Proton beam radiotherapy: report of the first patient treated at the Centro Nazionale di Adroterapia Oncologica (CNAO)

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ABSTRACT

Proton beam radiotherapy, an innovative treatment modality, allows delivery of high radiation doses to the target while sparing surrounding healthy structures. The Centro Nazionale di Adroterapia Oncologica (CNAO), equipped with a synchrotron and capable of using both protons and ions, initiated its clinical activity in September 2011. The first treatment of a skull base tumor with protons is reported here. The case of a 26-year-old man with an intracranial low-grade chondrosarcoma of the right petroclival junction is discussed with emphasis on technical and clinical details. Two previous surgical interventions had achieved partial removal of the tumor and the patient was treated with protons for residual disease. The prescribed dose was 70 GyE in 35 fractions of 2 GyE. Treatment was completed with minimal acute toxicity consisting of grade 1 alopecia and nausea. Nine months after treatment the disease is locally controlled. Use of high-energy protons at CNAO is a safe and effective means of treating a tumor located near critical normal structures.

Introduction

Chondrosarcoma (CHS) is a malignant tumor characterized by cartilage formation. It accounts for 0.15% of all intracranial tumors and 6% of skull base neoplasms1. Treatment is challenging given the location and local aggressiveness of these tumors. Complete surgical excision remains the mainstay of treatment but is rarely feasible and adjuvant radiation can improve control rates.

CHSs are considered to be relatively radioresistant and the minimum useful dose has been found to be 60-65 Gy or even higher, especially in series where charged particles were used2-5. Protons have high spatial selectivity and enable better sparing of healthy tissues6,7, delivering a higher dose to the tumor compared to conventional radiotherapy8.

In Italy, the Centro Nazionale di Adroterapia Oncologica (CNAO) Foundation, established by the Italian Ministry of Public Health, launched a project to create a center dedicated to charged particle therapy for cancer care. Construction of the facility equipped with a synchrotron and 3 treatment rooms, 2 with horizontal and 1 with both horizontal and vertical beam lines, started in Pavia in 2005. Proton beams became available in October 2010 and after commissioning tests the clinical activity started in September 2011.

In the present article, we describe the clinical and technical characteristics of the first treatment of a deep-seated tumor using high-energy protons in Italy.

Case report

A 26-year-old Caucasian male presented with sudden onset of diplopia in July 2007; magnetic resonance imaging (MRI) revealed a contrast-enhancing lesion at the level...
of the right petroclival junction with extension into the right cavernous sinus. A short course of steroids resulted in resolution of the symptoms; however, in view of the risk of neurological injury associated with surgical intervention, he was kept on regular MRI surveillance. He was asymptomatic till January 2009, when diplopia reappeared and MRI revealed enlargement of the lesion; at that point a right-sided frontotemporal craniotomy achieved partial excision. The histological diagnosis was a chondroid neoplasm without cytological atypia or mitotic activity, compatible with a benign chondroma.

Diplopia persisted and the patient was kept under regular MRI surveillance. In February 2011 he started having headaches and MRI revealed an increase in the size of the lesion. A second operation resulted in subtotal excision with a histological diagnosis of grade I-II CHS. Postoperative MRI showed residual tumor in the middle cranial fossa adjacent to the right temporal lobe, invading the ipsilateral cavernous sinus and the right aspect of the sphenoid sinus (Figure 1). After surgery the headaches regressed but diplopia persisted.

Because of persistent tumor, the patient was referred to CNAO in August 2011. Neurological evaluation revealed right-sided sixth and third cranial nerve palsy and deficits of the first and second branches of the fifth cranial nerve. Further findings were within normal limits and there was no evidence of metastases. After giving his informed consent, the patient was eligible for proton therapy as per prescription of the phase II trial on chordoma and chondrosarcoma of the skull base activated at CNAO.

For treatment simulation, a computed tomography (CT) scan (SOMATOM Sensation Open, Siemens, Germany) with the patient in the supine position with a customized head cast with a slice and interslice thickness of 2 mm and a T1-, T2-weighted MRI scan (3.0 T Magnetom Verio, Siemens, Germany) with gadolinium contrast and fat suppression sequences were performed. Image fusion of the CT and MRI data sets was performed using the treatment planning system (TPS) (Syngo VB10, Siemens, Germany) to delineate the residual tumor as the gross tumor volume (GTV) and the potential microscopic extension as the clinical target volume (CTV). A 2-mm expansion to the CTV was used to generate the planning target volume (PTV). The dose prescribed to the PTV was 70 GyE in 35 fractions of 2 GyE each, 5 days a week, considering a relative biological effectiveness value of 1.1. Normal structure dose constraints were as defined in the protocol.

