

**Title:** Image guided combination of  $^{177}\text{Lu}$ - DOTATATE and capecitabine peptide receptor  
chemoradionuclide therapy in metastatic mediastinal paraganglioma

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**Short running title:** PRCRT in metastatic paraganglioma

**Abstract:**

The peptide receptor radionuclide therapy (PRRT) targets highly expressed somatostatin receptors (SSTR) shown on SSTR imaging in well-differentiated neuroendocrine tumours (NETs) with stable or partial response in majority of inoperable/metastatic NETs patients. However NETs showing increased FDG uptake carry the poor outcome with limited treatment options and role of PRRT is still unclear. Here is a case of young male patient of mediastinal paraganglioma and extensive metastatic disease showing avidity both on SSTR and FDG imaging. The patient showed partial response and significant improvement in quality of life with peptide receptor chemo-radionuclide therapy (PRCRT) in the form of  $^{177}\text{Lu}$ -DOTATATE along with low dose capecitabine. This case highlights the utility of PRCRT in extensive disease with SSTR and FDG avidity where other treatment modalities may not be suitable.

**Keywords:**  $^{68}\text{Ga}$  DOTANOC PET/CT;  $^{177}\text{Lu}$ -DOTATATE; PRCRT; Neuroendocrine tumours; Paraganglioma

**Introduction:**

The well-differentiated neuroendocrine tumours (NETs) on somatostatin receptor (SSTR) imaging illustrate the disease extent and SSTR expression. The intense SSTR expression in the primary and metastatic sites helps in predicting the grade of the tumour and its suitability to peptide receptor radionuclide therapy (PRRT). Majority of inoperable/metastatic NETs patients treated with PRRT have shown stable or partial response. However NETs showing increased FDG uptake carry the poor outcome with limited treatment options and role of PRRT is still not well-defined. Here is a case of young male patient of mediastinal paraganglioma with extensive skeletal metastases having avidity both on SSTR and FDG imaging showed partial response and significant improvement in quality of life with peptide receptor chemo-radionuclide therapy (PRCRT) in the form of  $^{177}\text{Lu}$ -DOTATATE and low dose capecitabine, highlighting the utility of treatment where other treatment modalities may not be suitable.

**Case Report:**

Twenty-seven year-old wheel chair bound male patient with severe left-sided low backache following trivial injury of 2 months duration revealed soft tissue mass with osteolytic lesion in left iliac bone on X-ray and MRI pelvis., The whole body  $^{18}\text{F}$ -FDG PET/CT done with a suspicion of malignancy, showed intense tracer avid (SUVmax 40) right inferior mediastinal mass (~8.0x5.2x9.4cm), left iliac mass (SUVmax 47.6) and widespread lytic skeletal lesions on maximum intensity images (MIP) and in corresponding transaxial fused images (Fig.1a). Histopathology of inferior mediastinal mass was suggestive of paraganglioma, positive for S-100 and chromogranin immuno-stains.  $^{68}\text{Ga}$ -DOTANOC PET/CT done for SSTR expression assessment as an option of PRRT, showed intensely tracer avid posterior mediastinal mass (SUVmax 88) and multiple skeletal lesions (left iliac bone SUVmax 49.5) in concordance with

<sup>18</sup>F-FDG PET/CT findings (Fig.1b). The study protocol was approved by Institutional Ethics Committee and the subject in this study signed written informed consent for this study. Serum chromogranin-A was elevated (15013 ng/mL, normal < 98.1) while free metanephrine and dopamine levels were normal. The patient received 2 cycles of <sup>177</sup>Lu-DOTATATE infusion (200 mCi/ cycle) at 8 weeks interval along with low dose capecitabine as radiosensitizer in divided doses (1250 mg/m<sup>2</sup>) for 14 days starting from the first day of therapy. Positively charged amino acids (arginine and lysine) and saline infusion were also given with PRCRT to prevent the nephrotoxicity. <sup>177</sup>Lu-DOTATATE post-therapy scans acquired at 24 hours after first therapy showed tracer uptake in the primary and metastatic lesions (Fig.2a,b). The interim <sup>68</sup>Ga-DOTANOC PET/CT after 2 cycles of PRCRT showed significant decrease in tracer avidity within the lesions (SUVmax decreased from 88 to 16.4 in mediastinal mass and 49.5 to 20.1 in left iliac bone/soft tissue lesion) and concurrent decrease in lesions size (according RECIST 1.1 criteria), suggesting a partial metabolic/ morphological response (Fig.1c) with fall in serum chromogranin-A level to 2504 ng/ml. Patient had significant improvement in EORTC QLQ-C30 questionnaire used for quality of life assessment and started walking on his own from wheel chair bound position. His Karnofsky Performance Score improved to 80 from 50. The patient received two more cycles of PRCRT with total dose of <sup>177</sup>Lu ~800 mCi. Follow-up <sup>68</sup>Ga-DOTANOC PET/CT scan 2 months after 4th cycle of PRCRT revealed disease progression (Fig.1d). The patient finally succumbed to his disease after 3 months of last cycle of therapy received.

