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Case report

Cyberknife stereotactic radiosurgery and denosumab for giant cell tumour of the skull base: Case report

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ABSTRACT

Giant cell tumours (GCT) of the skull is a rare entity with only small number of cases reported in literature and optimal treatment is yet to be determined. These tumours have shown high recurrence rates after incomplete surgery, usually occurring during the first year. Even with new surgical techniques a complete resection in skull base tumours is not always possible without functional compromise. Therefore, adjuvant therapy is essential to enhance local control and quality of life. We report a rare case of a 34-year-old male with giant cell tumour (GCT) of the skull base involving the petrous bone, clivus and sphenoid body. The patient received Cyberknife stereotactic radiosurgery (CK SRS) and denosumab after surgery. This combined therapy allowed local control and tumour reduction with secondary neurological improvement during a 4-year follow up.

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1. Introduction

Giant cell tumours (GCT) of the skull base account for approximately 1% of all GCTs of the bone.[1] Despite being considered as a benign neoplasm, they are locally aggressive with high recurrence rates after incomplete surgery.[2] Even with new surgical techniques, a complete resection in skull base tumours is not always possible without functional compromise.[3] Therefore adjuvant therapy is essential to enhance local control and quality of life. Adjuvant therapy for GCT has changed over the past years, mainly with the use of modern radiotherapy (RT) techniques and the discovery of a specific monoclonal antibody.[4–6] To our knowledge, there are no other reports of CK SRS combined with denosumab in skull base GCT with long-term follow up.

2. Case report

2.1. Clinical history

The patient was a 34-year-old male with a three-month history of progressive right-sided hearing loss with no previous medical treatment. However, on the day of the admission he complained of dizziness, tinnitus and right facial palsy. On neurological examination, there was right peripheral facial nerve (CN VII) palsy and deficit of vestibulocochlear nerve (CV VIII). The rest of the physical examination and cranial nerves were found normal. Magnetic resonance imaging (MRI) of the brain revealed a hyper intense lesion infiltrating the petrous bone, clivus and sphenoid body (Fig. 1A). A subtotal tumour resection was performed with a right temporal craniotomy and endoscopic trans nasal trans sphenoidal approach (Fig. 1B). Histologically, the tumour was composed of multinucleated giant cells in a proliferative spindle cell stroma, consistent with giant cell tumour. The patient's case was evaluated in a multidisciplinary tumour board recommending adjuvant therapy with CK SRS and denosumab.

2.2. Treatment description

The procedure began with immobilization of the patient's head in a supine position using a thermoplastic mask. For stereotactic targeting and planning purposes, a computed tomography (CT) with and without contrast, slices of 1.25 mm thickness, along with brain MRI scans with gadolinium were acquired. Gross tumour volume (GTV) was defined as a macroscopic residual tumour visible on the MRI with a total volume of 20.6 cm^3 and the planning target volume (PTV) was equal to GTV (Fig. 2).

A highly conformal plan was created using the Multiplan® inverse planning software, version 3.5.1, and delivered using the 6D Skull Tracking System (Accuray, Inc., Sunnyvale, CA) which allows tracking and corrections, in real-time, of the tumour motion (Fig. 3). A total dose of 20.1 Gy in three fractions (6.7 Gy per fraction, three consecutive days) prescribed to the 84% isodose line was administered to the skull base residual tumour. One hundred and thirty-five treatment beams were used covering 95.88% of the target volume. The maximum dose was 23.93 Gy and the conformity index, 1.20. The approximate time per fraction was 35 min. Considering that the only hearing ear was on the left side, this cochlear was protected from excessive radiation. The treatment was completed uneventfully and with good tolerance.

2.3. Follow up

Three months after treatment, the patient received the first dose of denosumab 120 mg, administered monthly during the first year, every 3 months during the second year and every 6 months during the third and fourth year. No clinical or radiological radiation effects were observed during the follow-up periods. MRI imaging were done periodically showing progressive reduction in size and enhancement of the skull base lesion (Fig. 4). The patient continues with right-sided hearing loss but without facial palsy. No toxicity by denosumab was reported.

3. Discussion

Skull base giant cell tumours are locally aggressive tumours with a low tendency for metastasis.[7] Therefore, local treatment defines the prognosis and quality of life in these patients. Surgery has been historically the treatment of choice.[8] However subtotal resections result in high rates of recurrence, mostly occurring within the first year, justifying the use of adjuvant therapy.

