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Initial clinical experience with scanned proton beams at the Italian National Center for Hadrontherapy (CNAO)

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We report the initial toxicity data with scanned proton beams at the Italian National Center for Hadrontherapy (CNAO). In September 2011, CNAO commenced patient treatment with scanned proton beams within two prospective Phase II protocols approved by the Italian Health Ministry. Patients with chondrosarcoma or chordoma of the skull base or spine were eligible. By October 2012, 21 patients had completed treatment. Immobilization was performed using rigid non-perforated thermoplastic-masks and customized headrests or body-pillows as indicated. Non-contrast CT scans with immobilization devices in place and MRI scans in supine position were performed for treatment-planning. For chordoma, the prescribed doses were 74 cobalt grey equivalent (CGE) and 54 CGE to planning target volume 1 (PTV1) and PTV2, respectively. For chondrosarcoma, the prescribed doses were 70 CGE and 54 CGE to PTV1 and PTV2, respectively. Treatment was delivered five days a week in 35–37 fractions. Prior to treatment, the patients' positions were verified using an optical tracking system and orthogonal X-ray images. Proton beams were delivered using fixed-horizontal portals on a robotic couch. Weekly MRI incorporating diffusion-weighted-imaging was performed during the course of proton therapy. Patients were reviewed once weekly and acute toxicities were graded with the Common Terminology Criteria for Adverse Events (CTCAE). Median age of patients = 50 years (range, 21–74). All 21 patients completed the proton therapy without major toxicities and without treatment interruption. Median dose delivered was 74 CGE (range, 70–74). The maximum toxicity recorded was CTCAE Grade 2 in four patients. Our preliminary data demonstrates the clinical feasibility of scanned proton beams in Italy.

INTRODUCTION

Chordomas and chondrosarcomas are rare tumors that arise in the base of skull and along the vertebrae [1, 2]. Although surgical resection is the standard of care, complete resection is seldom successful [3, 4]. Radiation therapy (RT) has been used successfully in the adjuvant setting to reduce the rates of local recurrence [5, 6]. However, due to the location of these tumors near to critical organs such as the brain stem, optic chiasm and optic nerves, it is seldom possible to deliver the high radiation doses required to eradicate residual tumor after surgery [7–9]. Techniques using conventional radiation have shown local control rates of 17–50% for chordoma of the skull base. New radiation techniques such as intensity-modulated radiotherapy (IMRT), highly conformal RT techniques, and charged particles have been used to circumvent this limitation of conventional RT [10–17].

Protons and other charged particles have an inverted dose profile that allows delivery of high doses to the target while minimizing dose to the surrounding organs at risk [18, 19]. As charged particles travel through tissue they

gradually decelerate and transfer energy to tissues, resulting in molecular excitation and ionizations. A sharp rise in energy transfer, termed the Bragg peak, takes place near the end of the finite range of the particle. For protons, the radiation dose beyond the Bragg peak sharply drops to zero, resulting in no radiation dose beyond this point (no exit dose). This dose deposition differs dramatically from photon irradiation, in which the peak dose is relatively superficial in tissue followed by a gradual fall off in dose. As a result, the exit dose through normal tissues with photons can be substantial. The potentially lower dose to non-target tissue is the primary appeal of charged particle therapy. Proton RT has been shown to improve local control rates in patients with chordoma and chondrosarcoma [12, 20, 21].

In September 2011, the Italian Ministry of Health and the local ethics committee approved two Phase II clinical studies at the Italian National Centre for Oncological Hadrontherapy (CNAO) for the use of proton therapy (PT) for patients with skull base and sacral chordoma and chondrosarcoma. To date, 21 patients have been accrued to these two clinical studies and all have completed their PT treatment. During the course of proton treatment, all patients were assessed for acute toxicity using standardized criteria based on the Common Terminology Criteria for Adverse Events (CTCAE version 3.0) by the attending nurse practitioner [22]. We now report the acute toxicity rates recorded for the initial 21 patients.

MATERIALS AND METHODS

PT at CNAO

Patient recruitment

Patients are referred to CNAO from all regions of Italy. Based on the inclusion and exclusion criteria as stipulated in the two single-center prospective Phase II study protocols (CNAO 01/2011 and CNAO 02/2011), patients are accrued prospectively into either of the studies. Inclusion criteria include: completely or partially resected, recurrent or non-resectable histologically proven chondrosarcoma (World Health Organization [WHO] low grade) or chordoma of the skull base or sacrum, adequately staged (14–85 years) patients with good performance status (Karnofsky performance status ≥ 70) who are able to give consent for the study. Exclusion criteria include: patients with poor performance status (Karnofsky performance status <70) with metastatic disease with inadequate staging or histological diagnosis, previous radiotherapy in affected region, concomitant chemotherapy or high grade chondrosarcoma (WHO Grade 3), extensive metal instrumentation, inability to deliver prescribed dose without overdose to normal structures, or pregnancy. The primary endpoints were early local response (within 90 days) and acute toxicity. Secondary endpoints included: long-term local response, disease-free survival, overall survival and long-term toxicity.

