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# Combined $^{177}\text{Lu}$ -DOTATATE Peptide Receptor Radionuclide Therapy and Platinum-Based Chemotherapy in Recurrent, Metastatic Sinonasal Neuroendocrine Carcinoma: A Promising Therapeutic Option

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Sinonasal neuroendocrine carcinomas (SNCs), in contrast to neuroendocrine carcinomas at other sites, are notorious for their recurrent and locally aggressive nature. The clinical concern is primarily due to their complex anatomy and close proximity to vital structures, compounded by lack of proper understanding of pathogenesis, no definitive classification or staging system, and no established treatment guidelines. We present the promise of combined treatment with  $^{177}\text{Lu}$ -DOTATATE-based peptide receptor radionuclide therapy (PRRT) and platinum-based chemotherapy in a patient with high-grade, recurrent, and metastatic SNC (that demonstrated high uptake on both  $^{68}\text{Ga}$ -DOTATATE and  $^{18}\text{F}$ -FDG PET/CT), which showed a significant partial response. The case report highlights the feasibility and effectiveness of applying a combined protocol of  $^{177}\text{Lu}$ -DOTATATE and platinum-based chemotherapy in the management of high-grade, recurrent, metastatic SNC.

**Key Words:** sinonasal neuroendocrine carcinoma;  $^{68}\text{Ga}$ -DOTATATE PET/CT;  $^{18}\text{F}$ -FDG PET/CT;  $^{177}\text{Lu}$ -DOTATATE; peptide receptor radionuclide therapy; dual-tracer PET/CT

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**S**inonasal tumors with neuroendocrine differentiation—a group of tumors encompassing neuroendocrine carcinomas and olfactory neuroblastoma—are rare neoplasms with heterogeneous histologic growth patterns (1–3) and account for only 5% of all sinonasal malignancies (4). This report describes a case of high-grade sinonasal neuroendocrine carcinoma (SNC) with mediastinal and cervical node metastases. To the best of our knowledge, this is the first endeavor to demonstrate the promising role of combined  $^{177}\text{Lu}$ -DOTATATE-based peptide receptor radionuclide therapy (PRRT) and chemotherapy in SNC.

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## CASE REPORT

A 52-y-old man presented with bilateral nasal obstruction and occasional epistaxis, with the MR images showing a large, infiltrating mass with irregular dural enhancement completely obliterating the nasal cavity, with subsequent widening and erosion of the cribriform plate and abutment of the dura mater. The mass involved the cavernous sinus, with encasement of the left cavernous part of the internal carotid artery and abutment of the right internal carotid artery, along with local destruction, pressure symptoms, and perineural spread through the V3 division of the left trigeminal nerve. Suggestive uptake in the left cervical level II and right hilar lymph nodes was noted. Histopathologic examination and immunohistochemistry were suggestive of high-grade neuroendocrine carcinoma. Cytology from the right hilar lymph node was consistent with metastasis of neuroendocrine carcinoma.

There was a history of similar symptoms in 2007–2008 for which he had received neoadjuvant chemotherapy followed by local external radiotherapy. Complete resolution was achieved, with a disease-free interval of 11 y. On the basis of the history, a diagnosis of recurrent, metastatic SNC was made and the patient was referred for an investigation of the feasibility of PRRT.  $^{68}\text{Ga}$ -DOTATATE and  $^{18}\text{F}$ -FDG PET/CT showed an  $^{18}\text{F}$ -FDG-avid soft-tissue-density mass in the sinonasal region, with metabolically active left cervical level II and right hilar lymph nodes, all with increased  $^{68}\text{Ga}$ -DOTATATE uptake. In view of the recurrent, metastatic disease, the past history of external radiation therapy, and the limited treatment options, the patient received a first cycle of  $^{177}\text{Lu}$ -DOTATATE PRRT as per the institutional protocol (administration of a fixed activity of  $\sim 7.4$  GBq [200 mCi]), with standard mixed-amino-acid-based renal protective measures. On discharge, in view of the high-grade neuroendocrine carcinoma and  $^{18}\text{F}$ -FDG-avid disease, he was referred for chemotherapy in concurrence with the medical oncology division. He received 3 cycles of carboplatin and etoposide.

On follow-up for a second PRRT cycle, there was a complete symptomatic response. Follow-up scans showed a significant decrease in the size of the sinonasal mass ( $\sim 1.9 \times 0.8$  cm vs.  $7.0 \times 4.6 \times 5.0$  cm at baseline), with a significant decrease in

the size of the left cervical level II lymph node ( $1.5 \times 1.1$  cm vs.  $2.2 \times 1.3$  cm at baseline) and complete resolution of the right hilar lymph node. A comparative analysis showing maximum-intensity-projection and transaxial  $^{68}\text{Ga}$ -DOTATATE and  $^{18}\text{F}$ -FDG PET/CT scans at baseline and after the first cycle of PRRT and chemotherapy is shown in Figure 1. The baseline and follow-up  $\text{SUV}_{\text{max}}$  on  $^{68}\text{Ga}$ -DOTATATE PET/CT showed a decrease in uptake in the sinonasal primary tumor (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 uptake on the baseline scan but was significantly less than liver uptake on the follow-up scan. A repeated second cycle of  $^{177}\text{Lu}$ -DOTATATE PRRT was administered at 12 wk with a curative intent.