The role of radiation therapy has been unclear and criticized in the past because of low rates of local control and concerns about side effects and malignant transformation.[4] Most of these series have been described using an outdated 2-D radiation technique with plain radiographs for tumour localization and orthovoltage techniques with low energies, resulting not only in decreased coverage of the tumour but also in high toxicity and probably increased rates of transformation.[4] Though in some proportion of GCTs, malignant transformation can be attributed to the natural biology of the tumour as it has been described in patients who have not been treated with radiation.[9]

Advances in radiation techniques, physics and computer technology during the past two decades have allowed safe dose escalation with high homogeneity/conformity indices and maximum adjacent tissue sparing resulting in high local control rates and the absence of major side effects. Cyberknife® radiosurgery system (Accuray, Inc., Sunnyvale, CA) is a non-invasive treatment that enables the delivery of high dose radiation to the tumour with extreme accuracy, while minimizing the damage to normal surrounding tissue, widely used in brain tumours. To the best of our knowledge, there is only one case previously reported of skull base GCT treated with CK SRS as a primary treatment modality.[10]

Due to the small number of cases of skull base GCT reported, there is no consensus on accepted fractionation or dose concept but most of the studies have shown that higher doses increase local control rates.[6] It has been reported that modern-era megavoltage radiation therapy with a dose of 45–60 Gy offers a safe and effective local therapy for patients with extensive, recurrent and/or unresectable GCT.[11,12]

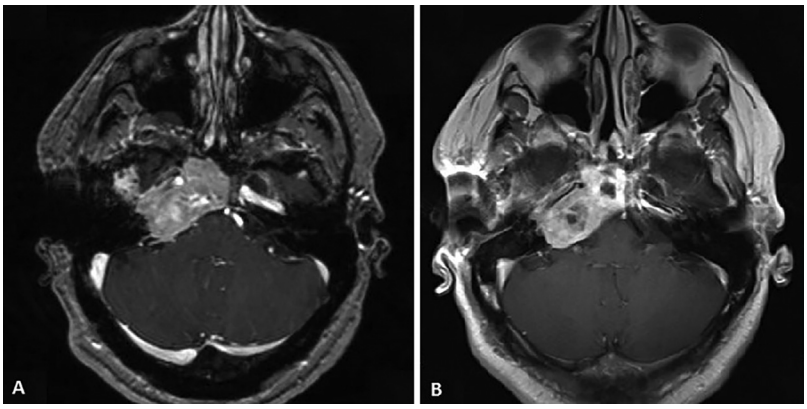

Fig. 1 – Magnetic resonance images before (A) and after (B) surgery of skull base tumour, showing a gross residual tumour with lower uptake in the central zone.

However, this prescription dose has been usually described for GCT involving long bones without nearby risk organs. To give a similar radiation dose, taking into account that the tumour is localized next to the brain stem, we calculated a total dose of 20.1 Gy in three fractions (6.7 Gy per fraction), which equals to an approximate 44 Gy biologically effective dose. We reported no acute and late side effects after 48 months follow up.

As well as radiation therapy, systemic therapy has evolved with the discovery of molecular pathways and the use of molecular target agents showing impressive results, as in the case of GCTs. Denosumab, a human monoclonal antibody, prevents the interaction of the Receptor Activator of Nuclear Factor Kappa-B-Ligand (RANKL) secreted by the spindle stromal cells with the receptor RANK expressed on the surface of GCT giant cells.[13] This drug, recently approved by the Food