For planning purposes, a single beam optimization strategy was applied. Two fixed active scanning beams with maximum energy of 160 MeV and 142 MeV at 340° and 260° angles along the coronal plane obtained by table rotation were used. The dose distribution is shown in Figure 2. In terms of target coverage, D98% for the GTV and CTV were 65 GyE and 61 GyE, while D2% for the same volumes were 77 GyE and 76.8 GyE, respectively.

The mean dose to the PTV was 70.35 ± 4.47 GyE. As the right optic nerve was within the GTV, target coverage was prioritized and 1.7% of the optic chiasm received a dose greater than 56 GyE, while the contralateral optic nerve was adequately spared. Prior to each treatment delivery, precise positioning of the target was ensured by means of an optical tracking system (VeriSuite®, MEDCOM, Germany) that detected the position of markers fixed on the patient mask and by comparing 2 in-room orthogonal radiographic images with the digitally constructed radiographs provided by the TPS (Figure 3).

Treatment started on September 22 and was completed within 49 calendar days. The maximum early toxicity during treatment was grade 1 nausea and alopecia at the beam entry points as per the Common Terminology Criteria for Adverse Events (CTCAE) v4.0. Evaluation at
3, 6 and 9 months after treatment revealed minimal changes on MRI. The last MRI revealed minimal volumetric reduction (-2 mm) in all dimensions with evidence of increasing fibrosis within the lesion while there were no signs of healthy tissue damage within the optic pathway, brain stem or temporal lobe. There was complete recovery of alopecia without any new neurological, visual or hearing deficits. As per the most recent update the patient is leading a normal life.

Discussion

Intracranial CHSs are rare malignant neoplasms with an indolent course, usually occurring in the third to sixth decades of life\textsuperscript{10}. They are thought to arise from chondrocytes within nests of endochondral cartilage responsible for the intramembranous growth of the bones of the skull base. The most common sites are the petrous portion of the temporal bone and the areas of the petrooccipital, sphenoccipital and sphenopetrosal synchondroses. The usual histological subtypes of intracranial CHS are the conventional and mesenchymal types, which are further graded as I-III. Grade I-II (low grade) tumors are quite indolent and tend to recur locally, while grade III tumors are more aggressive with high metastatic potential. The most frequent symptom of presentation is diplopia, followed by headache\textsuperscript{11}. The peculiar anatomic location makes radical excision difficult, and usually multiple operations are performed before the patient is referred to radiotherapy for residual disease, to achieve local control. Surgery alone has a 5-year recurrence rate of 44%, which is reduced to 9% with the addition of adjuvant photon radiotherapy\textsuperscript{11}.

In this particular case, the onset of symptoms was much earlier, at the age of 22 years, with a symptom-free interval of 2 years before surgical intervention. The clinical presentation was similar to that reported in the literature and 2 operations had been performed before the patient was referred for radiotherapy. The notable feature about treatment with protons at CNAO was the use of active scanning to deliver the prescribed dose using just 2 beams, with minimal exposure of normal tissues. Precise positioning of the target was ensured using the optically guided setup and radiographic verification.

CHSs are slow responding tumors and dramatic shrinkage of the tumor on imaging is not expected after radiotherapy. Accordingly, the general consensus is to define “tumor control” as the status with no clinical or radiological signs of tumor progression. The posttreatment and follow-up MRI scans of this patient continue to show a persistent lesion without any volumetric changes; more significantly, no imaging changes attributable to normal tissue damage have been detected. The patient is clinically stable and has no clinical symptoms related to treatment toxicity or tumor progression.

The first treatment of a deep-seated skull-base chordoma using active scanning beams with high-energy protons was successfully completed at CNAO without any significant toxicity and with good preservation of the patient’s quality of life. Further follow-up is needed to assess the long-term outcome. Protocols on chordoma and chondrosarcoma are currently ongoing with a good rate of patient accrual.
References


