Unresectable Ameloblastoma Successfully Treated with Definitive Proton Therapy

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Abstract

We report the case of an 87-year-old man affected by an unresectable ameloblastoma of the right jaw that was successfully treated by definitive proton therapy up to a dose of 66 Gy in 33 fractions. Treatment was well tolerated, and there were no interruptions due to toxicity. At follow-up visits, the patient experienced complete response to treatment with no evidence of disease and complete recovery from acute side effects. In this report, we discuss the potential and possible pitfalls of proton therapy in the treatment of specific settings.

Keywords: ameloblastoma; head and neck cancer; paranasal sinus cancer; proton therapy

Introduction

Ameloblastoma is a rare benign odontogenic tumor arising from the mandible and the maxilla with potential local aggressive behavior. Malignant ameloblastoma (ie, metastasizing ameloblastoma and ameloblastic carcinoma) is uncommon. Cancer growth is usually slow; however, significant morbidity can occur due its local invasiveness. Surgery is the mainstay of treatment. When feasible, it is considered a definitive treatment with local control ranging from 69% (if enucleation alone is performed) to 96% with resection [1]. The role of radiation therapy (RT) is unclear due to the paucity of data reported in literature regarding its efficacy in the treatment of this disease [2].

Proton therapy (PT) represents a unique method to deliver RT that exploits the physical properties of these particles of a finite range in tissue to ensure low entrance dose and quasi-zero dose beyond the end of their path [3]. These features make this treatment particularly suitable for several specific clinical settings with the aim of improving outcome, reducing side effects, and ameliorating quality of life [4, 5].

Here, the case of an unresectable ameloblastoma definitively treated with PT is reported. The patient gave written consent to the use of their data for the scientific report.

Case Report

In May 2013, an 85-year-old man with a previous history of rectal cancer was admitted to the Trento Hospital emergency department with uncontrolled epistaxis. Radiologic exams revealed a complex, polylobate mass arising from the right jaw with local invasiveness into the nasal cavity and the ethmoid and maxillary sinuses (**Figure 1**). Histologic

Submitted 27 Feb 2017
Accepted 06 Jul 2017
Published 26 Sep 2017

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Report

DOI
10.14338/IJPT-17-00008.1

http://theijpt.org

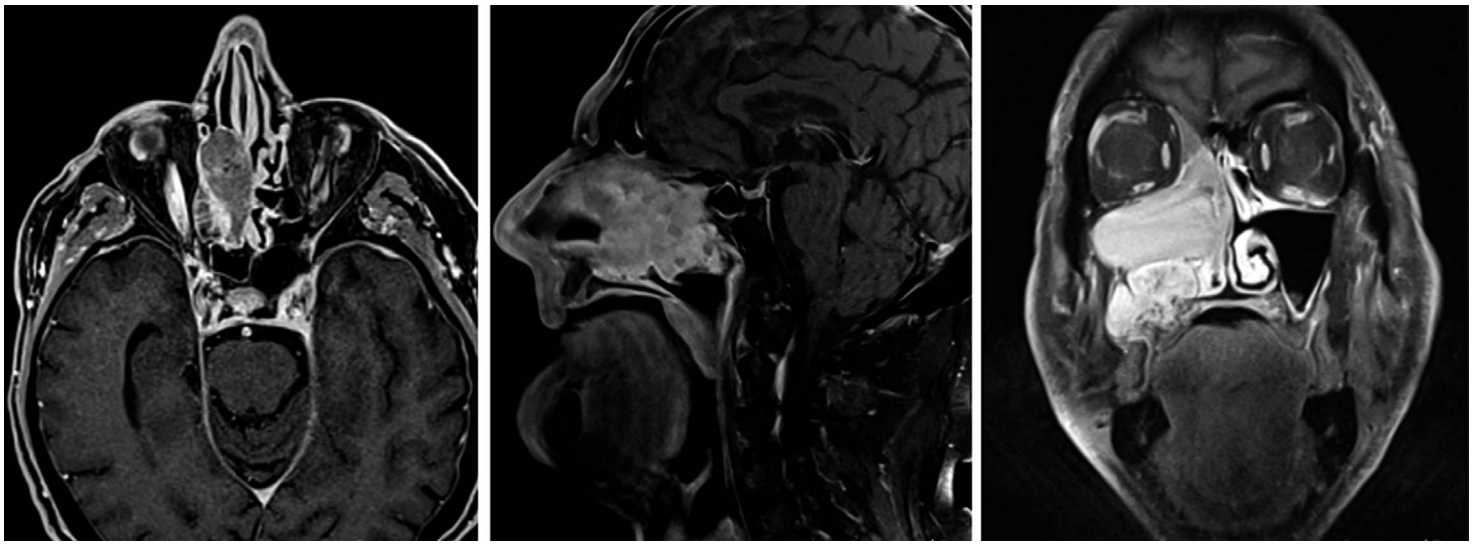


Figure 1. Axial, sagittal, and coronal contrast-enhanced magnetic resonance images showing ameloblastoma extension on May 2013.