## DISCUSSION

SNC was first proposed as an entity by Silva et al. in 1982 (3). Since then, there has been only sparse and scattered

literature on the topic, predominantly as case reports and case series. The largest available study is in the form of a metaanalysis done retrospectively on 701 cases by van der Laan et al. (5). The authors concluded that the most important predictors for survival in SNC are differentiation grade and the associated choice of treatment modality, whereas tumor staging was found to have limited value in prognostication and treatment planning. Unlike other types of head and neck carcinomas, SNC most commonly involves the ethmoid sinus (4), is more common in men in fifth and sixth decades of life, and has no specific etiologic factors. Manifestation is usually nonspecific, with common symptoms being nasal obstruction, epistaxis, and a facial mass with or without facial pain and ophthalmic involvement.

Because the patient was diagnosed as having recurrent high-grade SNC with high uptake on  $^{18}\text{F}$ -FDG and  $^{68}\text{Ga}$ -DOTATATE, it was decided to treat him with chemotherapy followed by PRRT (combined  $^{177}\text{Lu}$ -DOTATATE and platinum-based chemotherapy). The combined protocol was considered in view of our institutional experience of favorable clinical outcomes in patients with gastroenteropancreatic, thoracic, and pulmonary neuroendocrine tumors, with both glucose transporter 4 and somatostatin receptor expression evident on  $^{18}\text{F}$ -FDG and  $^{68}\text{Ga}$ -DOTATATE PET/CT. Dual-tracer PET/CT with  $^{18}\text{F}$ -FDG and  $^{68}\text{Ga}$ -DOTATATE has now become a well-established strategy in neuroendocrine tumor management that effectively guides clinicians on personalized treatment planning and prognostication of neuroendocrine tumor patients. Three months after  $^{177}\text{Lu}$ -DOTATATE and platinum-based chemotherapy, the patient presented with an excellent overall symptomatic and morphologic imaging response (Fig. 1).

## CONCLUSION

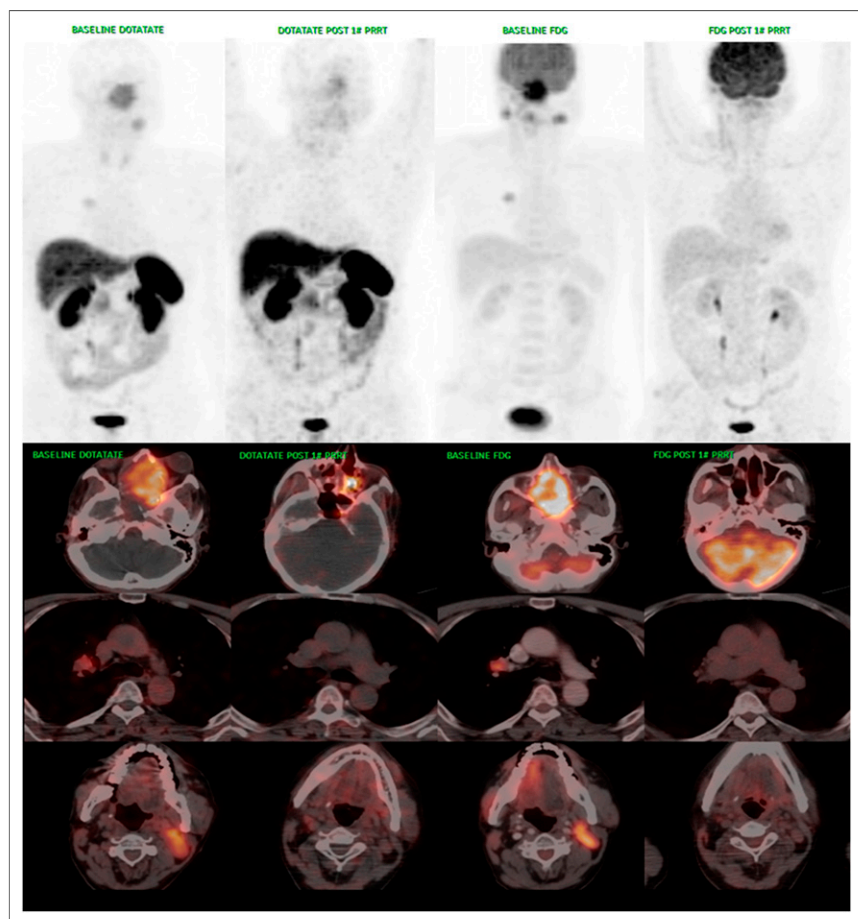
This study highlights the feasibility and efficacy of a combined approach using  $^{177}\text{Lu}$ -DOTATATE and platinum-based chemotherapy in the management of high-grade, recurrent, metastatic SNC.

## DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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**FIGURE 1.** Patient who presented with nasal obstruction diagnosed as recurrent, high-grade, metastatic sinonasal neuroendocrine tumor and was referred for PRRT in view of inoperable disease. Shown are maximum-intensity projections (top) and transaxial views (bottom) of  $^{68}\text{Ga}$ -DOTATATE scans (leftmost 2 columns) and  $^{18}\text{F}$ -FDG PET/CT scans (rightmost 2 columns) at baseline (left image of each set) and after combined  $^{177}\text{Lu}$ -DOTATATE and platinum-based chemotherapy (right image of each set). Posttreatment PET/CT scans show significant decrease in size and somatostatin receptor expression of primary sinonasal tumor ( $\text{SUV}_{\text{max}}$ , from 10.6 to 5.5) and left cervical level II lymph node ( $\text{SUV}_{\text{max}}$ , from 7.7 to 3.1), with complete metabolic resolution. Complete resolution of right hilar lymph node is also evident.

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### Erratum

In the article “Pharmacology, Part 1: Introduction to Pharmacology and Pharmacodynamics,” by Currie (*J Nucl Med Technol.* 2018;46:81–86), the dissociation constant is incorrectly defined as the ratio of the rate of association to the rate of dissociation, whereas it is instead the ratio of the rate of dissociation to the rate of association. We regret the error.