At CNAO, protons (and also carbon ions) are generated with a ring synchrotron and transferred to three treatment rooms with fixed horizontal and/or vertical beam lines. It is also possible to accelerate carbon ions up to 400Mev. Of the three treatment rooms, two are equipped with the lateral beam line only, while one has both vertical and horizontal beam lines. At the moment, protons of energies of 60–250 MeV are generated. Proton beams are scanned laterally and vertically across the target volume using scanning magnets, while variation in depth is modulated by energy changes in the synchrotron. This active system of delivery does not require the use of the heavy and expensive collimators and compensators used in passive delivery systems. This active system also reduces the amount of neutron contamination to the patient. The maximal field size of the beam line is 20×20 cm. All rooms are equipped with in-room optical tracking system (OTS) and patient verification system (PVS) for treatment position verification. Patients are moved into the treatment position by use of a robotic treatment couch with movement with six degrees of freedom.

Immobilization is performed using customized rigid non-perforated thermoplastic-masks, mouth-bites and head-rests and/or moldable body-pillows. The position of the patient's head may be rotated laterally and/or flexed/extended to achieve the optimal geometry of beam entry angles (for target coverage and/or OARs avoidance). A simulation CT scan without intravenous contrast is performed for every patient in the supine position with immobilization devices in place, to be used for treatment planning. The CT slice thickness is fixed at 2 mm. The simulation CT is used for calculating the treatment plan. Contrast medium is not used as this would affect particle range calculation. In order to convert Hounsfield numbers to stopping power for particles, images are acquired with a fixed exposition protocol. Magnetic resonance imaging (MRI) is performed in order to improve soft tissue visualization and tumor infiltration. Whenever possible MRI is performed with the patients immobilized in the exact set-up conditions (thermoplastic masks, customized mouth-bites and moldable pillows). Image fusion is performed with non-deformable algorithms based on anatomical landmarks.

The gross tumor volume (GTV) contains the primary or residual tumor. The volume includes all areas interpreted as involved by macroscopic tumor. Typically for chordoma, the GTV is defined as the area of hyperintense signal on T2-weighted MRI and the contrast-enhancing area on T1-weighted MRI sequences. The clinical target volume (CTV) includes the anatomical extension of the tumor, surgical field and suspected microscopic spread of disease. The planning target volume (PTV) is defined as the CTV plus 2 mm in the skull base and CTV plus 4 mm in the sacrum.

Treatment plans were generated on the Siemens SyngoPT treatment-planning system using the inverse treatment algorithm. Proton doses are expressed as cobalt grey equivalent (CGE) using a radio biological effect of 1.1 [23]. The prescribed doses are 70 CGE for chondrosarcoma and 74 CGE for chordoma using 2 CGE daily fractions, treating five days a week over 7–7.5 weeks. 70 CGE and 74 CGE were chosen based on previously published data and have been shown to be safe and effective. The intention of this study is to replicate previously published experience using the experimental in-house designed synchrotron at CNAO. Once its safety and efficacy has been shown, a further dose escalation study could be proposed. The median number of treatment fields is 2 (range, 1–3). PT is usually delivered in two phases: phase 1 to 54 CGE and then phase 2 to 70 or 74 CGE depending on tumor type. Phase 1 is usually delivered with single beam optimization (SBO) using two fields and phase 2 with intensity-modulated proton therapy (IMPT) using 2–3 fields to increase the robustness of the treatment plan. IMPT is analogous to IMRT for photons, using an inverse planning algorithm to optimize target coverage while maintaining dose constraints to organs at risk (OARs).

Quality assurance procedures

Daily quality assurance (QA) procedures include checks on the patient positioning system (PVS) and image verification system to ensure an accuracy of <±1 mm. This involves the use of imaging phantoms with implanted ball-bearings and cross-checks between the PVS and optical tracking system (OTS). This is done every day before the first patient is treated. Patient-specific quality procedures include treatment-plan verification using a water phantom and multiple pinpoint ion chambers to assess dose distribution, particularly in regions of high-dose gradients and tissue inhomogeneity. For the very first patient, post PT auto-activation PET imaging (within 10 min) was performed to assess the range of the treatment portals.

Acute toxicity

The attending physician and nurse practitioner assessed patients once a week during the course of PT (7–7.5 weeks). The nurse practitioner recorded the maximal acute toxicity for each patient based on standardized acute toxicity forms generated from National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 [22]. The assessment criteria and types of toxicity assessment depend on the site of treatment (i.e. skull base or sacrum). Clinical photographs are taken to document skin and/or mucosal toxicity if they develop. At the patient's first follow-up visit three months after completion of PT, re-assessment for resolution and/or persistence of any acute toxicity is performed. If any unexpected or severe toxicity should develop, PT was to be stopped and a review of the treatment plans and/or dose-volume histograms undertaken urgently to identify any potential cause.