diagnosis of plexiform ameloblastoma was made (**Figure 2**). The ear, nose, and throat team proposed surgery, but the patient refused. Medical management of symptoms was started. During follow-up, a slow and continuous enlargement of the lesion was noted beginning in October 2015. When symptoms worsened, the patient was admitted to the emergency department with oronasal bleeding, right lagophthalmos, and breathing difficulties. Magnetic resonance (MR) showed an increase in tumor extension (measuring 97, 62, and 70 mm in the anteroposterior, transversal, and craniocaudal diameters, respectively) and new involvement of the nasopharynx, orbit (floor and medial wall), and inferior rectus muscle (**Figure 3**).

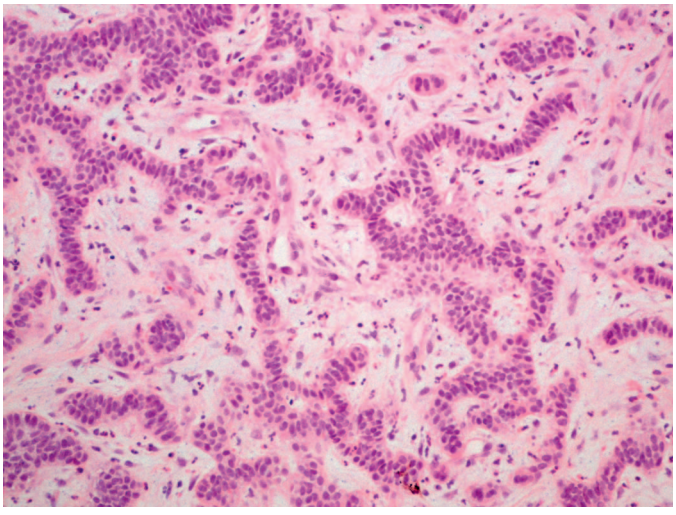
The case was discussed in the multidisciplinary board, where the lesion was deemed unresectable due to the patient's age, comorbidity, and refusal to undergo surgical intervention. The board recommended PT, which had been in operation in Trento since October 2014, as local treatment with radical intent, taking into account tumor extension and its close proximity to optical structures.

Proton Therapy Treatment

Setup procedures consisted of patient immobilization on a base of skull-specific headframe with an individual 3-point thermoplastic mask. A mouth bite was suggested to depress the tongue and oral cavity away from the treated volume. However, it was not used because of the patient's poor compliance to the device.

The simulation planning computed tomography (CT) scan (2-mm slice thickness) was registered with diagnostic MR and CT for target volume and organ at risk (OAR) delineation.

Figure 2. Typical plexiform growth of the tumor, arranged in anastomosing double columns of cuboidal cells, with minimal evidence of central stellate reticulum. Hemaoxylin and eosin stained, 200×.



