Radiotherapy and Oncology 120 (2016) 169–174

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Proton therapy

Long term outcomes of patients with skull-base low-grade chondrosarcoma and chordoma patients treated with pencil beam scanning proton therapy

Damien C. Weber [a,b,c,*], Robert Malyapa [a], Francesca Albertini [a], Alessandra Bolsi [a], Ulrike Kliebsch [a], Marc Walser [a], Alessia Pica [a], Christophe Combescure [d], Antony J. Lomax [a,e], Ralf Schneider [a]

[a] Center for Proton Therapy, Paul Scherrer Institute; [b] University of Bern; [c] University of Zürich; [d] Unité d'Epidemiologie Clinique, Hôpitaux Universitaire de Genève; and [e] ETH, Zürich, Switzerland

ARTICLE INFO

Article history:
Received 3 February 2016
Received in revised form 26 April 2016
Accepted 16 May 2016
Available online 28 May 2016

Keywords:
Skull base tumors
Chordoma
Chondrosarcoma
Pencil beam scanning
Proton therapy

ABSTRACT

Purpose: To evaluate the long term tumor control and toxicity of skull base tumors treated with pencil beam scanning proton therapy (PT).

Materials and methods: PT was delivered to 151 (68%) and 71 (32%) chordoma and chondrosarcoma (ChSa) patients, respectively. Mean age of patients was 40.8 ± 18.4 years and the male to female ratio was 0.53. The postoperative tumor was abutting the brainstem or optic apparatus in 71 (32.0%) patients. The postoperative mean gross tumor volume (GTV) was 35.7 ± 29.1 cm^3. The delivered mean PT dose was 72.5 ± 2.2 Gy_{RBE}.

Results: After a mean follow-up of 50 (range, 4–176) months, 35 local (15.8%) failures were observed between 10.9 and 85.4 months. The estimated 7-year LC rate for chordoma (70.9%; CI95% 61.5–81.8) was significantly lower compared to the LC rate for ChSa patients (93.6%; 95%CI 87.8–99.9; $P = 0.014$). The estimated 7-year distant metastasis-free- and overall survival rate was 91.6% (95%CI 91.6–98.6) and 81.7% (95%CI 74.7–89.5), respectively. On multivariate analysis, optic apparatus and/or brainstem compression, histology and GTV were independent prognostic factors for LC and OS. The 7-year high grade toxicity-free survival was 87.2 (95%CI 82.4–92.3).

Conclusions: PBS PT is an effective treatment for skull base tumors with acceptable late toxicity. Optic apparatus and/or brainstem compression, histology and GTV allow independent prediction of the risk of local failure and death in skull base tumor patients.

Chordoma arises from remnants of the embryonal notochord, located usually at the superior and lower aspect of the axial skeleton. This rare tumor, with an incidence of approximately 0.8–1 per million [1] and accounting for approximately 1–4% of all bone tumors [2], is characterized by its locally aggressive growth and a propensity for local recurrences. As a result of the close proximity of critical structures, the surgical management of these tumors is challenging and maximally safe resection with postoperative high-dose radiation therapy is usually recommended. Likewise, chondrosarcoma (ChSa) of the skull of base is an even rarer bone tumor [3,4] that arises from the chondrocytes or their precursor cells involved in the endochondral ossification, most commonly in the petroclival junction. These tumors are also managed with cytoreductive surgery and with postoperative radiotherapy in most cases [5].

Particle beam therapy including but not limited to proton therapy (PT) and carbon ion therapy, is usually administered to these challenging patients because these radiation modalities can deliver high-dose radiation, while sparing organs at risk (OARs) in direct vicinity of the target volume. The advantages of PT, which is usually delivered with a passive scattering paradigm, are their finite range in tissue, lower integral patient-dose and zero exit dose. Protons can be magnetically deflected and scanned within the tumor, allowing an optimization of the proximal dose deposition when compared to passive scattered protons [6]. Pencil beam scanning (PBS) PT has been pioneered by the Paul Scherrer Institute (PSI) since the 1990s [7] and over 1100 patients have been safely treated with PBS.

We have evaluated the outcome of skull base patients with chordoma and ChSa treated with PBS PT and have assessed the major prognostic factors for these two locally invasive tumors.

* Corresponding author at: Center for Proton Therapy, Paul Scherrer Institute, WPTA 144, CH-5232 Villigen West, Switzerland.

E-mail addresses: damiencharles.weber@uzh.ch, damien.weber@psi.ch (D.C. Webe.

http://dx.doi.org/10.1016/j.radonc.2016.05.011
0167-8140/

Materials and methods

Patient characteristics

Between October 1998 and October 2012, 222 patients with histologically proven diagnosis of low grade chondrosarcoma (ChSa; $n = 71$; 32.0%) and chordoma ($n = 151$; 68.0%) of the skull base were treated with curative intent at the PSI. The male to female ratio was 0.53 (Table 1). The patient's characteristics are detailed in Table 1.

Chordoma patients were significantly older than those with ChSa ($P = 0.004$). Chordoma patients were also significantly ($P = 0.01$) more likely to undergo multiple staged surgical procedures, when compared to ChSa patient. Likewise, ChSa patients were significantly ($P = 0.03$) more likely to have optic apparatus tumor compression when compared to those with chordoma. A trend toward significance was observed with gender occurring more frequently in males ($P = 0.09$). No other characteristic's variances were found to be statistically significant (Table 1).