Mini mental state exam

There is a suggestion that the use of PT can reduce impairment of neuropsychological and intelligence quotient development [24]. However even with PT, patients with skull base tumors may still receive significant radiation to the neighboring brain tissues [25, 26]. To assess the neurocognitive impact of PT on patients receiving PT to the skull base, we used the mini mental status examination (MMSE) [27]. The attending physician and nurse practitioner performed this examination during weeks 1 and 7 of PT and at the first follow-up appointment. This MMSE is a validated tool for neurological function assessment in patients receiving RT to the brain. The toxicity may be subsequently correlated to both dose and volume parameters in the treatment plan. The MMSE was initially derived to screen and quantify the severity of cognitive dysfunction in patients with dementia and was first developed by Folstein in 1975 [27]. MMSE has been used to assess neurotoxicity after brain RT. Understandably, the volume of brain receiving RT in photon RT for primary brain tumors will be much larger than the volume of brain irradiated in patients with skull base PT. However as our patients are expected to have favorable prognosis after PT, it is important to document any neurological impact after PT.

The MMSE is divided into the following sections: orientation to time, orientation to place, immediate recall, attention, delayed verbal recall, naming, repetition, three-stage commands, reading, writing and copying. The MMSE offers a quick and simple way to quantify cognitive function and screen for cognitive loss. It tests the individual's orientation, attention, calculation, recall, language and motor skills. Each section of the test involves a related series of questions or commands. The individual receives one point for each correct answer. To give the examination, the individual needs to be seated in a quiet, well-lit room. The tester asks the patient to listen carefully and answer each question as accurately as he/she can. The score is determined by adding the number of correct responses. The individual can receive a maximum score of 30 points. A score below 20 usually indicates cognitive impairment.

Follow-up during and after PT

During the course (7–7.5 weeks) of PT, patients have repeated 3-Tesla (3T) MRI scans every 1–2 weeks. This has been mandated by the health authorities to document early response to treatment (or progression), and to study early radiological changes within the tumor, as PT is still considered experimental therapy in Italy. In addition to the non-enhanced and fat-suppressed T1 and T2 weighted magnetic resonance (MR) images, diffusion weighted (DW) images were acquired with motion-probing gradient (MPG)

pulses applied sequentially along three directions (x, y, and z axes) with four b-factors (0, 50, 400 and 1000 seconds/mm^2). The minimum, maximum, mean and standard deviation values of apparent diffusion coefficients (ADC) were generated after placing regions of interest manually, encompassing the GTV on the ADC map.

At the first follow-up appointment (three months after completion of PT), patients have another MRI for tumor response assessment. Patients are followed up three-monthly for the first and second year, then six-monthly for the third and fourth years, and thereafter annually up to 10 years. Late toxicity is scored using the CTCAE version 3.0 as defined by toxicity occurring after 90 days of PT [22]. These toxicity scores are to be re-categorized using the RTOG or LENT/SOMA criteria, especially when documenting late effects [28, 29]. It is crucial that patients continue to be followed up here at CNAO with clinical visits and MRI scans and assessed by the same team of doctors and same MRI unit.

RESULTS

Demographic data

From September 2011 to September 2012, 21 patients were recruited into the two study protocols and completed PT. Eleven patients (52%) have had their first post-treatment clinical follow-up and MRI scans.

Patients were equally divided between the sexes and their median age was 50 years (range, 21–74). There were 16 patients with chordoma and five with chondrosarcoma. 15 patients had tumors of the skull base and six had tumors of the sacrum. The most common tumor was chordoma of the skull base. The majority of patients had primary disease and had undergone prior surgery. The median incidence of surgical resection was one, but some patients had been treated with up to four resections in recurrent cases (Table 1). Major symptoms at presentation included visual disturbance/diplopia, pain/paresthesia, and mass/swelling. The median dose delivered was 74 CGE (range, 70–74) and the median treatment time was 50 days (range, 44–58) (Table 2). A typical treatment plan and dose distribution is shown in Fig. 1.

Acute toxicity

The mean follow-up time was five months (range, 1–12). The maximal grade of toxicity recorded by patients was Grade 2 (skin and nausea). The most common types of toxicity were radiation dermatitis (skin) and headaches (Table 3). With regards to the temporal pattern of acute toxicity, the start and/or peak of toxicity was usually recorded in the final three weeks of PT and then resolved completely by the first follow-up. All patients had complete resolution of acute toxicity at the first follow-up (at three months), but some patients had persisting symptoms from before surgery, i.e. tumor-related rather than PT-related symptoms, which at times was a confounding factor. The management of these acute side-effects included special skin-care (topical treatment), steroids, painkillers and anti-nausea medication. We should specifically mention certain types of expected toxicity: two patients with pharyngeal toxicity with tumor with pharyngeal extension. We have separated tumours of the skull base from those of the sacrum/pelvis in our description of toxicity events.