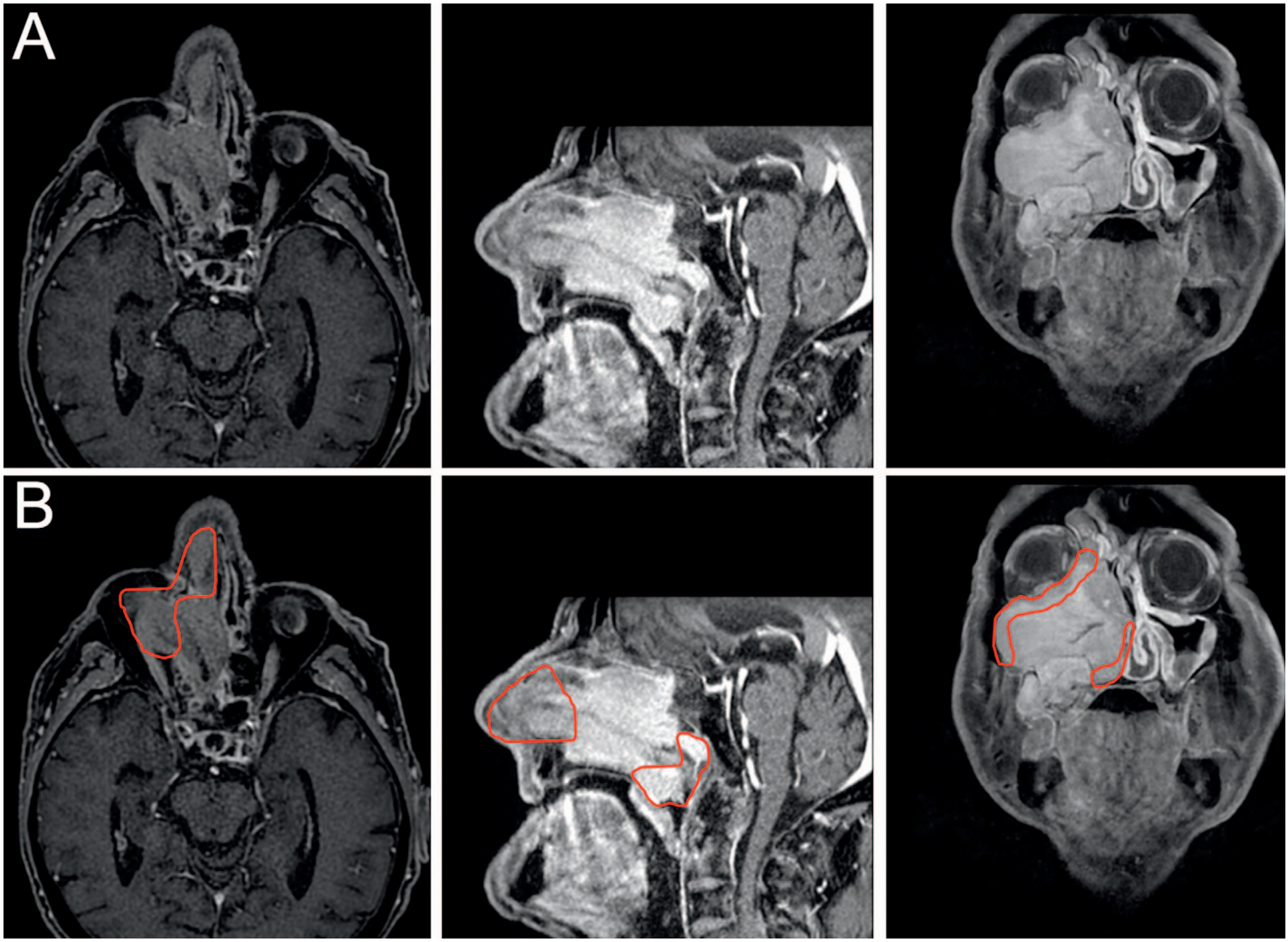


Figure 3. (A) Axial, sagittal, and coronal contrast-enhanced magnetic resonance images taken on October 2015. (B) Areas inside the red lines represent the increase in tumor extension and invasiveness compared with baseline images.

The clinical target volume was defined by adding a 3-mm margin around the gross tumor volume. The planning target volume consisted of a 4-mm isotropical clinical target volume expansion. A 1.5-mm isotropic margin around the optic nerves and chiasm was added to create the planning at-risk volume. The planning target volume prescription dose was 66 Gy (RBE) in 33 daily fractions with maximum accepted dose to 1% of optic structures $\leq$54 Gy (RBE) (**Figure 4**).

The proton plan was generated using an XIO planning system (Xio Proton; Elekta AB, Stockholm, Sweden) using active scanned protons (energy range, 70 to 230 MeV; spot sigma at 32 g/cm^2 $\sim$ 2.65 mm) accelerated by a cyclotron and delivered by a 360° rotational gantry (Ion Beam Applications, IBA, Louvain-La-Neuve, Belgium). A single-field optimization technique, which employs individually optimized PT fields that each deliver a homogeneous dose to the target was used for the present case. A 3-field coplanar and non-coplanar beam arrangement (250° couch 0°, 110° couch 0°, 340° couch 90°; 0°, 280° couch 90°, 240° couch 90°) was chosen. An energy adsorber was employed for superficial layers of the non-coplanar beam. Spot spacing was set at 0.3 cm.

