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^{177}Lu-DOTATATE PRRT as promising new treatment approach in Recurrent Skull Base Phosphaturic Mesenchymal Tumor causing paraneoplastic oncogenic osteomalacia: a potential therapeutic application of PRRT beyond NET

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Short running title: ^{177}Lu-DOTATATE PRRT in oncogenic osteomalacia

Abstract:

The potential of peptide receptor radionuclide therapy (PRRT) is described in recurrent inoperable phosphaturic mesenchymal tumor involving left basi-occiput causing tumor-induced osteomalacia (TIO), for which the patient had undergone two times surgery previously. Following one cycle of PRRT, there was good symptomatic improvement, modest reduction of uptake on both ^{68}Ga-DOTATATE PET/CT and FDG-PET/CT suggesting favourable response and hence was considered for second cycle. Being somatostatin receptor avid, this rare group of tumors when inoperable or recurrent may be potentially targeted with PRRT. Well-tolerated and non-invasive, PRRT could evolve as a promising targeted treatment approach in this clinical setting. In summary, TIO with ^{68}Ga-DOTATATE avid inoperable/recurrent tumor can be considered as a potential and novel clinical treatment application of PRRT beyond neuroendocrine tumors.

Introduction

Oncogenic osteomalacia is a relatively rare paraneoplastic syndrome with prominent musculoskeletal complaints (such as skeletal pain, fatigue, fracture, muscle ache) that could make the patient wheel-chair bound. The causative tumors of TIO are usually benign mesenchymal or mixed connective tissue tumors [1] or rarely malignant mesenchymal tumors [2]. Recently, FGFR1 translocation has been described in a fraction of phosphaturic mesenchymal tumors of head and neck [1]. A substantial fraction of these tumours demonstrate somatostatin receptor expression and ^{68}Gallium-DOTA-Octreotate (DOTA-TATE) PET-CT has evolved as an important imaging modality to locate the causative tumors [3]. The condition quickly corrects following complete resection of tumor with gradual normalization of skeletal abnormalities. In absence of tumor identification, supportive medical management with phosphorus and calcitriol is considered. Cinacalcet, a calcimimetic, which acts by allosteric activation of the

calcium-sensing receptors, and octreotide have also been found useful in patients with resistant hypophosphataemia [4].

The present report explores the potential therapeutic application of ^{177}Lu-DOTATATE PRRT in recurrent inoperable phosphaturic mesenchymal tumor of the skull base.

Case Report

A 53 year old female, diagnosed with Vitamin D resistant hypophosphataemic osteomalacia (presented 2 years previously with bilateral groin pain and difficulty in walking and was evaluated with MRI and bone densitometry, serum calcium and vitamin D profiles), was treated initially with vitamin D3 supplements. On further investigation, her serum phosphorus level was found to be low (1.5 mg/dl; reference range: 2.3-4.5 mg/dl) and serum fibroblast growth factor 23 (FGF23) was high (725 RU/ml; reference range: < or =180 RU/mL) and was started on phosphate supplements. A somatostatin receptor PET-CT and MRI brain demonstrated large expansile osteolytic lesion with cortical breach and soft tissue component measuring 3.5 x2.7 cm involving base of skull, left basi-occiput including clivus and occipital condyle with erosion of mastoid and petrous part of adjacent temporal bone and occlusion of left jugular foramen. She underwent retromastoid craniotomy with excision of extra-axial tumor. The histopathology demonstrated benign giant cell rich lesion and was suggestive of a phosphaturic mesenchymal tumor (a differential diagnosis made with brown tumor of hyperparathyroidism). MRI brain undertaken at 4 months follow-up after surgery in view of recurrent symptoms showed a recurrent left occipital skull base tumor around 3.2 x 1.6 x2.1cm in around the jugular foramen involving the left arch of atlas and mastoid temporal bone, for which she underwent craniotomy and repeat exicision with occipito-cranial fusion; the histopathology was suggestive of recurrent/residual tumor consistent with initial diagnosis. A ceCT at 3 months showed

residual enhancing lesion 1.8x2.2x1.6cm, in and around left hypoglossal canal. The serum phosphorus levels were consistently in lower range and she was put on phosphorus supplements. A ^{68}Ga-DOTATATE PET-CT at 6 months following ceCT (9 months following second surgery) demonstrated an increasing lesion size (2.3x1.9x2.1cm), in left jugular foramen region involving the left hypoglossal canal (Fig 1). The patient had persistence of pain during walking with some improvement and serum phosphorus level was maintained at low normal level (2.6 mg/dL), with phosphorus supplements.