All patients completed their PT without any delays. In total, 19 patients had acute toxicity: four patients recorded nine Grade 2 acute toxicity events; 18 patients recorded 104 Grade 1 events. Two patients did not experience any acute toxicity at all during PT. Nineteen (90%) patients had toxicity of Grade 1–2; 18 (86%) had Grade 1 toxicity; four (19%) had Grade 2 toxicity; none (0%) had Grade 3–4 toxicity. The most common and/or persistent toxicity events

Table 1. Patient characteristics

	n	%
Total	**21**	**100**
Histology		
Chordoma	16	76
Chondrosarcoma	5	24
Location		
Skull base	15	71
Sacrum	6	29
Sex		
Male	11	52
Female	10	48
Median age (years)	50	Range, 21–74
Extent of disease at PT		
Primary	16	76
Recurrent	5	24
Previous surgery		
Yes	18	86
No	3	14
Median no. of surgery	1	Range, 1–4
Presenting symptoms at diagnosis		
Diplopia/visual disturbance	7	33
Pain/paresthesia	4	19
Mass/swelling	4	19
Ear symptoms	1	5
Speech symptoms	1	5
No symptoms	1	5

Table 2. Treatment and tumor characteristics

	n	%	Range
PT Dose			
74CGE/37#	16	76	
70CGE/35#	5	24	
Median treatment time (days)	50		44–58
Median no. of fields	2		1–3
Mean follow-up (months)	5		1–12
No. of patients with first follow-up/MRI scans	10	48	
	Mean	**Median**	**Range**
GTV (mls)	126	17	0.6–1429.6
Skull base	20	18	0.6–99.1
Sacrum	389	144	10.6–1429.6
CTV1 (mls)	138	47	14–998.1
Skull base	58	37	14–221.7
Sacrum	363	144	103.6–998.1
CTV2 (mls)	208	45	6.7–2311.6
Skull base	39	22	6.7–123.5
Sacrum	573	199	50.3–2311.6
PTV1 (mls)	178	64	21.0–1134.4
Skull base	75	48	21.0–279.6
Sacrum	467	227	181.4–1134.4
PTV2 (mls)	238	51	11.1–2847.8
Skull base	48	31	11.1–150.0
Sacrum	712	283	90.3–2847.8

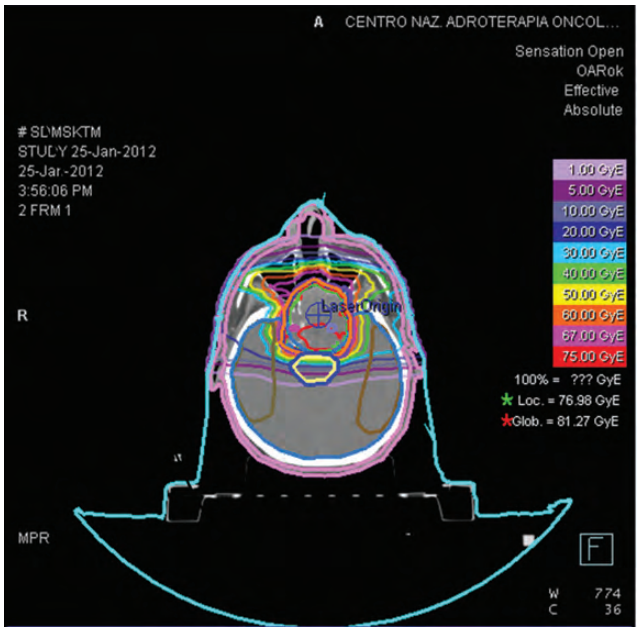

Fig. 1. Dose distribution of a patient with skull base chordoma.

Table 3. Incidence of toxicity events

	Total events recorded[a]	Number of patients affected	%
Total		21	100
No toxicity		2	10
Toxicity any grade	113	19	90
G1 toxicity	104	18	86
Skull base	95	14	67
Sacrum	9	4	19
G2 toxicity	9	4	19
Skull base	5	2	10
Sacrum	4	2	10
G3 toxicity	0	0	0

[a]May be extension of same event, i.e. from week 1 to 2 without resolution.

recorded in patients with skull base PT were skin toxicity/RT dermatitis and headache (Table 4 and Fig. 2). The incidence increased after week 5 and peaked in the final (seventh) week. The remaining types of toxicities were sporadic and competely resolved within 1–2 weeks. The most common toxicity in tumors of the sacrum/pelvis was RT dermatitis (Table 5 and Fig. 3). All patients had complete resolution of acute toxicities after PT (at first follow-up three months after completion of PT).

MMSE

Of the patients with skull base PT, we collected data for 14 patients with MMSE at the beginning of PT and 10 patients at the end of PT (Fig. 4). In the initial assessment (week 1): the mean score was 27, median score was 28, minimum score was 20, maximum score was 30, and valid number of tests was 14. At the end of PT (week 7): the mean score was 28, median score was 29, minimum score was 24, maximum score was 30, and valid number of tests was 10. At the first follow-up: the mean score was 28, median score was 28, minimum score was 28, maximum score was 28, and valid number of tests was 2 (Table 6).

