

Gratifying results with combined Chemo-PRRT (^{177}Lu -DOTATATE and platinum-based chemotherapy) in Recurrent Metastatic Sinonasal Neuroendocrine Carcinoma with high uptake on both ^{68}Ga -DOTATATE and ^{18}F -FDG PET-CT: a Promising Therapeutic Option

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Abstract:

Sinonasal neuroendocrine carcinomas (SNC), in contrast to other sites, are notorious to be recurrent and locally aggressive. The clinical concern is primarily due to complex anatomy and close proximity to vital structures compounded by lack of proper understanding of pathogenesis, no definitive classification and staging system and established treatment guidelines. The promise of combined treatment with ^{177}Lu -DOTA-(Tyr3)-octreotate (DOTATATE) based peptide receptor radionuclide therapy (PRRT) and with platinum-based chemotherapy in a patient of high grade recurrent and metastatic SNC (that demonstrated high uptake on both ^{68}Ga -DOTATATE and ^{18}F -FDG PET-CT), with significant partial response is presented. The study report highlights the feasibility and effectiveness of combined Chemo-PRRT protocol in management of SNC demonstrating promising results in high grade recurrent metastatic SNC.

Introduction:

Sinonasal tumours with neuroendocrine differentiation, that encompass neuroendocrine carcinomas (NECs) and olfactory neuroblastoma (ONB), are rare neoplasms with heterogeneous histological growth patterns (1-3) and accounts for only 5% of all sinonasal malignancies (4). This report describes a case of high grade SNC with mediastinal and cervical nodal metastases. To the best of our knowledge, this is the first endeavor to demonstrate the promising role of combined ^{177}Lu -DOTATATE based PRRT and chemotherapy in SNC.

Case report:

A 52-years-old male presented with bilateral nasal obstruction and occasional epistaxis, the MRI showing a large enhancing infiltrating mass completely obliterating nasal cavity with subsequent widening and erosion of cribriform plate with abutment of duramater and irregular dural enhancement. The mass involved cavernous sinus with encasement of left cavernous part of internal carotid artery (ICA) and abutment of right ICA along-with features of local destruction and pressure symptoms as well as perineurial spread through V₃ division of left trigeminal nerve. Suspicious left cervical level II and right hilar lymph nodes were noted. Histopathology and immunohistochemistry were suggestive of high grade neuroendocrine carcinoma. Cytology from right hilar lymph node was consistent with metastasis of neuroendocrine carcinoma.

There was history of similar symptoms in 2007-08 for which he had received neoadjuvant chemotherapy followed by local external radiotherapy. There was complete resolution with disease free interval of 11 years. Based on above history, a diagnosis of recurrent metastatic SNC was made and was referred for feasibility of PRRT. ^{68}Ga -DOTATATE and ^{18}F -FDG PET-CT showed FDG avid soft tissue density mass in sinonasal region with metabolically active left cervical level II and right hilar lymph nodes, all with

increased ^{68}Ga -DOTATATE uptake. In view of recurrent metastatic disease, past history of external RT and limited treatment options, he received 1st cycle of ^{177}Lu -DOTATATE PRRT as per the institutional protocol (administration of fixed activity approx. 7.4 GBq or 200 mCi) with standard mixed amino acid based renal protective measures. On discharge, in view of high-grade neuroendocrine carcinoma and FDG avid disease, he was referred for chemotherapy in concurrence with medical oncology division. He received 3 cycles of Carboplatin and Etoposide.

On follow up for second PRRT cycle, there was complete symptomatic response. Follow-up scans showed significant decrease in size of sinonasal mass (approx. 1.9x0.8 cm vs 7.0x4.6x5.0 cm at baseline) with significant decrease in size of left cervical level II lymph node (1.5x1.1 cm vs 2.2x1.3 cm at baseline) and complete resolution of right hilar lymph node. Comparative analysis showing maximum intensity projection (MIP) and trans-axial views of ^{68}Ga -DOTATATE and FDG PET-CT scans at baseline and post 1st cycle of PRRT and chemotherapy is shown below (Figure 1). The baseline and follow-up SUVmax on ^{68}Ga -DOTATATE PET-CT showed decrease in uptake in sinonasal primary tumour (from 10.6 to 5.53), left cervical lymph node (7.7 to 3.1) and right hilar node (4.45 to complete resolution). The uptake was comparable to liver in baseline scan whereas, was significantly less than liver in the follow-up study. A repeat second cycle of ^{177}Lu -DOTATATE PRRT was administered at 12 weeks with a curative intent.

