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Successful Treatment with ^{177}Lutetium-Dotatate and Maintenance Octreotide in a Patient with Esthesioneuroblastoma with Central Nervous System Invasion: Case Report and Review of the Literature

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Abstract

This article presents a case of a patient with relapsed esthesioneuroblastoma (ENB), an aggressive rare tumor that arises from the specialized sensory epithelial olfactory cells in the skull base area, which was initially treated with endoscopic surgery, followed by adjuvant radiotherapy. After local relapse, new surgical approaches and subsequent lines of platin-based chemotherapy were performed. A PET-CT with ^{68}GALIUM DOTATATOC (PET-DOTATOC) showed intense uptake of disease, compatible with the presence of somatostatin receptors, in the face, nodes, liver, bones, and meningeal area. Treatment with 4 cycles of ^{177}Lutetium-Dotatate was performed, followed by maintenance octreotide, with a major radiological and clinical response that is lasting more than 1 year after treatment. This article describes a rare case of a skull-base tumor, with multiple recurrences, in which disease control was achieved with a targeted Peptide Receptor Radionuclide Therapy (PRRT) with ^{177}Lutetium-Dotatate, and discusses factors that could influence the incorporation of this form of therapy. Previous case reports proved the potential efficacy of this therapy usually given for low-grade neuroendocrine tumors and will be carefully reviewed.

Keywords

Esthesioneuroblastoma, Olfactory Neuroblastoma, Peptide Receptor

Radionuclide Therapy, PRRT, ^{177}Lutetium

1. Introduction

First described in 1924 by Berger [1], esthesioneuroblastoma (ENB), also known as olfactory neuroblastoma (ONB), is a rare tumor originating from the olfactory epithelium, with histopathology variation between a pure neurological neoplasm, neuroblastoma or paraganglioma, and an epithelial tumor with neuroendocrine differentiation [2] [3].

The tumor arises from the specialized sensory epithelial olfactory cells, normally situated at the upper part of the nasal cavity, including the superior nasal concha, the roof of the nose, and the cribriform plate [4], and represents 2% to 6% of all tumors of the nasal and paranasal cavity, in addition to corresponding to 0.3% of all neoplasms of the upper aerodigestive tract [5].

The most common symptoms are nasal obstruction, epistaxis, and nasal discharge and less commonly it can present with visual changes, ocular proptosis, headache, hyposmia, and anosmia [6].

There are no randomized studies dictating the best approach for ENB. When the disease is localized, complete surgical resection is usually attempted, followed or not by adjuvant radiotherapy [7]. In unresectable/advanced cases, platin-based chemotherapy is usually the option of choice but is not usually associated with long-term disease control and also has limiting toxicities [8] [9] [10] [11] [12].

Previous studies have demonstrated that ENB may present with diverse clinical behaviors, ranging. For a more aggressive clinical course to a slow-growing disease, this heterogeneity has also been indicated by the presence of somatostatin receptors (SR) in many patients with this tumor type, in an analogy of what is usually observed in low-grade neuroendocrine tumors (NET), analyzed by a high uptake of SR in PET-CT scans with 68GALIUM DOTATATOC (PET-DOTATOC) [13]. Treatment of NETs using radionuclides bound to somatostatin analogs (PRRT) is well established in clinical practice, therefore, therapies with radionucleotides associated with somatostatin analogs such as Dota-octreotate therapeutic known as ^{177}Lutetium-Dotatate have emerged as a possible therapeutic strategy to be tested in relapsed or metastatic ENB that expresses SR confirmed by high uptake of the lesions in PET-DOTATE [14].

Until the date of this manuscript, four articles were published using ^{177}Lutetium-Dotatate, a Peptide Receptor Radionuclide Therapy (PRRT), as a treatment for metastatic ENB [13] [14] [15] [16].

This study reports the case of a female patient diagnosed with ENB, with a history of previous surgical resection and radiotherapy, followed by several new surgical interventions after local recurrence and progression to metastatic disease in the face, nodes, bones, and central nervous system, with high expression of SR in all lesions and uptake on PET-DOTATOC, that subsequently under-

went treatment with ^{177}Lutetium-Dotatate followed by maintenance with monthly Octreotide, and achieved a long term partial response evidenced by sequential PET-CT and MRI as will be detailed below. Other cases and series will be reviewed and the rationale for further studies with PRRT in ENB will be explored.

This paper was approved by the ethics committee Plataforma Brasil and informed consent was obtained from the patient.