Treatment was delivered between November 2015 and January 2016 with daily online setup verifications. Weekly CT scans were performed to verify consistent target coverage and OAR sparing during treatment. No replanning was needed (**Figure 5**).

As of toxicity, the patient experienced acute G3 radiation dermatitis and mucositis, which required topical creams and temporary use of opioid analgesics. There were no treatment interruptions due to acute toxicity. Complete recovery from skin and mucosal toxicity was observed at the 1-month and 2-month follow-up, respectively.

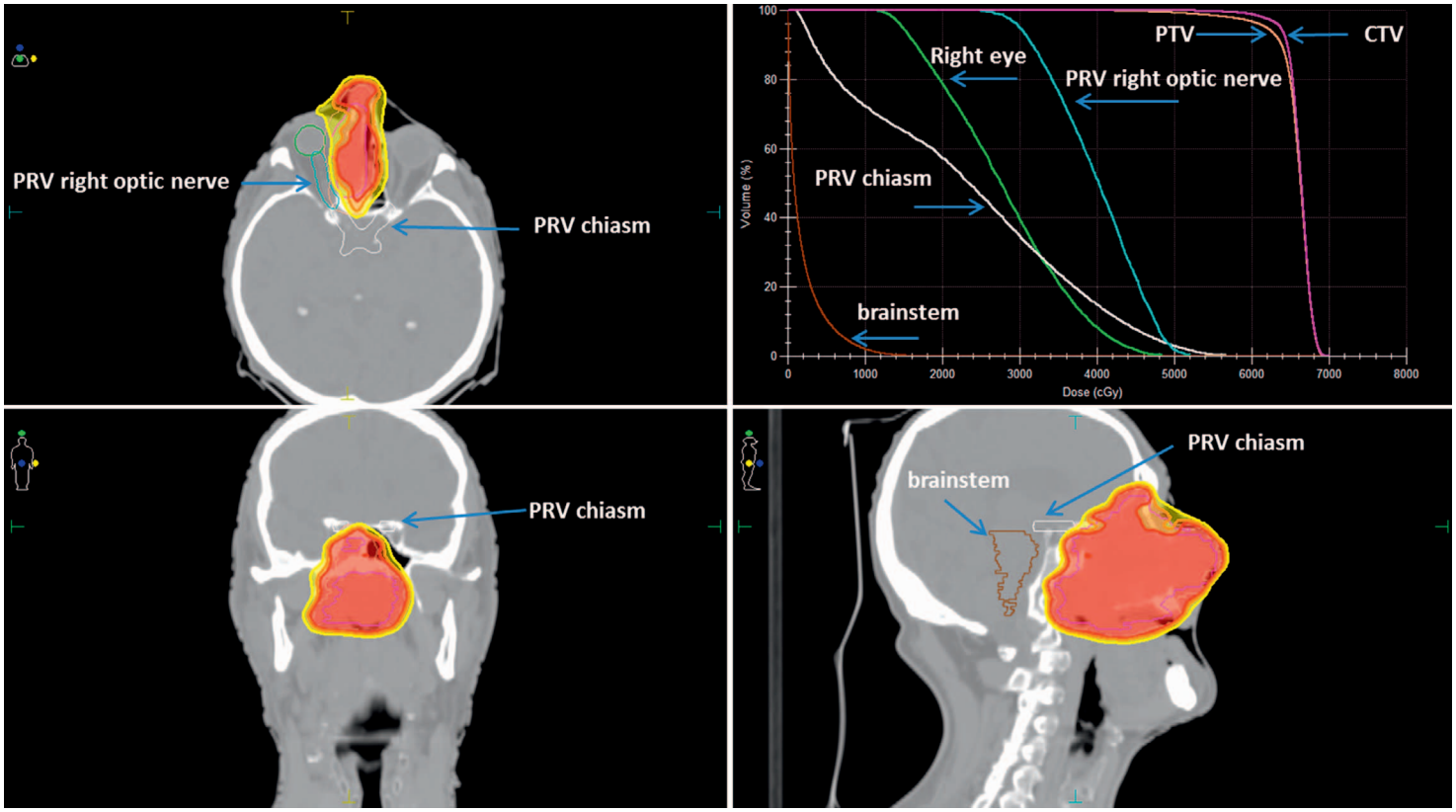


Figure 4. A dose-volume histogram where the yellow, orange, and red isolines represent the 54, 60, and 62.7 Gy isodose lines, respectively.