MRI during PT and DW imaging/ADC evaluation

There were no significant changes in tumor size in any of the 21 patients, based on the Response Evaluation Criteria In Solid Tumors criteria on serial MRI scans performed during PT. In the preliminary analysis for the first three patients (data not shown), the initial ADC for skull base

Table 4. Cumulative score for each symptom for skull base PT patients per week

Cumulative score for each symptom for skull base PT patients per week	1	2	3	4	5	6	7	8	first follow-up
Vomiting	0	1	2	0	0	0	0	0	0
Nausea	0	1	2	0	1	1	1	0	0
Fatigue	0	0	0	0	0	0	0	0	0
Headache	0	2	3	3	4	5	4	2	0
Hypersomnia	0	0	0	0	0	0	0	0	0
RT dermatitis	0	0	2	4	9	12	12	0	0
Soft tissue swelling	0	0	0	0	0	0	0	0	0
Oral mucositis	0	0	1	1	1	1	1	1	0
Dysphagia	0	1	1	0	0	0	0	0	0

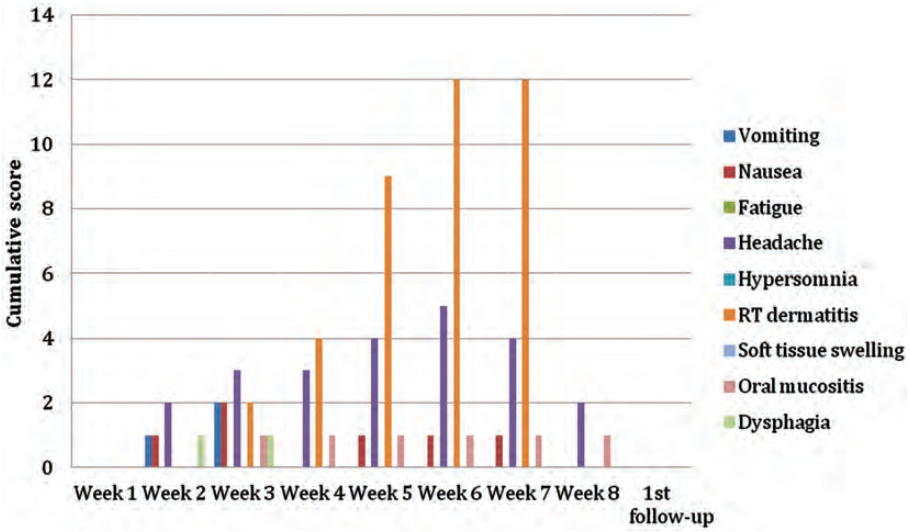

Fig. 2. Cumulative toxicity scores by type of toxicity per week of proton therapy (PT) for patients with chordoma or chondrosarcoma of the skull base.

Table 5. Cumulative score for each symptom for pelvic PT patients per week

Cumulative score for each symptom for pelvic PT patients per week	1	2	3	4	5	6	7	8	first follow-up
Diarrhea	0	0	0	0	0	0	0	0	0
Nausea	0	0	0	0	0	0	0	0	0
Rectal pain	0	0	0	0	0	0	0	0	0
Cystitis (non-infective)	0	0	0	0	0	0	0	0	0
Superficial tissue swelling	0	0	0	0	0	0	0	0	0
Proctitis	0	0	0	0	0	0	0	0	0
Dermatitis	0	1	1	2	2	5	6	0	0

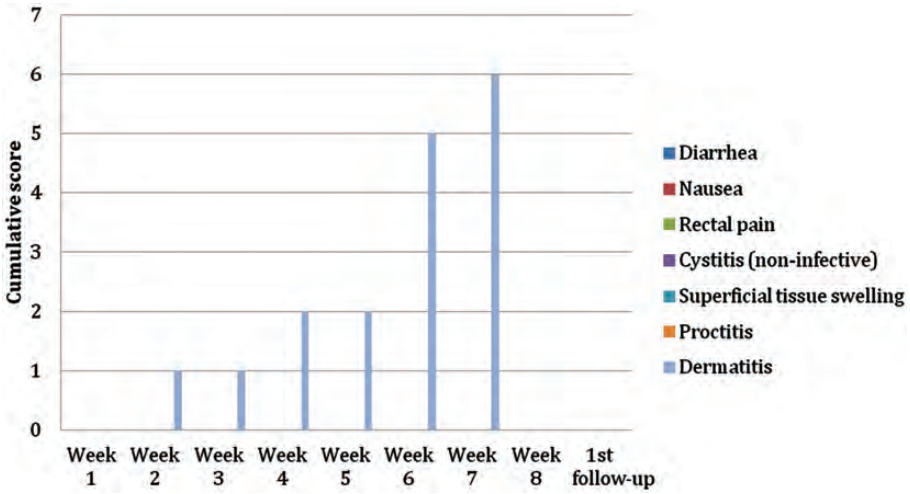

Fig. 3. Cumulative toxicity score by type of toxicity per week of proton therapy (PT) for patients with chordoma or chondrosarcoma of the sacrum.