2. Case Report

In 2009, a previously healthy 60-year-old woman, with no history of alcoholism or smoking, complained of rhinorrhea, epistaxis, and left nasal obstruction that persisted for 3 months. After clinical investigation, a skull-based tumor was identified and an endonasal biopsy was positive for esthesioneuroblastoma (ENB) entirely involving the left nasal cavity. She was submitted to a complete endoscopic surgical resection, followed by 25 fractions of intensive modulated radiotherapy (IMRT) for up to 60 Gy. After 7 years of follow-up, a Fluorodesoxyglucose PET-CT (PET-FDG) performed in 2016 confirmed an isolated left cervical nodal progression, that was managed with ipsilateral neck dissection and thyroidectomy. In 2017, the patient presented with a local disease progression in the paranasal area, requiring a new surgical approach.

One year after the last approach, another salvage surgery was necessary due to progression in the left nasal sinus, skull base, and with intimate contact with the left carotid artery, requiring a skull prosthesis. This surgery, however, was incomplete and was quickly followed by an unresectable progression on the left retro-orbital area, causing pain and facial deformity. The unresectable disease was first treated with systemic chemotherapy that consisted of 4 cycles of intravenous etoposide and cisplatin performed until August 2019 with partial response to therapy.

Less than 6 months after chemotherapy, an MRI showed disease progression. A PET-DOTATOC was also performed and revealed strong radiotracer uptake in multiple foci in the skull, neck, and thorax, revealing an indication of increased molecular expression of the SSTR2 and SSTR5 somatostatin receptors at these sites. Of note, all sites of metastatic disease revealed high uptake (SUV) on PET, with a SUVmax of 28.7 on the lymph node located on level II-A of the neck on the right **Figure 1**.

Due to the short interval of fewer than 6 months from previous therapy, and toxicity related to previous chemotherapy, treatment with Peptide Receptor Radionuclide Therapy (PRRT) was indicated based on PET-DOTATOC results.

Treatment with PRRT was planned with a 6-week interval, for up to 4 cycles, based on images and toxicities during therapy. Before the start of therapy, with ^{177}Lutetium-Dotatate, the patient had a local, unresectable disease involving: the superomedial area of the left orbit, left frontal parafalcine, inseparable from the superior sagittal sinus, also affecting the retropharyngeal space, invasion of the frontal bone, in addition to local meningeal thickening suggesting central nervous

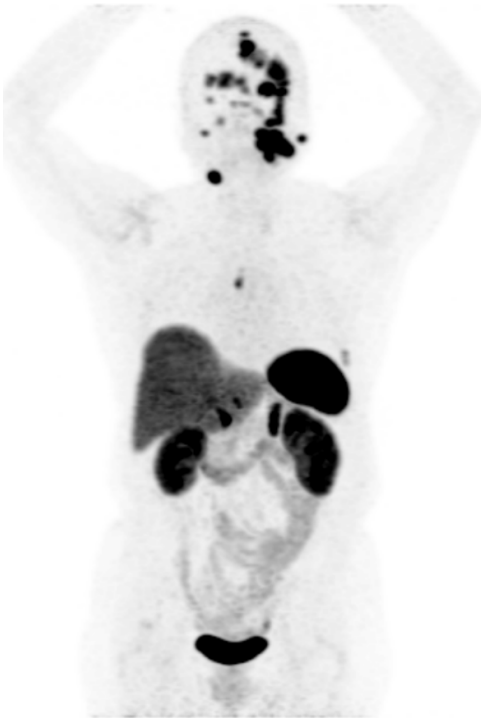


Figure 1. MIP projection of PET-DOTATOC of 08/2020 which revealed strong radiotracer uptake in multiple metastatic sites in the head, neck, mediastinal, bone, and liver. Which consisted of an increased expression of the sstr2 and sstr5 somatostatin receptors at these metastatic sites.

system (CNS) invasion as well as other sites of distant metastasis, like liver and mediastinal nodes.