The first MR after PT was performed 3 months after treatment and showed a complete response with no evidence of tumor. The ear, nose, and throat consultations during the following 18 months confirmed no evidence of disease. At 18 months after the end of PT, the patient had no evidence of disease clinically and radiologically, with an Eastern Cooperative Oncology Group performance status of 0 and very good quality of life. **Figure 6** illustrates the consolidated post-PT MR images. No visual toxicity has been observed so far. The patient recently renewed his driving license.

Discussion

Herein is reported the case of a large amelobastoma successfully treated by definitive PT. The use of RT in the treatment of ameloblastoma or ameloblastic carcinoma is rarely reported in literature.

The study of Kennedy et al [2] reported a local control of 67% with a median radiation dose of 66.2 Gy (range, 63 to 74.4 Gy) in 6 patients treated with curative intent with either RT alone (n = 2) or following surgery (n = 4) between 1973 and 2007 at a median observed follow-up of 7.8 years.

Similarly, radiation doses were reported in the study of Philip et al [6]. Between 1973 and 2004, doses between 63 and 72 Gy in conventional fractionation were administered to 5 patients affected by ameloblastic carcinoma or ameloblastoma. At the 2.1-year follow-up, 4 patients were alive and had evident disease; 1 patient had died of other causes. In 1 patient, RT was given alone; 4 patients received RT after surgery with close or microscopically positive margins.

Koca et al [7] recently reported a partial response using tomotherapy up to a dose of 60 Gy in 30 fractions for a recurrent ameloblastic carcinoma. The tumor size was 57 × 56 × 63 mm, approximately half of the tumor size reported in the present study. Mendenhall et al [8] summarized the few existing reports regarding RT in the treatment of ameloblastoma. Local control was achieved in 7 of 9 patients irradiated for gross disease and 3 of 3 patients treated postoperatively. In their review, the authors suggested the use of PT for extensive maxillary ameloblastomas to adequately treat the tumor and reduce the dose to OARs (eg, the central nervous system and optic structures).