### **Discussion:**

Paragangliomas are derived from the neural crest cells thereby having neuroendocrine differentiation. The sympathetic chains around the aorta (para-aortic) and para-vertebral

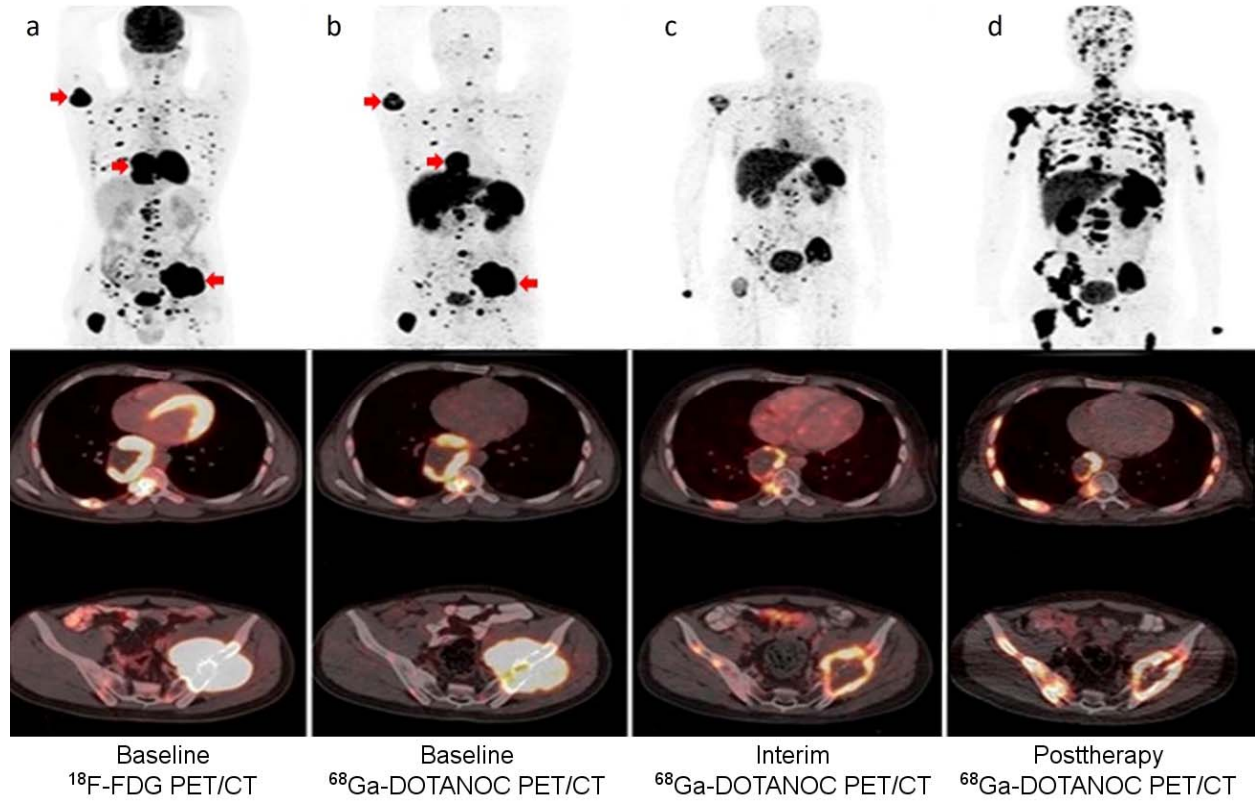
locations give rise to mediastinal paragangliomas, though commonly seen in the head and neck region with malignancy ranging from 0-20% among all the paragangliomas. The SSTR expression in paragangliomas is well documented in recent times with predominance of SSTR2A and 3 subtypes in particular with SDH deficient pheochromocytomas and paragangliomas. Functional imaging like  $^{18}\text{F}$ -FDG,  $^{68}\text{Ga}$ -DOTANOC and  $^{123}\text{I}$ -/ $^{131}\text{I}$ -meta-iodobenzylguanidine may be used for extent of disease, prognosis and to decide the therapeutic options (1-4). FDG avid NETs may show transient response to combination chemotherapy but outcome is usually poor with significant adverse effects. They are presumed to be more radiosensitive and additional SSTR expression of these tumour cells delivers the radiation dose to the proliferating tumour cells.