Thus, in view of two previous skull base surgeries, persistence of symptoms and a recurrent lesion at the same site, alternative therapeutic approaches was sought for. The tumor being ^{68}Ga-DOTATATE avid (Krenning score IV), PRRT with ^{177}Lu-DOTATATE therapy was considered in a multidisciplinary meeting. She was administered 5,661 MBq of ^{177}Lu-DOTATATE following standardized treatment protocol. Three months after first cycle, she reported good symptomatic improvement (>25% compared to baseline) and reduction of SUV on ^{68}Ga-DOTATATE PET (from 33.85 g/ml to 23.93 g/ml, reduction 29.6%) (Fig 2 and 3) and on FDG-PET/CT (from 16.98 g/ml to 12.88 g/ml, reduction of 24.15%) (Fig 4).

Discussion

Tumor-induced osteomalacia is an uncommon paraneoplastic condition, typically characterized by phosphaturia, hypophosphataemia and osteomalacia, caused by enhanced tumor production of fibroblast growth factor 23 (FGF23) that (i) inhibits phosphate reabsorption in the proximal convoluted tubule (by reducing the expression of NPT2, a sodium-phosphate cotransporter in renal PCT) [5] and (ii) reduces renal calcitriol production (by inhibiting 1-alpha-hydroxylase, thus suppressing its activational function of Vitamin D and thus preventing calcium absorption) [6]. Encoded by FGF 23 gene located on chromosome 12, loss of *FGF23* activity can

cause hyperphosphataemia and calcinosis while enhanced levels (e.g. by phosphaturic mesenchymal tumor) or activity (mutation in autosomal dominant hypophosphatemic rickets) of FGF23 causes rickets and osteomalacia [2].

PRRT with ^{177}Lu-DOTATATE can be potentially employed in an inoperable/recurrent phosphaturic tumor following documentation of high somatostatin receptor expression in the causative tumor [i.e. Krenning score III/IV uptake on ^{68}Ga-DOTATATE PET-CT]. This treatment approach could be more efficacious compared to other presently existing medical management options, with a convenient 3 monthly administration schedules and well-tolerability.

Conclusion:

To best of our knowledge, the present report is the first literature description of ^{177}Lu-DOTATATE PRRT in a recurrent inoperable phosphaturic mesenchymal tumor. More such endeavours undertaken in this direction could establish PRRT as potential and effective targeted novel therapeutic approach in patients of resistant TIOs with inoperable/recurrent tumors.

