006 and October 2012, 106 patients with skull base chordoma were treated by combined photon and proton irradiation. Prescribed dose levels were 68.4, 70.2, 72 and 73.8 Gy(RBE) in once daily fractionation of 1.8 Gy(RBE). Dose level and dosimetric constraints to organs at risk depended on postoperative residual Gross Tumor Volume (GTV) coverage. Local control (LC) and overall survival (OS) were evaluated using the Kaplan–Meier method.

Results: With a median follow-up of 61 months, the 2-year, 4-year, and 5-year LC rates were 88.6%, 78.3%, and 75.1%, respectively. GTV > 25 mL ($p = 0.034$, HR = 2.22; 95%CI 1.06–4.62) was an independent unfavorable prognostic factor of LC.

The 2-year, 4-year, and 5-year OS rates were 99%, 90.2%, and 88.3%, respectively.

Grade 3–5 late toxicity was observed in 7 patients, resulting in 93% 5-year freedom from high-grade toxicity.

Conclusions: This study suggests that the probability of LC of skull base chordomas depends on postoperative GTV. The dose adaptive protocol achieves acceptable local control. Future studies should investigate whether further dose escalation to doses in excess of 74 Gy(RBE) would achieve better results.

Skull base chordoma is a rare and slow-growing bone tumor of fetal notochord origin. Due to its localization adjacent to critical structures such as brainstem and optic pathways, complete resection is rarely feasible [1] and even after total resection alone, there remains a risk of disease recurrence [2].

Despite a low potential for metastasis [3] LC is the most important prognostic factor for OS [4]. Optimal surgery followed by radiation therapy (RT) is considered to be the treatment of choice. However, in order to respect dose constraints to adjacent critical organs, conventional photon irradiation techniques are used to deliver a total dose to target volume limited to 55–60 Gy [5]. Proton RT allows dose escalation to the tumor and delivery of substantially lower doses to critical structures compared to photons, as a result of the ballistic characteristics of protons. Previous studies [4–6] have shown that proton therapy (PT) after surgery provides a significant improvement of LC compared to conventional photon radiation therapy. Indeed Terahara et al. [7] suggested that the low-dose region in the target volume was likely to be the main cause of local recurrence. This inhomogeneity is related to the intimate contact of the tumor with critical structures. Noel et al. [8] demonstrated a correlation between LC and homogeneity of the dose delivered to the tumor volume.

The purpose of this study was to evaluate the long-term results and safety of a dose adaptive protocol based on postoperative GTV coverage and dosimetric constraints to organs at risk (OAR) for the treatment of skull base chordoma.

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Materials and methods

Patients

The study protocol was approved by the Institutional Review Board committee.

From May 2006 to October 2012, 106 patients with histologically proven skull base chordoma for whom magnetic resonance imaging (MRI) and clinical information were available until the date of analysis or the patient's death, were included at the Orsay PT center. The date of analysis was September 2016.

Treatment planning and delivery

Irradiation consisted of a combination of photons and protons in 91 patients, while 15 patients were treated exclusively by proton beams due to the increased capacity of the PT facility. Beam and apparatus characteristics have been previously published [9–10]. 3D-RT with 6–20 MV beams were used for the photon therapy step. For the PT step, from 2006 to 2010, a 201-MeV fixed horizontal beam was used in 80 patients. Since October 2010, a 230 MeV proton beam has been used to deliver irradiation via a gantry in 26 patients.

After implantation of three to five gold fiducial markers in the outer skull bone under local anesthesia, an individual customized thermoplastic immobilization was made for each patient.

The contouring of GTV and OAR was performed after 3-dimensional image correlation with T2-weighted and contrast-enhanced T1-weighted MRI.

The high-risk (HR) clinical target volume (CTV) included the postoperative GTV or surgical cavity when complete resection was performed.

The low-risk (LR) CTV included the HR CTV with a 3D margin of 5 mm, plus regions of suspected microscopic spread (clivus and all of the 2 cavernous sinuses), sphenoid sinus in the case of transsphenoidal surgery and the first five millimeters of posterior pharyngeal wall in the case of an anterior surgical approach.

The HR planning target volume (PTV) encompassed the HR CTV with a 3D margin of 1 mm and LR PTV was automatically defined with a 3D margin of 2–3 mm from the LR CTV for proton therapy and 3–6 mm for photon therapy, respectively.