Targeted internal radiotherapy in combination with capecitabine led to favourable biochemical and imaging response without any significant toxicity, though patient later succumbed to the disease in the index case. A personalised approach in the form of PRCRT with acceptable toxicities is appropriate when other treatment options are limited (5-6).

**Conclusion:** PRCRT may have role in FDG and SSTR avid inoperable and widespread paraganglioma where other options are either limited or ineffective.

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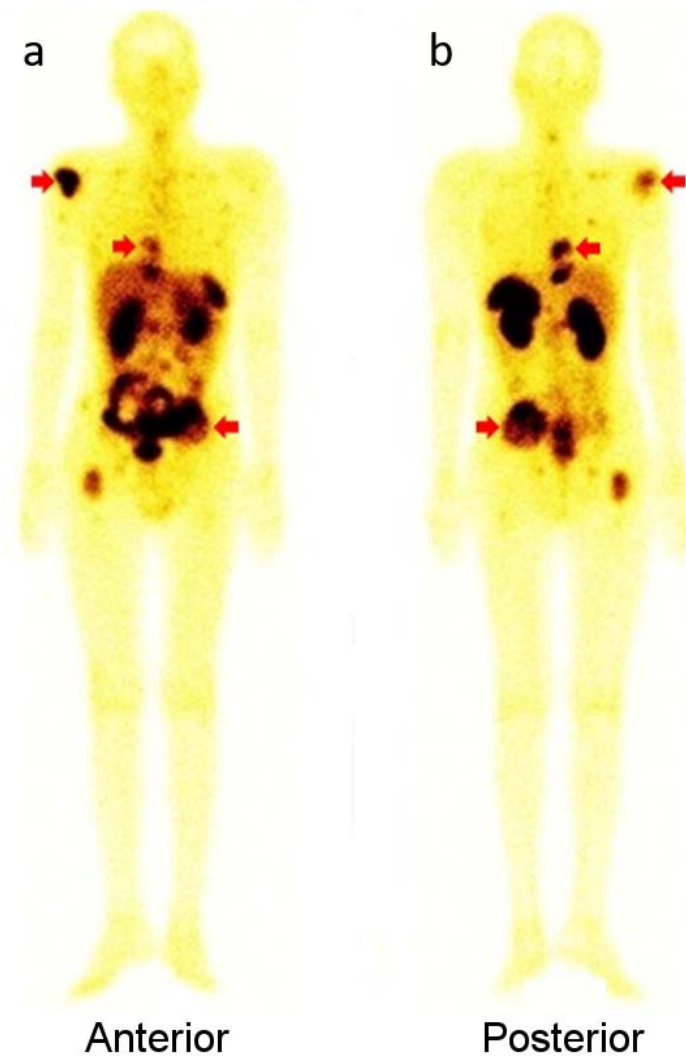
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**Fig 1:** Baseline  $^{18}\text{F}$ -FDG PET/CT MIP and transaxial fused images showed intense tracer avid (SUVmax 40) right inferior mediastinal mass ( $\sim 8.0 \times 5.2 \times 9.4 \text{ cm}$ ), left iliac mass (SUVmax 47.6) and widespread skeletal lesions (a). Baseline  $^{68}\text{Ga}$ -DOTANOC PET/CT showed intensely tracer avid posterior mediastinal mass (SUVmax 88) and multiple lytic skeletal lesions (left iliac bone SUVmax 49.5) (b). Interim  $^{68}\text{Ga}$ -DOTANOC PET/CT showed significant decrease in tracer avidity within the lesions (SUVmax 88 to 16.4 in mediastinal mass and 49.5 to 20.1 in left iliac bone/soft tissue lesion) and concurrent decrease in size of mass lesions (c).  $^{68}\text{Ga}$ -DOTANOC PET/CT scan 2 months after 4th cycle of PRCRT revealed disease progression (d)

*MIP: maximum intensity projection*





**Fig 2:**  $^{177}\text{Lu}$ -DOTATATE post-therapy whole-body scans (anterior and posterior images) acquired at 24 hours after first therapy showed tracer uptake in the primary and metastatic lesions (a,b)