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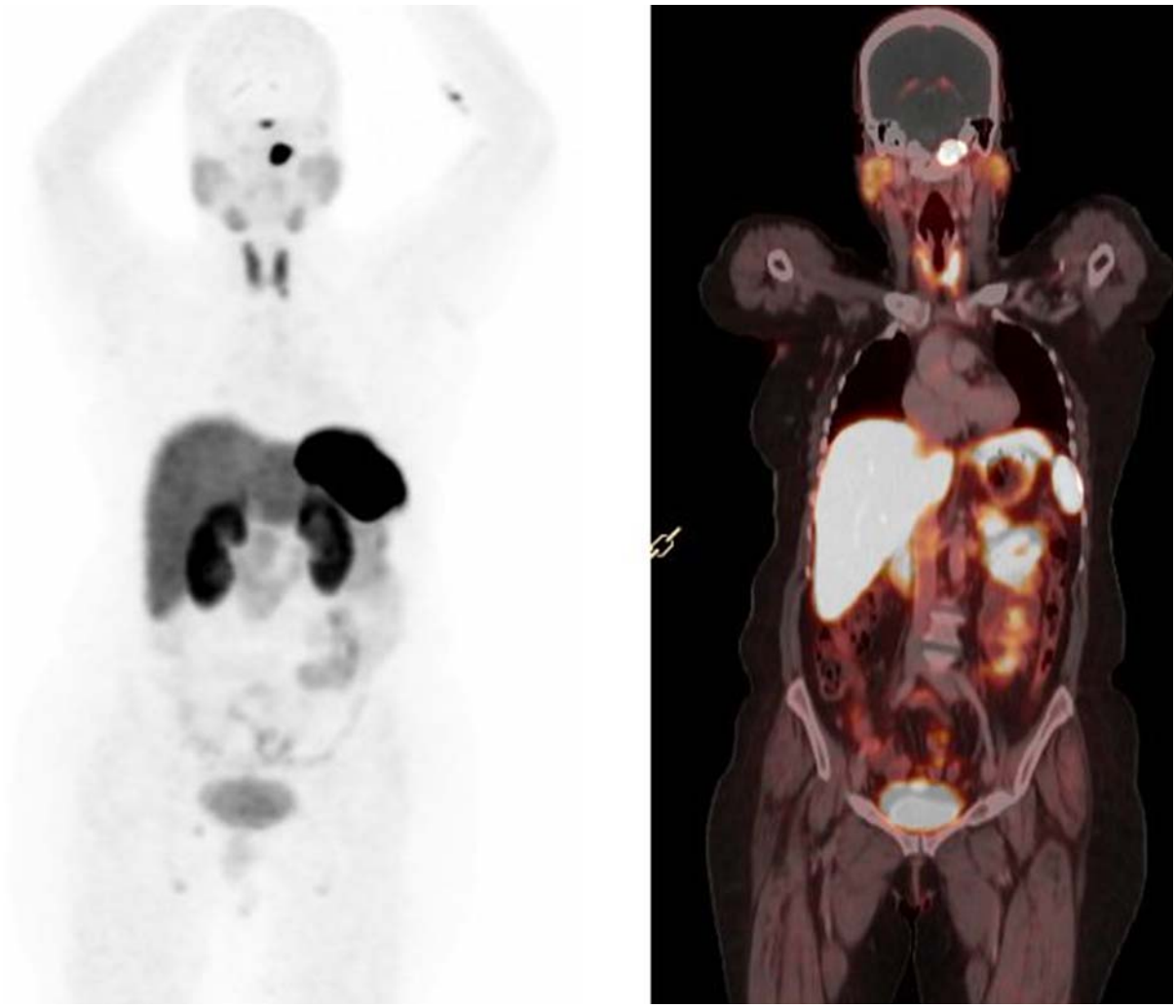
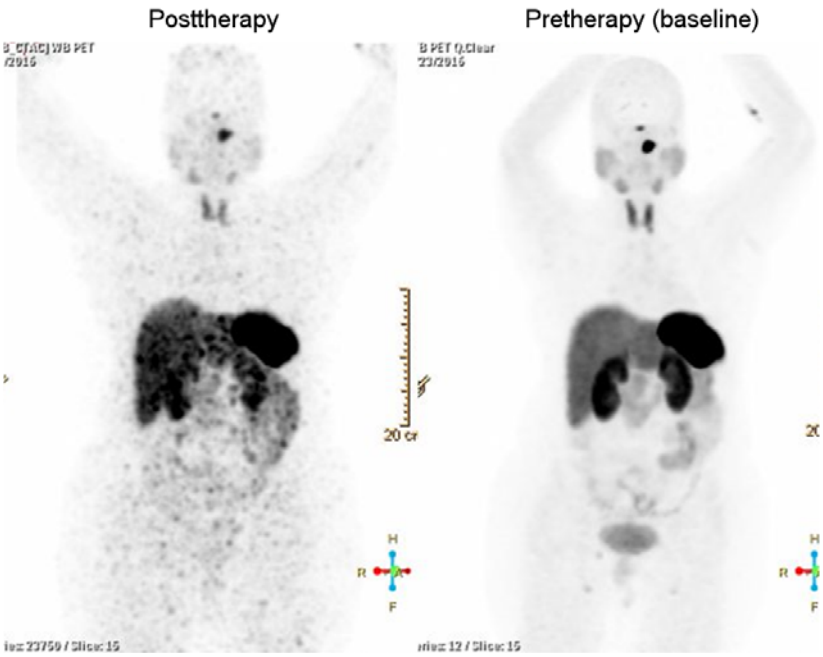


Fig 1. 68Ga-DOTATATE PET-CT (MIP and fused coronal view) demosntrating enhancing soft tissue lesion (2.3x1.9x2.1 cm) in the left basiocciput and left occipital condyle involving the left jugular foramen and left jugular foramen



