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Clinical Investigation: Central Nervous System Tumor

Temporal Lobe Toxicity Analysis After Proton Radiation Therapy for Skull Base Tumors

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Summary

Temporal lobe toxicity constitutes one frequent late adverse event in high-dose protontherapy for skullbase tumors. We analyzed clinical events with dosimetric parameters in our patients cohort treated with spot-scanning protontherapy. No statistically significant dose/volume threshold was detected, but a strong trend for Grade 1−3 events was observed. Our data suggest that tolerance of temporal lobes to fractionated radiotherapy correlates with volume included in high-dose regions, supporting the concept to establish organ-at-risk constraint for brain parenchyma.

Purpose: Temporal lobe (TL) parenchyma toxicity constitutes one of the most frequent late adverse event in high-dose proton therapy (PT) for tumors of the skull base. We analyzed clinical events with dosimetric parameters in our patients treated for skull base tumors with spot-scanning PT.

Methods and Materials: Between 1998 and 2005, a total of 62 patients received PT to a median dose of 71.7 Gy (relative biologic effectiveness [RBE]) (range, 63−74 Gy). The dose−volume histogram of each TL and the entire brain parenchyma (BP) were analyzed according to maximum, mean, and minimum dose as well as doses to 0.5, 1, 2, and 3 cc of brain volume ($D_{0.5}$, D_1, D_2, D_3) and correlated with clinical events. Generalized equivalent uniform dose (gEUD) values were calculated.

Results: At a mean follow-up of 38 months (range, 14−92 months), 2 patients had developed symptomatic Grade 3 and 5 patients asymptomatic Grade 1 TL toxicity. Mean doses to a 2-cc volume of BP increased from 71 ± 5 Gy (RBE) for no toxicity to 74 ± 5 Gy (RBE) for Grade 1 and to 76 ± 2 Gy (RBE) for Grade 3 toxicity. TL events occurred in 6 of 7 patients (86%) at or above dose levels of ≥64 Gy (RBE) D_3, ≥68 Gy (RBE) D_2, ≥72 Gy (RBE) D_1, and ≥73 Gy (RBE) $D_{0.5}$, respectively (p = NS). No statistically significant dose/volume threshold was detected between patients experiencing no toxicity vs. Grade 1 or Grade 3. A strong trend for Grade 1 and 3 events was observed, when the gEUD was 60 Gy.

Conclusions: A statistically significant normal tissue threshold dose for BP has not been successfully defined. However, our data suggest that tolerance of TL and BP to fractionated radiotherapy appears to be correlated with tissue volume included in high-dose regions. Additional follow-up time and patient accrual is likely needed to achieve clinical significance for these dose−volume parameters investigated. Our findings support the importance of establishing an organ-at-risk maximally permissible dose for BP.

Keywords: Spot scanning, Proton therapy, Skull base tumors, Late effects, Temporal lobe toxicity

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Introduction

The first patient with skull base (SB) chordoma was treated with fractionated proton therapy (PT) at the Massachusetts General Hospital (MGH)/Harvard Cyclotron Laboratory (HCL) in 1974. Over the last 35 years, particle therapy has established itself worldwide for SB chordomas and chondrosarcomas, and is considered by many the modality of choice for unresectable disease, for patients with postoperative residual disease, or postoperatively for selected situations after complete surgical resection (1). The group at MGH/HCL was the first to establish standards of target prescription doses, as well as organ-at-risk (OAR) dose tolerance levels for proton therapy based on their early outcomes data (2). Subsequently, their principal concepts of target volume definition, dose prescription, dose fractionation, and OAR limitations have been generally adopted by the majority of particle therapy centers.