Dose adaptive protocol

The dose adaptive protocol was performed by taking into account 3 different levels of constraints to OAR according to clinical presentation and GTV coverage (Table 1). The aim was to deliver at least 95% of the total prescribed dose to 95% of the GTV. This dosimetric criterion is called V95/D95. If the V95/D95 criterion was not achieved despite surgery, the total dose was then decreased by 1.8 Gy(RBE) steps from 73.8 Gy(RBE) to a minimum dose of 68.4 Gy (RBE). When GTV coverage remained unsatisfactory at a dose of 68.4 Gy(RBE), constraints to OAR were softened (level C).

Finally, four prescribed dose levels were defined: 73.8 Gy(RBE) ($n = 36$), 72 Gy(RBE) ($n = 21$), 70.2 Gy(RBE) ($n = 23$) and 68.4 Gy (RBE) ($n = 26$).

Prescribed doses to target volumes were 52.2 Gy(RBE) (RBE = 1.1) [11] in LR PTV and from 16.2 to 21.6 Gy(RBE) in HR PTV in once daily fractions of 1.8 to 2 Gy(RBE).

The median duration of irradiation was 56 days (range, 42–76).

Table 1
Dose constraints to critical organs.

Organs	Levels		
	A	B	C
	Maximum Dose		
Chiasma	58 Gy(RBE)		
Contralateral optic nerve	58 Gy(RBE)		60 Gy(RBE)
Ipsilateral optic nerve	58 Gy(RBE)	60 Gy(RBE)	62 Gy(RBE)
Invaded functional optic nerve	60 Gy(RBE)		68 Gy(RBE)
Brainstem	64 Gy(RBE) in		
	<0.5 cc	<1 cc	<1.5 cc
	Surface: 64 Gy(RBE)		
	Center: 55 Gy(RBE)		
	Bottom: 48 Gy(RBE)		
Spinal cord	Surface: 55 Gy(RBE)		
	Center: 48 Gy(RBE)		
Contralateral cochlea	58 Gy(RBE)		
Ipsilateral cochlea	58 Gy(RBE)	64 Gy(RBE)	No limit
Temporal/Front lobes	70 Gy(RBE) in <2 cc		

Follow up evaluation

After treatment, follow-up including clinical examination and MRI was planned every three months for the first two years, every six months for the following three years, and every year thereafter. Blood hormone assays and audiometric and visual examinations were performed annually.

Early (up to 90 days after RT completion) and late (after 90 days) toxicities were evaluated according to the Common Terminology Criteria for Adverse Events, version 4.0 grading system [12].

Statistical analysis

Overall survival (OS) and LC rates were calculated according to the Kaplan–Meier method. LC was defined by clinical and radiological arguments: absence of an increase in tumor mass on MRI and absence of suspicious clinical symptoms. Time to LC and OS were determined from the date of the first day of irradiation. Locally controlled patients were censored at the time of their last follow-up visit or death, whichever occurred first. OS was calculated from the initiation of RT until death or last follow-up (censored data).

Survival curves were compared by the LogRank (Mantel-Cox) method with a p value of 0.05 considered to indicate a statistically significant difference. Only parameters found to be significant on univariate analysis were included in multivariate analysis. The following potential prognostic factors were analyzed: age, sex, number and quality of resection (complete or incomplete), treatment phase (primary or recurrent disease regardless of number of resections), GTV value, OAR abutment (optic pathway, brainstem), extension to cervical spine, tumor control and dosimetric parameters (minimum dose to GTV).

Statistical analyses were performed on XLSTAT (Microsoft Excel; version 2015.2, Redmond, WA, US).

Results

Patient characteristics are shown in Table 2.

Median follow-up after irradiation was 61 months (range, 11–119).

Local control

The 2-year, 4-year, and 5-year LC rates were 88.6% (95% confidence interval [CI] 84.4–92.8), 78.3% (95% CI 71.2–85.4), and 75.1% (95% CI 66.6.-83.6), respectively (Fig. 1).

Relapse occurred in 31 of 106 patients. After further analysis, the origin of recurrence was determined to be situated in GTV in 23 cases and outside the PTV in 3 cases. Five metastatic recurrences were observed after radiation therapy, three of them occurred in the cervical spine, one in the cerebellum and one in the lungs. The median times to local recurrence and distant metas-

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