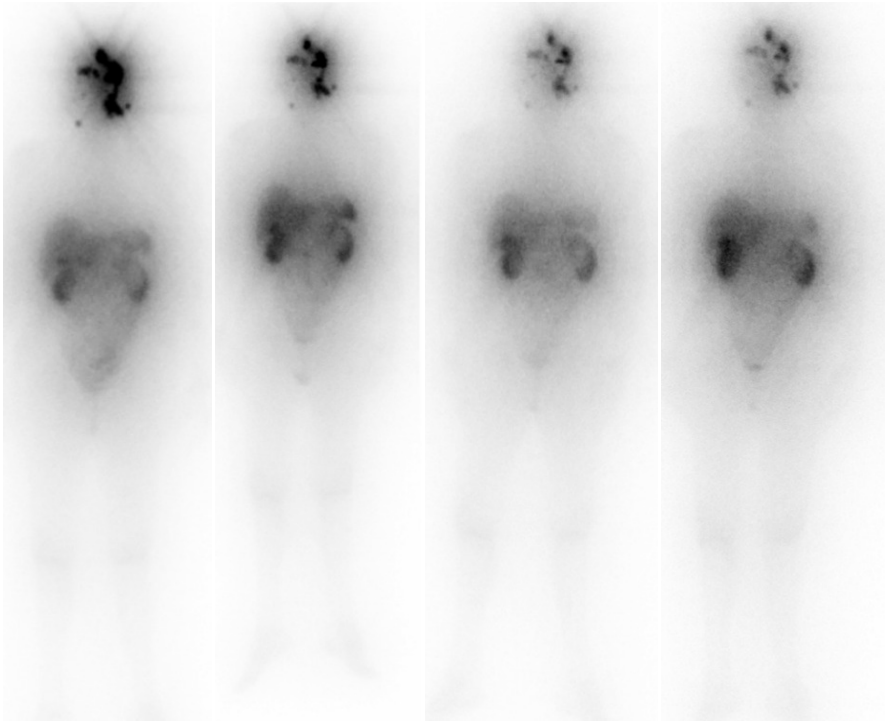
^{177}Lutetium-Dotatate started in October 2020 (1˚ cycle: 10/28/2020, 2˚ cycle 12/09/2020, 3˚ cycle 03/10/2021, 4˚ cycle 05/05/2021.) A delay of a few days between programmed cycles (every 6 weeks schedule), was related to technical issues (tracer availability) due to the COVID-19 pandemic.

We can observe **Figure 2** scans performed before each ^{177}Lutetium-Dotatate infusion, showing decreased uptake of the lesions during therapy.

After the first two applications of ^{177}Lutetium-Dotatate, we already observed a decrease in SR uptake on the left orbit area and left frontal parafalcine/superior sagittal sinus, together with a decrease in the disease volume, reduction in facial deformity and facial pain, that continues to improve after more than 12 months (**Figure 3**).

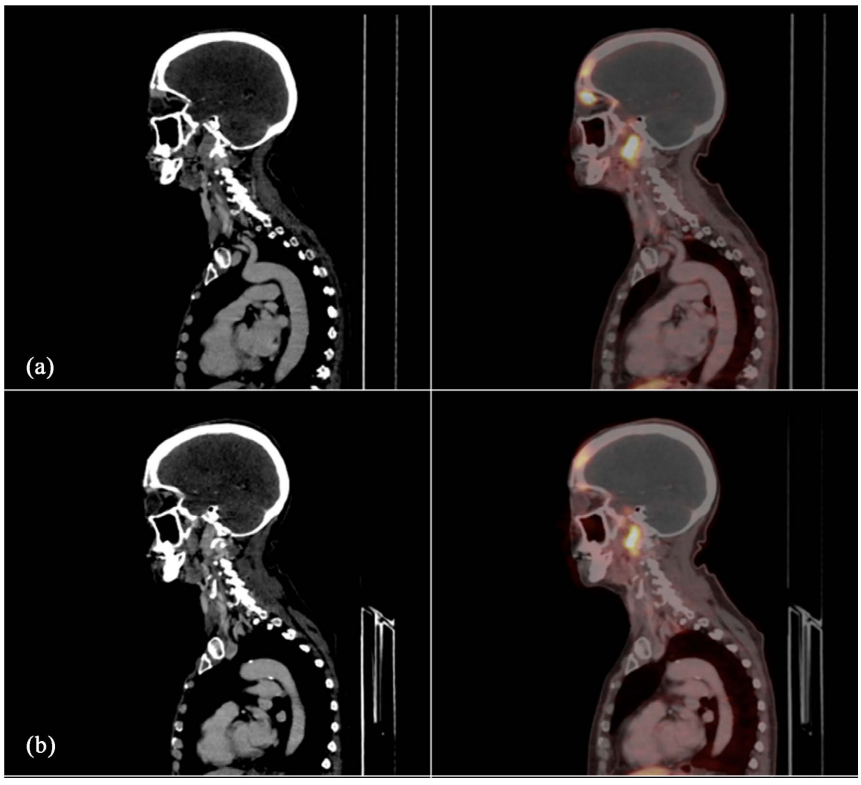
In May 2021, after the fourth and final dose of ^{177}Lutetium-Dotatate, due to the favorable response to therapy (partial radiological response, metabolic reduction of the targeted lesions, and clinical response), we decided to continue with targeted therapy, but switch to monthly maintenance intra-muscular octreotide (octreotide LAR 20 mg), in an analogy of what is usually performed in the treatment of low-grade NETs.