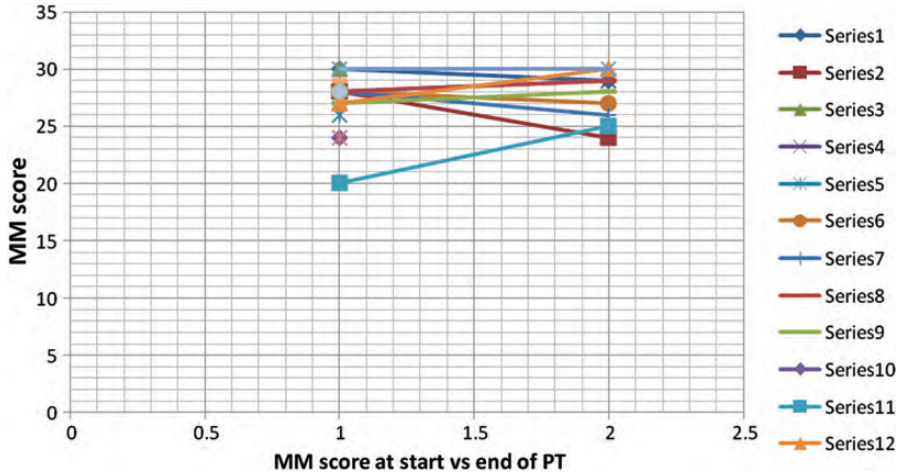

Fig. 4. Mini Mental State Exam (MMSE) scores at start and end of proton therapy (PT).

Table 6. MMSE scores at the start and end of PT

	Start of PT	End of PT
Mean MMSE score	27	28
Median MMSE score	28	29
Range	20–30	24–30
Valid scores	14	10

chondrosarcoma appears to be much higher than for that of chordoma. The median ADC over the proton treatment was 2×10^{-3} mm^2/sec and 1.5×10^{-3} mm^2/sec in the chondrosarcoma and chordoma, respectively. There was no apparent difference in the normalized ADC during proton treatment for the three patients. However, a slight decrease at the first follow-up (after three months) was noted for the patient with chondorsarcoma of the skull base.

Statistical analysis

We performed the paired student *t*-test, which showed no significant difference. Therefore, we concluded that there is no statistical change of scores for the MMSE from the start to end of PT. However, we need more patients and longer follow-up (potentially with MMSE at the one-year follow-up and annually) for more concrete conclusions.

DISCUSSION

Apart from increased tumor control from dose escalation, another major promise of PT is to decrease the incidence of acute and late treatment-related effects by reducing the

amount of radiation given to normal tissues. This is especially relevant in pediatric patients, young adults or patients with curable cancers. As technology advances with the development of pencil-beam scanning we can further reduce the dose to normal tissues using passive delivery systems [30, 31]. This reduction in late effects is often cited as the justification for investment in these expensive systems.

We have compared our data to published trials. Unfortunately, there have been only a few papers on late effects and even fewer papers with details on acute effects [21, 32–36]. The published studies reported on late effects predominantly, with few details on acute toxicity. The section below includes a short literature review of the published data on PT in skull base chordoma and chondrosarcoma.

Early effects of PT

Noel *et al.* from Orsay described the early effects during PT and six weeks after PT [21]. All patients described early side-effects of: asthenia, loss of appetite, transitory temporal and/or fronto-parietal alopecia, mild erythema and nausea. There were no early side-effects that required discontinuation of RT or hospitalization. A total of 42 patients experienced one or more late complications. The median time of onset of late complications was eight months (range, 2–43 months). Late complications recorded were: eight patients with visual disorders; two patients with loss of vision; 11 patients with clinical neuropsychological disorders; there were no cases of brain necrosis or leukoencephalopathy, but one patient had asymptomatic bilateral temporal necrosis on imaging; 21 patients experienced decreased hearing loss comprised of 16 with unilateral and five with bilateral hearing loss; 17 patients had decreased pituitary function, of which nine patients had complete pituitary hormonal replacement, and eight had partial pituitary dysfunction.

Ares 2009 *et al.* of the Paul Scherrer Institut (PSI) only reported on late events [34]. There were four patients with high-grade (Grade 3–4) toxicity, and the actuarial five-year freedom from high-grade toxicity was 94%. One patient had Grade 3 unilateral optic neuropathy compression on chiasm, supra-sellar extension; one patient had Grade 4 unilateral optic neuropathy that developed 12 months after PT; two patients had Grade 3 temporal lobe parenchyma damage, requiring high doses of steroids; five patients had asymptomatic circumscribed white matter changes in the temporal lobe (Grade 1 leukoencephalopathy); 7.8% of patients had temporal lobe lesions confined to the high-dose region of PT, which included a 2–5 mm margin toward the temporal lobes. In four patients, MRI changes remained stable or resolved completely. In one patient, MRI changes continued to progress up to the time of analysis. Weber *et al.* at the PSI reported on late events that were seen in four (14%) patients [33]. Four patients had pituitary insufficiencies and required hormonal replacement therapy. No brainstem or optical pathway necrosis was observed despite high dose to these critical structures. The overall three-year complication-free survival rate was 82.2%. Rutz 2008 *et al.* reported on pediatric patients with tumors of the skull base and spine and reported acute Grade 1–3 skin reaction, and Grade 1 alopecia [35].