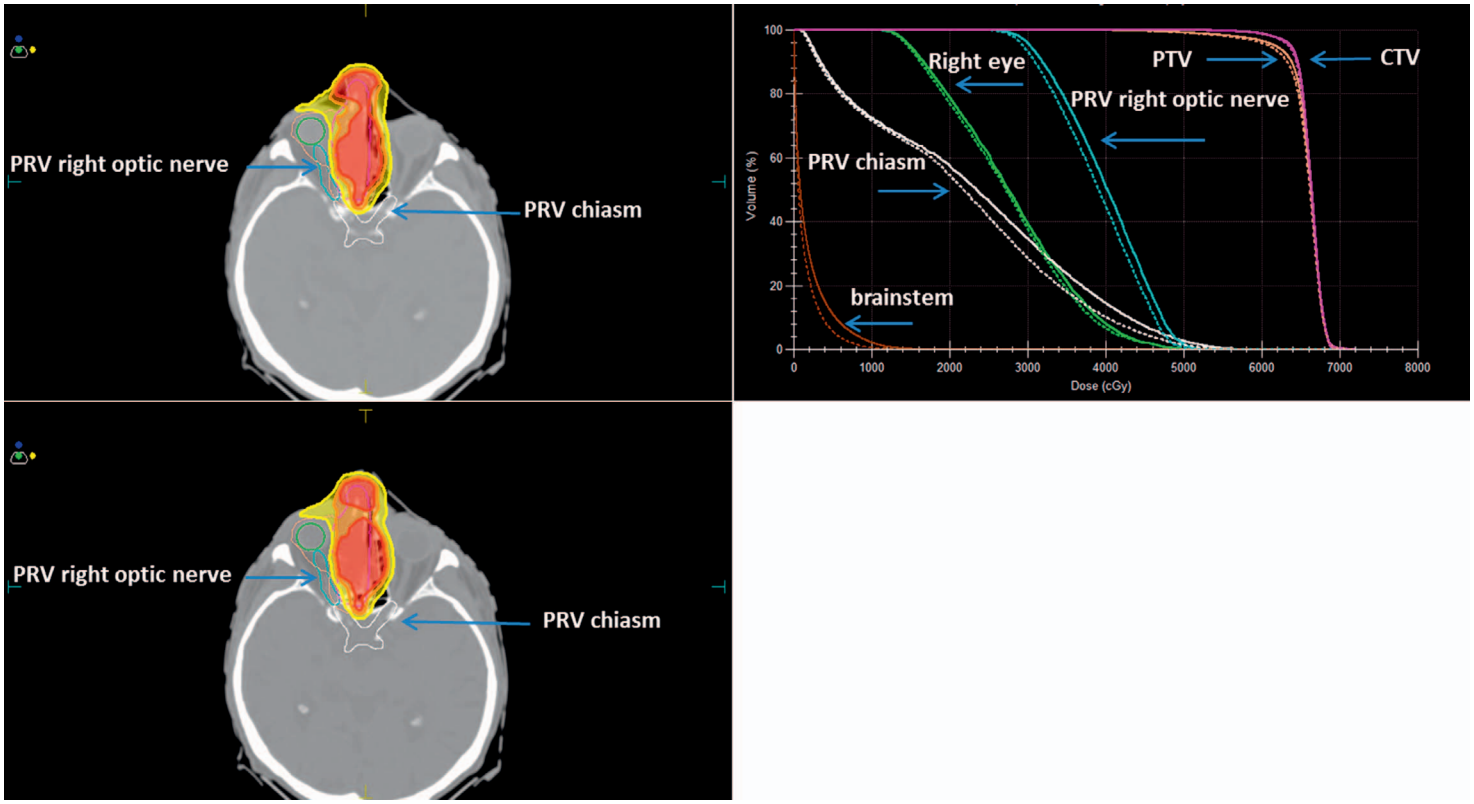


Figure 5. Comparison of a planning dose-volume histogram and a dose-volume histogram obtained from a weekly computed tomography scan showing consistency in target coverage and sparing of the organs at risk.

To our knowledge, this is the first reported case of PT in the treatment of ameloblastoma. Regarding heavier particles, Jensen et al [9] described a case of a locally recurrent ameloblastic carcinoma positively treated with carbon ion therapy at Heidelberg with a dose of 60 Gy (RBE) in 20 fractions.

In both cases, a rapid and complete response was observed. Given the relatively indolent natural history of these tumors, such a rapid response would not have been expected. Conversely, in the reported study of x-ray radiation therapy by Koca et al [7], only a partial response was reported at the 1-year follow-up. A possible explanation of the conflicting results between these studies could lie in the higher radiation doses administered and the use of charged particles with their peculiar radiobiology [10] that could have affected the rapidity and completeness of tumor response.

The use of charged particles, indeed, could be advantageous when treating head and neck cancers, specifically paranasal sinus cancers, where high doses are usually needed to treat large and complex target volumes surrounded by critical OARs, such as the visual apparatus or the brainstem. Several dosimetric studies and, more recently, clinical studies showed promising results and potential advantages for PT compared with x-ray therapy in the treatment of head and neck cancers [11–14]. Moreover, a recent meta-analysis by Patel et al [15] reported significantly better outcomes in terms of disease-free survival and local-regional control for paranasal sinus and nasal cavity cancer treated with charged particles in comparison with patients treated with photon therapy.

In this case report, we clearly depicted the potential of active scanning PT to successfully deliver radical doses to large treatment volumes close to critical OARs, reducing the risk of treatment toxicity. The present report shows another potential indication for PT: its use for radical treatment in elderly and frail [15] patients with head and neck conditions who have a limited ability to compensate for treatment side effects [16]. The potential of PT to reduce acute and late sequelae compared with conventional RT should be considered by multidisciplinary boards when recommending definitive RT for elderly and frail patients with curable head and neck conditions.

A potential pitfall of this technique in sinonasal cancer treatment is the complex interaction between setup errors and anatomical uncertainties (ie, variations in nasal cavity and paranasal sinuses filling) that could occur during treatment with