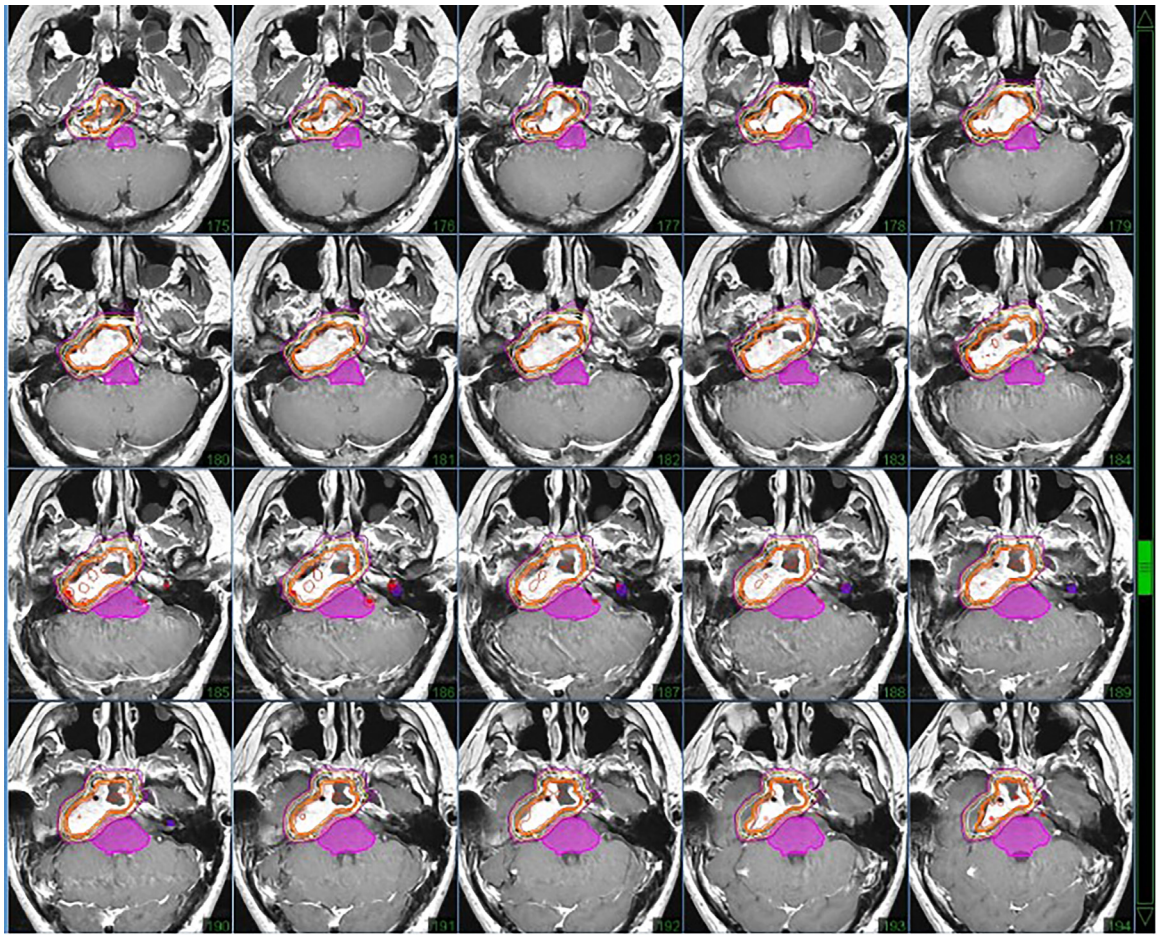

Fig. 2 – Magnetic resonance images fusion with CT planning scan for tumour targeting.