Results at our own institution using spot-scanning–based PT were recently updated (3). The 5-year actuarial tumor control rates of 81% for chordomas and 94% for chondrosarcomas confirmed the excellent prospect of long-term tumor control and survival for patients treated with PT. Our reported actuarial 5-year risk rate of 6% for incidence of high-grade late adverse events confirmed the modest risks of late toxicities after high-dose PT. The OAR with the highest likelihood of adverse event remains brain parenchyma (BP), specifically temporal lobes (4–6). Our own experience mirrors the results of most other particle centers. Analogous to the policy at our center, all particle centers have placed stringent, "hard" OAR dose tolerance limits on optic nerves, the optic chiasm, and the brainstem. However, in the case of BP, most centers assign either no specific OAR constraints or apply only relatively "soft" dose constraints or "dose/volume goals" in the treatment planning process.

For tumors of the upper SB, specifically clival or petroclival lesions, medial portions of temporal lobe(s) are routinely at risk for receiving levels close to or at prescription dose. Frequently, tumor infiltrates either the cavernous sinus or protrudes into the middle cranial fossa. Hence, tumor is either abutting or compressing one or both temporal lobes. Although most SB tumors do not infiltrate BP *per se*, the creation of a planning target volume (PTV) to expand the clinical target volume (CTV) or gross tumor volume (GTV) essentially places peripheral portions of the PTV within the medial temporal lobe(s).

Risks of TL damage are well documented following initial reports on particle therapy. Temporal lobe damage can result in amnesia with a specific memory impairment profile depending on the severity (grade) of toxicity (7, 8). At present, a dose–volume relationship, including a reproducible normal tissue threshold dose, has not been successfully defined.

Designation of OAR dose constraints has greatly contributed to the reduction of brainstem and optic apparatus high-grade toxicities. In the present study, we analyzed various dose–volume parameters of BP damage to determine a threshold dose. The goal of this study was to identify predictive parameters of TL damage that would potentially lead to treatment planning recommendations in our clinical practice.

Methods and Materials

Patients and procedures

A total of 62 patients with histologically proven SB chordomas or chondrosarcomas were treated between October 1998 and November 2005 at our institution using spot-scanning–based, fractionated PT. The mean age of the patient population was 44.5 years and ranged from 12 to 74 years at time of PT. The minimum time period of follow-up was 14 months, and the mean follow-up time was 38 months (range, 14–92 months). Disease, treatment, and outcome characteristics for the entire cohort are summarized in Table 1.

All patients were immobilized using a combination of body cast and vacuum-assisted bite-block system or thermoplastic mask for precise positioning. The GTV was defined as the macroscopic tumor identified on the planning computed tomography (CT) and magnetic resonance imaging (MRI). The CTV included the GTV and the preoperative tumor extension, plus regions of suspected microscopic spread. The planning target volume (PTV) encompassed the CTV, plus a margin of uncertainty. A relative biologic effectiveness (RBE) factor for protons of 1.1 (relative to ^{60}Co) was used, and proton doses were expressed as follows: Gy (RBE) (1 Gy [RBE] = physical proton-Gy × 1.1 RBE factor) (9). Patients with chordomas received a mean dose of 73.5 Gy (RBE) (range, 67–74 Gy), and patients with chondrosarcomas received

Table 1 Characteristics of 62 patients with skull base tumors

	Chordoma $n = 40$	Chondrosarcoma $n = 22$	Total $n = 62$
Follow-up period (mo)			Mean 38 (range, 14–92)
Sex			
Male	17	13	30
Female	23	9	32
Age (y)			
<20	3	3	6
20 to 60	27	18	45
>60	10	1	11
GTV volume			
≤25 ml	23	15	38
>25 ml	17	7	24
Proton RT			
For primary	31	14	45
For recurrence	9	8	17
Total dose (Gy) (RBE)	73.5 (67–74)	68.4 (63–74)	
Local failure	5	1	6
Actuarial 5-year local control	81%	94%	
Actuarial 5-year disease-free survival	81%	100%	
Actuarial 5-year overall survival	62%	91%	
Actuarial 5-year freedom from high-grade toxicity			94%