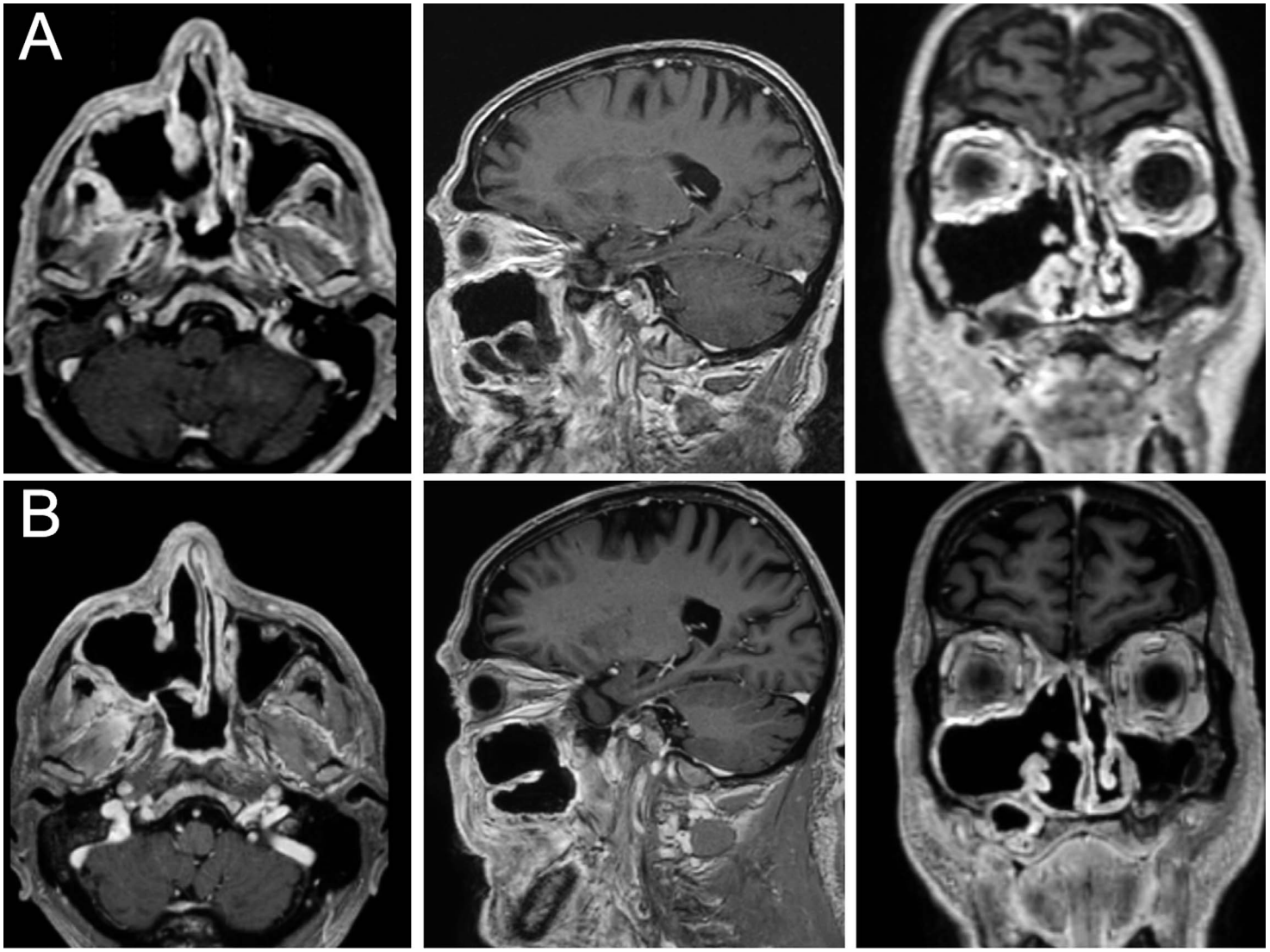


Figure 6. Consolidated post–proton therapy images showing complete response taken at (A) 3 months after the end of proton therapy and (B) 1 year after the end of proton therapy.

potential relevant differences between the nominal dose distribution (calculated on the planning CT) and the actual delivered dose [17]. In light of this, weekly verification CT scans with the implementation of 3-dimensional image-guided protocols in proton therapy [18] are recommended to establish the need for replanning. Moreover, the development of robustness tools to ensure the delivery of high-quality plans is essential, especially when nonuniform, nonhomogeneous fields are used as in multifield optimization (ie, multifield optimization or intensity-modulated PT) planning [19].

Conclusion

We reported the positive outcome of definitive PT in the treatment of a large unresectable ameloblastoma in an elderly patient, confirming and supporting the role of PT for specific challenging clinical scenarios (eg, sinonasal cancers, large target volumes, definitive treatments, and curable, elderly and frail patients).

ADDITIONAL INFORMATION AND DECLARATIONS

Conflicts of Interest: The authors have no conflicts to disclose.

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