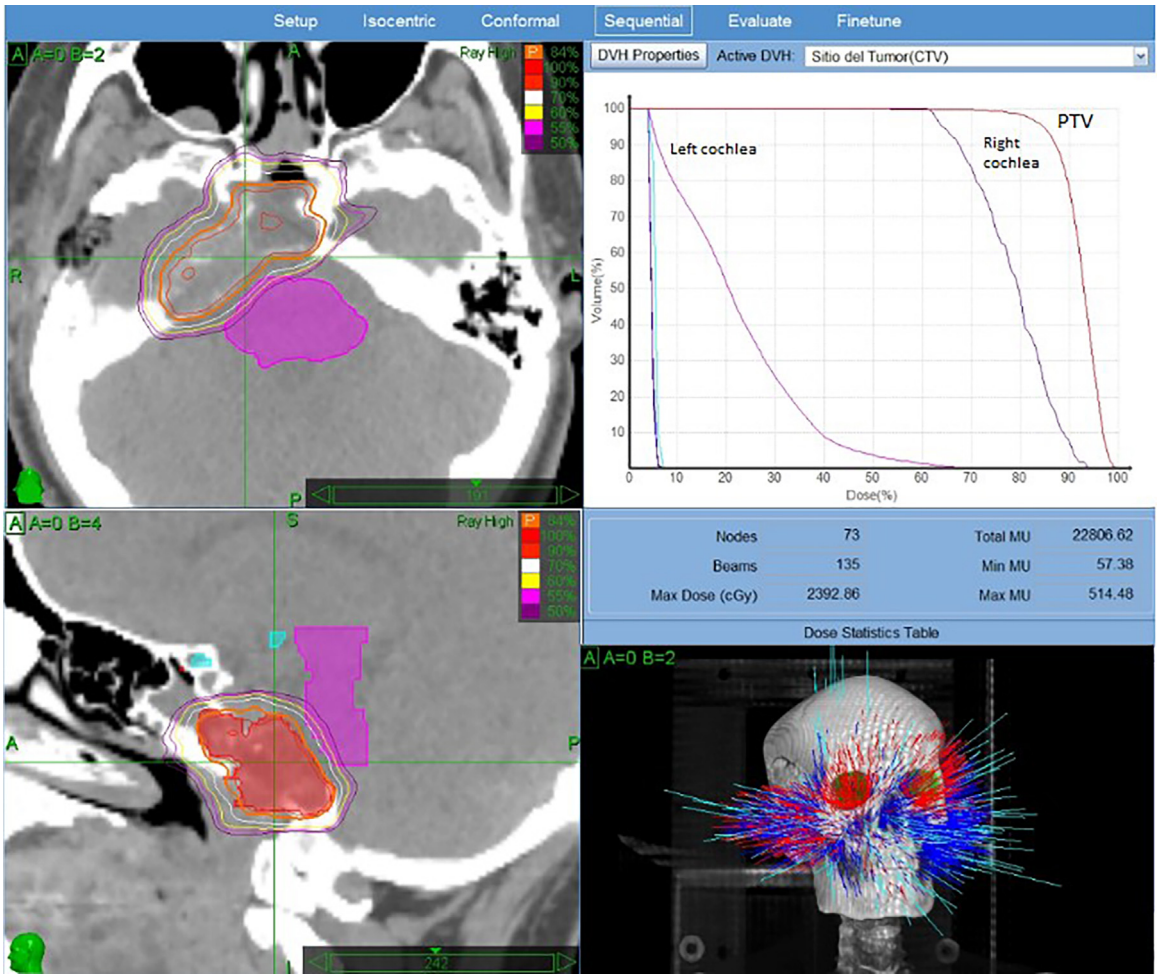

Fig. 3 – Dose–volume histogram and dose distribution for a total dose of 20.1 Gy using 135 beams protecting the hearing ear (left cochlea).

and Drug Administration (FDA) and the European Medicines Agency (EMA) for GCT, inhibits the recruitment and differentiation of the giant cell component of the tumour.[14] The first results of denosumab included eight patients with skull base GCT showing superimposable results; however, the final analysis is not completely published and treatment duration and long term effects still need to be defined. Due to the minimal efficacy of denosumab against the stromal cells, tumour regrowth is expected after discontinuation of the drug suggesting the need for prolonged treatment or combined therapy.[14]

The rationale of denosumab and its timing with surgery and radiotherapy in GCT has not been established. We initiated adjuvant treatment with radiosurgery at the time the first results of denosumab were published but FDA and EMA

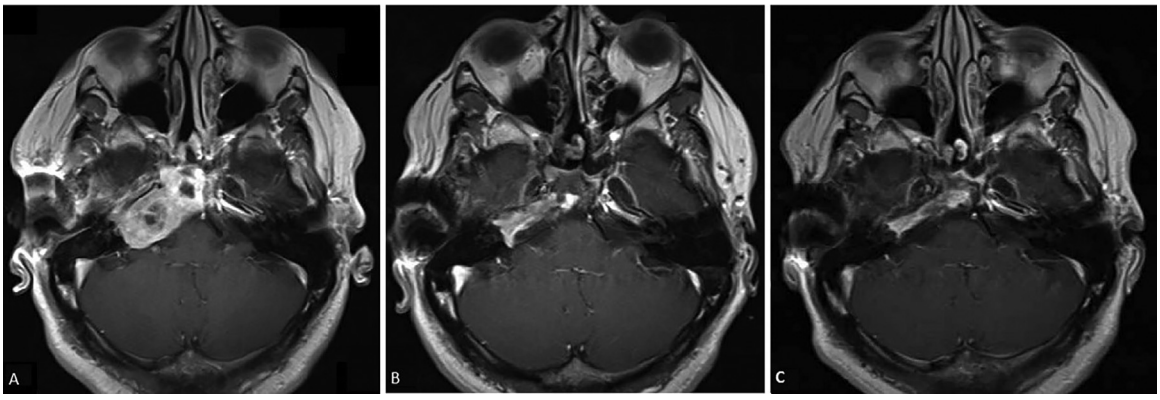

Fig. 4 – GCT of the skull base with residual tumour after surgery (A) showing a marked reduction in volume and enhancement after 24 (B) and 48 (C) follow-up.

approval was still pending. An update of the denosumab trial was recently published showing that this drug used preoperatively could downstage surgery in 38% of the patients (222 evaluable patients). Other anti-angiogenic drugs such as sunitinib and pazopanib in combination with erlonitib have shown some activity for GCT in early stage reports (Phase II and Phase I trials, respectively).[15,16]

4. Conclusion

Our case represents a rare case of skull base GCT managed successfully using CK SRS and denosumab after surgery, with improvement in neurological deficit and no radiation-induced complications. To our knowledge, there are no other reports of CK SRS combined with denosumab in skull base GCT with long-term follow up. Modern radiotherapy techniques, such as CK SRS, could be an effective treatment option for the management of cranial GCTs used as adjuvant and/or combined therapy. Longer follow-up without denosumab is required.

Conflict of interest

None declared.

Financial disclosure

None declared.

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