Hug 2002 *et al.* reported on pediatric patients where he found acute side-effects during PT to be within the expected range [36]. For most patients, the side-effects consisted of temporary epilation over the treatment area, skin erythema, occasional headaches, fatigue, and loss of appetite. No treatment breaks were required for patients undergoing proton RT alone. Severe late effects were observed in two (7%) of 29 patients: one patient had cerebellar and brainstem parenchyma damage. This patient required two surgical resections for posterior fossa regrowth followed with pre- and post-operative combined photon and proton RT at 75.4 CGE. The patient then developed right-sided weakness and ataxia. One patient had temporal lobe damage, which was unilateral and associated with upper extremity sensory deficit. Eight patients (27%) developed intra- and parasellar tumors.

Late effects of PT

The possible late effects as reported in the literature included: pituitary dysfunction, visual impairment, temporal lobe necrosis, cochlear and hearing loss. The patients in this study will be followed up with neurologists, ophthalmologists, audiometrists and endocrinologists for late treatment effects.

Munzenrider 1999 *et al.* reviewed the late effects on the following normal organs [20]:

Brain stem and cervical spinal cord

The probability of survival free of significant brain stem toxicity was 92% vs 87% (five and 10 years after PT; $n = 367$, dose 63–79.2 CGE, mean follow-up = 42.5 months). Three patients died from brain stem injury, and 3.9% of patients had significant cervical myelopathy ($n = 78$, chordoma and chondrosarcoma, mean follow-up = 46.4 months, PT dose 64.5–79.2 CGE).

Brain

The probability of temporal lobe injury was 8% and 13% at 2 and 5 years, respectively. Neuropsychological function was evaluated prospectively in 38 patients, for temporal lobe doses of 69.6–75.6 CGE. Significant psychomotor slowing of reaction time and motor speed was shown for the group as a whole.

Vision, hearing and cranial nerve function

Optic neuropathy occurred in 12 of 274 patients (4.4%) who received doses of 63.4–79.4 CGE; the median dose to

the optic structures in injured patients was 62.1 CGE. The patch technique was significantly related to development of optic neuropathy. Patch techniques meant that passive delivery systems were used, as compared to the active beam scanning system at CNAO. Significant audiographical hearing loss occurred 2–5 years after PT in 15 of 33 patients. Two-thirds of patients who received ≥ 62.7 CGE to the cochlea or auditory nerve progressed to hearing loss quite rapidly after onset (which later led to reduced dose constraints ≤ 62 CGE, at least on one functional side). Cranial injury was observed in 15 of 27 patients; the estimated probability of neuropathy rose from 1% at 62 CGE to 5% at 73.2 CGE. The defined dose constraints for the brainstem, optic nerves, chiasm, cochlea, and auditory nerves were as above.

Endocrinopathy

There were 79 patients with skull base sarcoma who received ≥ 40 CGE to the pituitary gland. The prescribed doses were 50.8 – 79 CGE (median 71.5 CGE), and 32 patients (40%) developed endocrinopathy (15–23% had deficiencies in luteinizing hormone, prolactin, thyroid-stimulating hormone, and/or cortisone) and the latent period to endocrinopathy was 8–10 years.

Carbon ion radiotherapy

Ions such as carbon ions have also been used to treat chordoma and chondrosarcoma with excellent results [15, 16, 37–39]. Ions combine the physical advantages of protons with the higher radiobiological effect of ions within the Bragg peak due to the increased linear energy transfer (LET). Published rates of acute and late toxicity are comparable if not less than with protons [15, 16]. Both technologies are still developing and it remains to be seen which will prove the superior treatment modality. The paucity of published data makes it difficult to compare toxicity rates of ions, protons and photons (i.e. SRT, SRS, Gamma Knife series).

In agreement with published data, the rates of acute toxicity recorded in this study were negligible, even when a high dose (74 CGE) was delivered to large tumors (GTV > 2000 mls). None of the patients required any treatment breaks attributable to acute toxicity, and treatments were completed without significant delays. Although the data presented here (from only 21 patients) are very preliminary, this study provides some evidence that scanned PT appears to have minimal acute effects on patients during PT. Hopefully this can translate into low or no late effects with extended follow-up. All our patients were treated using active pencil-beam scanning PT and we hope to compare their results to those of patients treated using passive systems at other centers by matched pair analysis when data are more mature. This paper is not intended to prove the superiority of one system (pencil beam scanning (PBT) vs passive systems); rather it is meant to show that the system developed at CNAO is safe and efficacious for the treatment of skull base and sacrum chondrosarcoma and chordoma.

It is largely accepted that PBT is on the evolutionary path in the development of PT, as it avoids the need for fabrication of heavy compensators and collimators, has the ability to achieve a sharper dose fall-off, and avoids the need for patch fields and junction shifts. However, such a high level of precision and accuracy is more challenging when treating moving targets or varying organ-filling or tissue densities. New techniques are being developed to mitigate these issues: smaller spot sizes, faster or volumetric rescanning, and daily cone beam CT image guidance. Thus the decision for passive or active systems is dependent on the costs, existing infrastructure, man-power, and patient population at each center.

The reported rates of late toxicity range from 5–17% with some cases of serious Grade 4 damage [20]. This compares to a rate of 0–5% ate toxicity in studies with conventional, stereotactic radiotherapy and radiosurgery [10, 11, 40, 41]. However maximal RT doses delivered in these RT studies were 60–65 Gy, with a correspondingly much lower rate of local control (five-year local control for chordoma = 36–56% vs 54–70% for PT). Therefore, one can see the pitfalls and difficulties in comparing RT with PT.