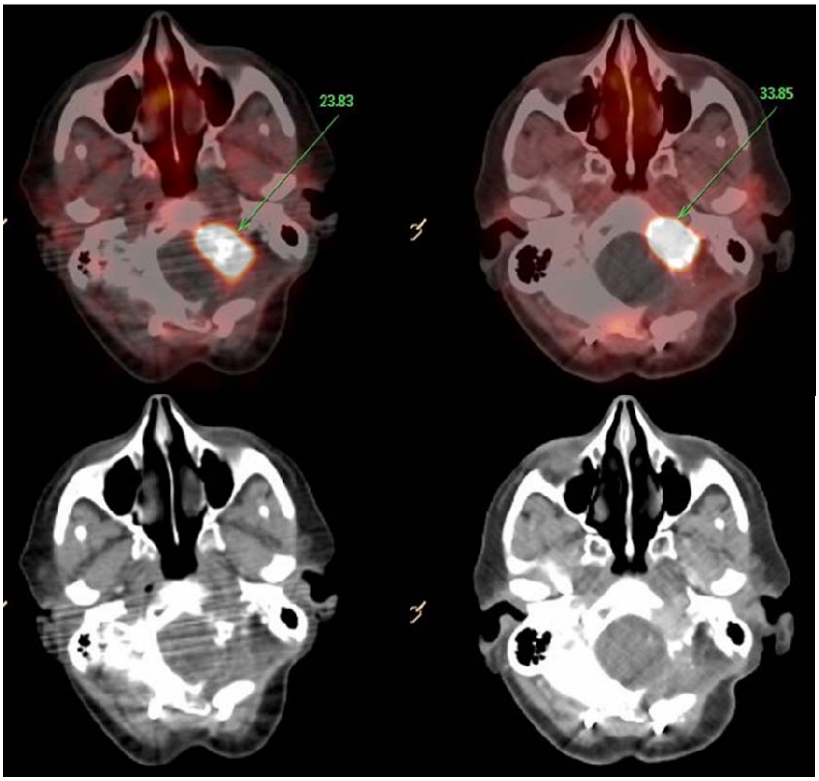


Fig 2 and 3. 68Ga-DOTATATE PET-CT (Pre- and Post- 1st cycle of ^{177}Lu-DOTATATE PRRT) at 3 months demonstrating modest decrease in the uptake with 1 cycle of PRRT.

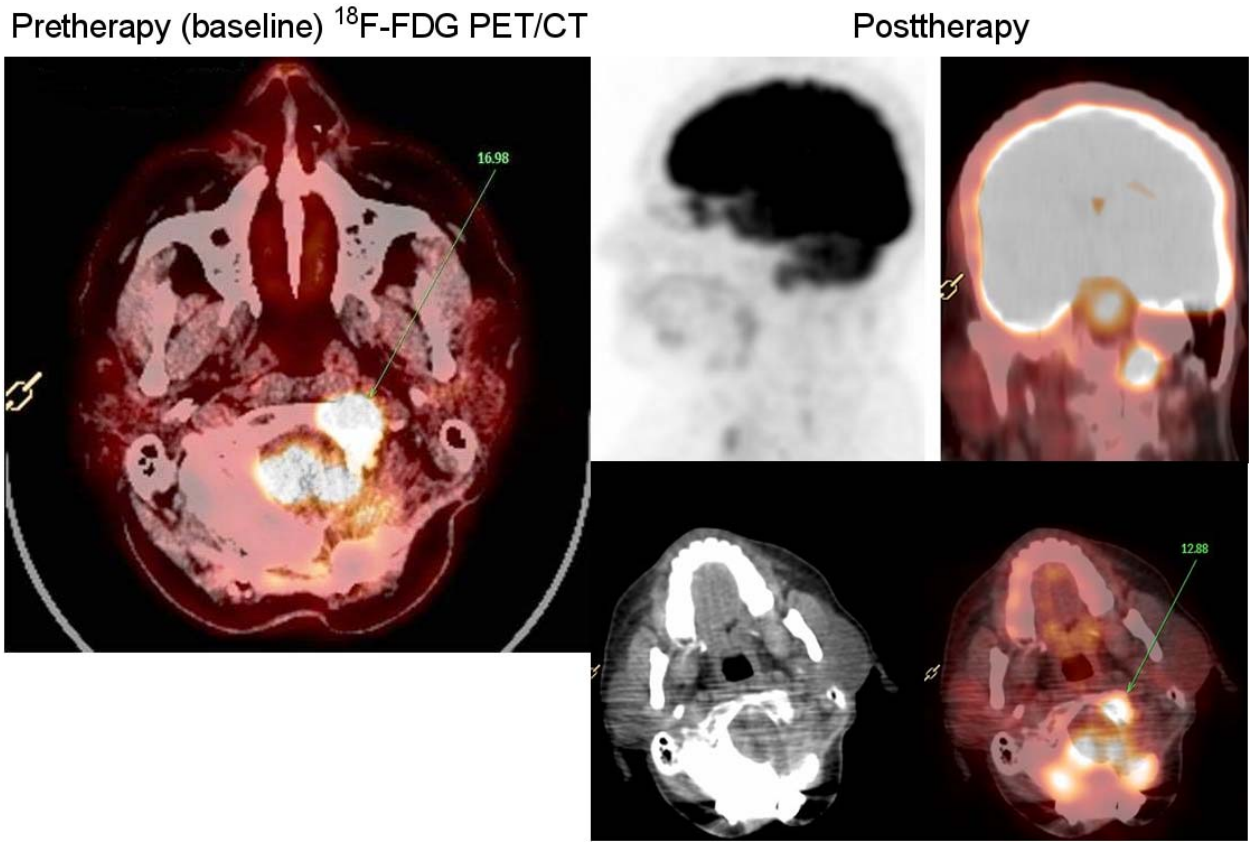


Fig 4. FDG-PET/CT (Pre- and Post- 1st cycle of ^{177}Lu-DOTATATE PRRT) at 3 months showing reduction of tracer uptake from 16.98 to 12.88 i.e. reduction of 24.15%.