Patient treatments

All patients underwent surgery with curative intent at initial presentation ($n = 171$; 76.9%) or for recurrent disease ($n = 51$; 23.1%). The postoperative mean gross tumor volume (GTV) was 35.7 ± 29.1 cm^3.

The GTV (Table 1) was defined as the macroscopic tumor identified on the planning computed tomography and the postoperative MRI. The prescribed dose for chordoma and ChSa was usually 74 and 70 Gy_{RBE}, respectively. The administered mean dose was 72.5 ± 2.2 Gy_{RBE} at 1.8–2.0 Gy_{RBE} per fraction (with 1.1 relative biologic effectiveness) [8]. Patients were treated using the PBS technique at our two scanning gantries by using energy-degraded beams from the 590-MeV or 250-MeV medical dedicated cyclotrons. Patient treated with the former received 4 weekly PT fractions due to weekly maintenance, while patients treated with the latter received 5 weekly fractions. Single-field uniform dose (SFUD) plans and IM proton therapy (IMPT) plans were used sequentially at PSI [9]. Treatment plans were optimized to maximize the coverage of the GTV, while observing OAR dose constraints.

Follow-up evaluation

Patients were followed clinically and radiographically with MRI ± CT of the brain in regular intervals after treatment. Within the first 2–3 years, follow-up examinations were scheduled in intervals of 3–6 months and annually thereafter. Radiologic criteria for local tumor control were defined as stable or reduced tumor volume on consecutive MRI ± CT scans compared with pre-PT images. Locally controlled patients were censored at the time of their last follow-up or death.

Late adverse events were defined as side effects observed after 90 days following completion of PT and classified according to the NCI Common Terminology Criteria for Adverse Events, CTCAE, v4.0 grading system.

Statistical analysis

Local control (LC), toxicity-free survival (TFS) and overall survival (OS) were assessed using the Kaplan Meier method. Locally controlled patients were censored at the time of their last follow-up or death, whichever occurred first. OS was calculated from the initiation of PT until death or lost to follow-up (censored data). Tumor control was defined as lack of progression by clinical or radiological assessment. Any enlargement of the tumor on subsequent radiological studies was considered a local recurrence. Patients' characteristics were compared between histology using the Chi-square or Fisher's exact test if one expected count was $\leqslant 5$. The log-rank test was used to compare different survival functions according to clinical (histology, patient's age, gender,

Table 1
Comparison of Characteristics of patients with skull base chordoma ($n = 151$) and ChSa ($n = 71$) patients treated with PBS proton therapy. Significant P values ($P < 0.05$) are in bold.

Parameter		Total $N = 222$	Chordoma $N = 151$	ChSa $N = 71$	p value*
Age (years)	Mean (SD)	40.8 (18.4)	43.3 (18.1)	35.6 (18.3)	**0.004**
Gender	Female (%)	105 (47.3)	65 (43.0)	40 (56.3)	0.09
	Male (%)	117 (52.7)	86 (57.0)	31 (43.7)	
Recurrent disease	No (%)	171 (77)	115 (76.2)	56 (78.9)	0.76
	Yes (%)	51 (23)	36 (23.8)	15 (21.1)	
GTV (cc)	Mean (SD)	35.7 (29.1)	35.4 (27.5)	36.1 (32.5)	0.87
Brainstem compression	No (%)	151 (68)	100 (66.2)	51 (71.8)	0.62
	Abutment (%)	46 (20.7)	34 (22.5)	12 (16.9)	
	Yes (%)	25 (11.3)	17 (11.3)	8 (11.3)	
Optic apparatus compression	No (%)	154 (69.4)	113 (74.8)	41 (57.7)	**0.03**
	Abutment (%)	44 (19.8)	26 (17.2)	18 (25.4)	
	Yes (%)	24 (10.8)	12 (7.9)	12 (16.9)	
Compression any type	No (%)	109 (49.1)	76 (50.3)	33 (46.5)	0.70
	Yes (%)	113 (50.9)	75 (49.7)	38 (53.5)	
Surgery	Subtotal resection (%)	215 (96.8)	147 (97.3)	68 (95.8)	0.68
	Complete resection (%)	7 (3.2)	4 (2.7)	3 (4.2)	
Number of surgeries	1 (%)	101 (46.8)	63 (43.4)	38 (53.5)	**0.013**
	2 (%)	78 (36.1)	59 (40.7)	19 (26.8)	
	3 (%)	23 (12.0)	14 (9.7)	12 (16.9)	
	4 (%)	6 (2.8)	6 (4.1)	0 (0)	
	5 (%)	3 (1.4)	3 (2.1)	0 (0)	
	6 (%)	2 (0.9)	0 (0)	2 (2.8)	
	Missing data, n				
Postoperative complications	No (%)	154 (69.4)	106 (70.2)	48 (67.6)	0.89
	Yes (%)	68 (30.6)	45 (29.8)	23 (32.4)	

Abbreviations: SD: standard deviation; ChSa: low grade chondrosarcoma; GTV: gross tumor volume.
* *Chi*-square test.