As PT progressed during the seven weeks, there was a gradual increase in acute toxicity events recorded. By the final (seventh) week of PT, only four patients remained without toxicity. The cumulative toxicity scores were low, with Grade 2 being the most common cumulative score. The most common grade of toxicity scored was Grade 1, with only four patients with Grade 2 toxicity developing in the final weeks of PT. By the first follow-up appointment three months after PT, all patients had complete resolution of their toxicity symptoms. Figure 5 shows the distribution of maximal grades of toxicity recorded for all patients. About half the patients developed Grade 1 toxicity within the first weeks of PT, while the rest developed Grade 1 toxicity only after week 4. Four patients developed Grade 2 toxicity after week 5, while one had Grade 2 toxicity symptoms with rapid complete resolution in week 2. At first follow-up, all patients had complete resolution of toxicity. Basically there was no significant change in the MMSE scores before and after PT, but we should continue assessing MMSE at first follow-up and one-year intervals to identify any late neurocognitive effect in these patients.

It would be unrealistic to expect that PT will have no acute effects, especially given that some patients have large treatment volumes and previous surgical resections (or even multiple resections). Therefore it may not be easy to separate the effects from surgery from those due to PT (i.e. exacerbation of surgical symptoms during PT such as nausea or headaches). However, our data shows that acute toxicity during PT is generally mild and lower than expected, given

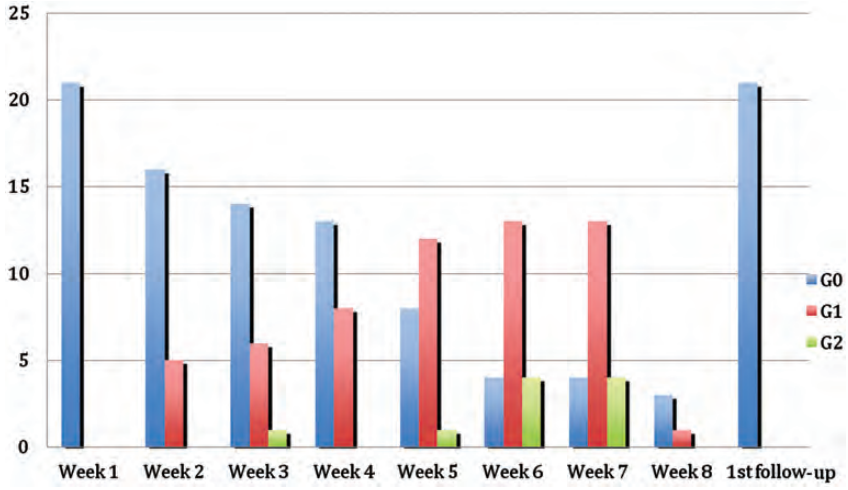

Fig. 5. Incidence of maximal grade of acute toxicity per week of proton therapy (PT).

the same reasons mentioned previously (high doses used, big treatment volumes, multiple surgeries). The effect of physical dose distribution, active scanning or dose constraints applied at CNAO will need further investigation, as do patient factors: some patients may have some symptoms but not find them bothersome.

As has been previously mentioned, there is a perceived lack of good evidence to justify the routine use of PT in cancer treatment [42–46]. It has been suggested that well-designed Phase II trials should provide the minimal level of evidence needed to convince the funders, governments and public of the justification of continued research in this field to improve the technology and reduce the costs of equipment. We wish to emphasize the importance of standardized toxicity assessment to minimize introduction of bias into any comparison between new and old technology. Furthermore, patient-based scoring systems should be incorporated, along with physician-based assessment, and quality of life (QoL) instruments should be used. In addition to physician-directed objective assessment, subjective patient-centered assessment instruments assessing patients' QoL may also be important. At CNAO, we have embarked on collecting QoL data during and after PT, and attempts will be made to correlate toxicity to QoL.

CONCLUSION

This Phase II study has demonstrated the safety of PT for patients with chordoma or chondrosarcoma of the skull base who received scanned beam PT at our center (CNAO). The acute side-effects recorded were predominantly Grade 1–2 and were completely resolved after PT. There were no Grade 3–4 toxicities recorded. We will continue to enroll additional patients and follow up existing patients within the two clinical studies to investigate the relationship between acute and late toxicity. We have a total of 10 clinical protocols approved in CNAO; seven are for PT and three for carbon ions. Four protocols (utilizing protons) are actively recruiting patients. Within 2–3 years, we hope to have more data on local control, acute and late effects. To gather the evidence needed to convince the community of the safety of PT, multicenter trials or pooled data from several centers may be required for these rare tumors. Objective standardized toxicity assessment and treatment with standard protocols is crucial for meaningful analysis of such pooled data. Some of these initiatives are being explored with multi-center/institutional projects within Europe such as Union of the Light Ion Centers of Europe (ULICE), the European training network in digital medical imaging for radiotherapy (ENTERVISION) and the Particle Training Network for European Radiotherapy (PARTNER).

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