Discussion:

Sinonasal neuroendocrine carcinoma was first proposed as an entity by Silva et al. in 1982 (3). Since then there are sparse and scattered literature, predominantly as case reports and case series. The largest available study is in form of meta-analysis done retrospectively in 701 cases by Laan et al. (5). The authors concluded that most important predictors for survival in SNC are differentiation grade and associated choice of treatment modality, while tumour staging was found to have limited value in prognostication and treatment planning. Unlike other types of head and neck carcinomas, SNC most commonly involves ethmoid sinus (4), is more common in males in 5th and 6th decades of life, with no specific etiological factor. Manifestation is usually non-specific with common symptoms being nasal obstruction, epistaxis and facial mass with or without facial pain and ophthalmic involvement.

As the patient was diagnosed as recurrent high grade SNC with high uptake on FDG and ^{68}Ga -DOTATATE, he was decided for chemotherapy followed by PRRT (Chemo-PRRT) protocol. Combined

protocol was considered based on our institutional experience of favorable clinical outcome in patients of gastroenteropancreatic, thoracic and pulmonary NETs with both GLUT₄ and SSTR expression evident on FDG and ⁶⁸Ga-DOTATATE PET-CT. Dual tracer PET-CT with FDG and ⁶⁸Ga-DOTATATE has now been a well-established strategy in NET management that effectively guides clinicians regarding personalized treatment planning and prognostication of NET patients. Three months post Chemo-PPRT, he presented with excellent overall symptomatic and morphological imaging response (Figure 1).

Conclusion:

In conclusion, this study highlights the feasibility and efficacy of combined Chemo-PPRT approach in the management of SNC demonstrating promising results in high grade recurrent metastatic SNC.

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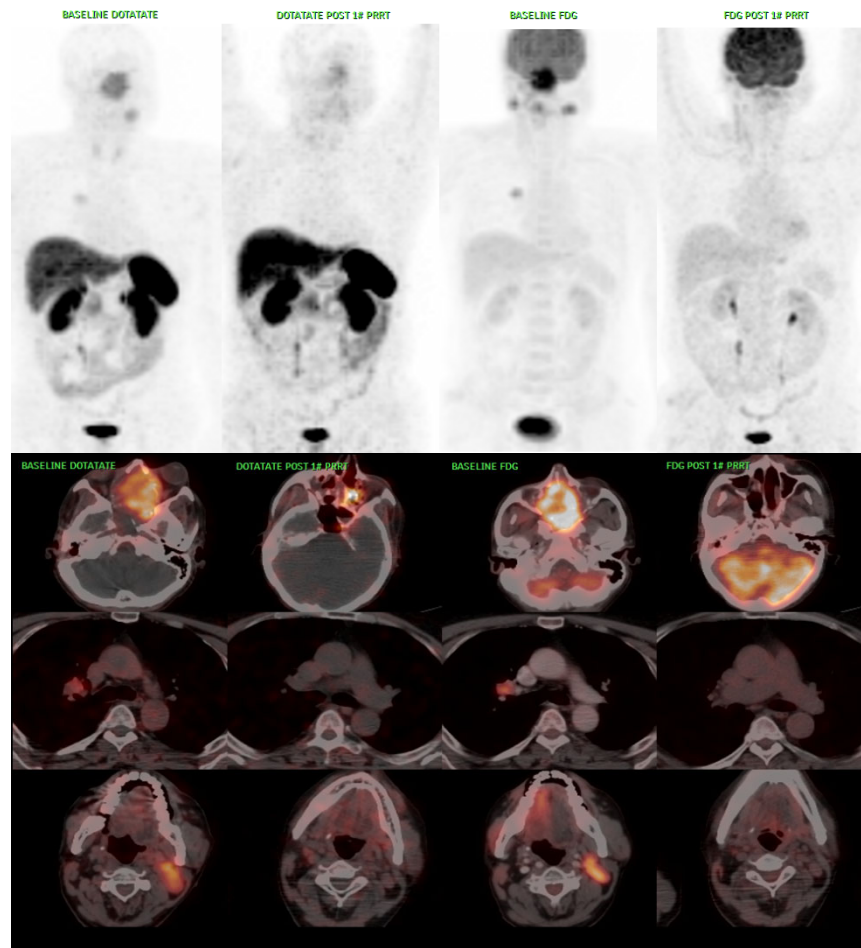


Figure 1: Comparative analysis of FDG and ^{68}Ga -DOTATATE PET-CT scans at baseline and post Chemo-PRRT. The patient presented with nasal obstruction, diagnosed as recurrent, high grade metastatic sinonasal NET, was referred for PRRT in view of inoperable metastatic disease. Maximum intensity projection (MIP) and transaxial views of ^{68}Ga -DOTATATE and FDG PET-CT scans at baseline and post Chemo-PRRT is shown above. Post-treatment PET-CT scans showed significant decrease in size and SSTR expression of primary sinonasaltumor (SUVmax 5.5 from 10.6) with complete metabolic resolution on FDG-PET/CT. Significant decrease in size and SSTR expression of left cervical level II lymph node (SUVmax 3.1 from 7.7) with complete metabolic resolution. Complete resolution of right hilar lymph node is evident from comparative analysis.