The patient has been followed for more than one year after the last ^{177}Lutetium-Dotatate dose. There was a clear reduction in the uptake of all target lesions



(a) (b) (c) (d)

Figure 2. (a) Whole-body image 24 hours after administration of the 1st cycle of ^{177}Lutetium-Dotatate. (b) Whole-body image 24 hours after administration of the 2nd cycle of ^{177}Lutetium-Dotatate. (c) Whole-body image 24 hours after administration of the 3rd cycle of ^{177}Lutetium-Dotatate. (d) Whole-body image 24 hours after administration of the 4th cycle of ^{177}Lutetium-Dotatate.



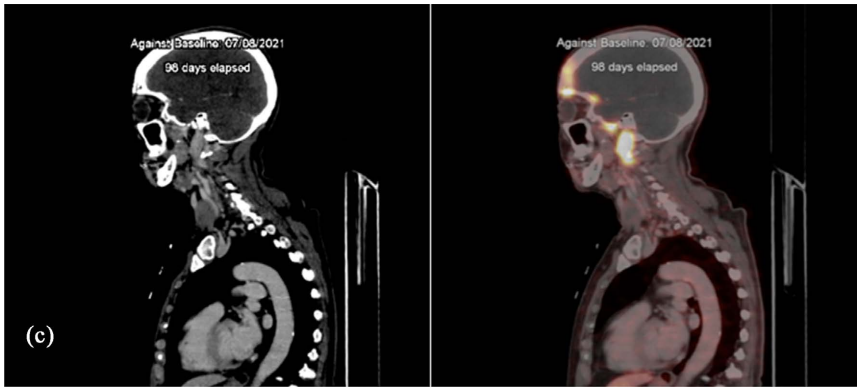


Figure 3. PET-CT images showing evolutive decreased uptake on the frontal bone, left periorbital, and retropharyngeal space lesions, more than 1 year after the first dose of therapy (6 months from the last dose). (a) PET-CT images of 08/2020 with uptake on the on the frontal bone, left periorbital, and retropharyngeal space lesions. (b) PET-CT images of 08/2021 with uptake on the on the frontal bone, left periorbital, and retropharyngeal space lesions. (c) PET-CT images of 11/2021 with uptake on the on the frontal bone, left periorbital, and retropharyngeal space lesions.

Table 1. Target lesions uptake and morphological evolutive analysis on PET-CT DOTATOC.

Target Lesion	PET-CT DOTA 08/2020	PET-CT DOTA 08/2021	PET-CT DOTA 11/2021
Left retropharyngeal space	SUV_{max} 23.2/44 × 16 mm	SUV_{max} 2.4/45 × 13 mm	SUV_{max} 10.1/45 × 13 mm
Left periorbital	SUV_{max} 25.0/24 × 18 mm	SUV_{max} 13.7/17 × 15 mm	SUV_{max} 7.12/17 × 15 mm
Left temporal	SUV_{max} 19.7	SUV_{max} 12.8	SUV_{max} 6.9
Left pre auricular lymph node	SUV_{max} 14.6/9 × 7 mm	SUV_{max} 17.8/11 × 9 mm	SUV_{max} 10.2/11 × 9 mm
Right II-A lymph node	SUV_{max} 28.7/12 × 9 mm	SUV_{max} 22.5/10 × 6 mm	SUV_{max} 8.3/10 × 6 mm
Subcarinal lymph node	SUV_{max} 8.3/8 × 5 mm	SUV_{max} 4.6/7 × 5 mm	SUV_{max} 2.0/7 × 5 mm

of the face, chest, liver, and skull, with a reduction in the size of the periorbital lesions on the face. The benefit was in the consistency of the serial images done and there are still no signs of disease progression or new disease-related symptoms. Table 1 shows the PET-CT DOTATOC response analysis with detailed SUV information in major target lesions in the face and nodes (major areas of target lesions).

Treatment was also well tolerated, with no serious side effects during or after PRRT. Side effects reported by the patient during therapy were all mild, with only grade 1 fatigue, hyporexia, weight loss, alopecia, and dysgeusia. No grade 3/4 events were noticed during the 4 cycles of treatment or even after treatment. During treatment, no laboratory abnormalities were identified, as shown in Table 2.

3. Discussion

ENB is a rare tumor entity and its origin is not completely understood. The histopathology of ENBs varies from a pure neurological neoplasm of the olfactory system, neuroblastoma, paraganglioma, or epithelial tumor with neuroendocrine

Table 2. Laboratory tests were performed during treatment with ^{177}Lutetium-Dotatate and one month after the end of therapy.

	Date (mm/yyyy)	Dose Lutetium (mCi)	Hemoglobin (g/dL)	Leukocytes (μL)	Platelets (μL)	Total bilirubin (mg/dL)
1˚	10/2020	198.0	13.7	5620	300.000	0.4
2˚	12/2020	202.7	12.7	5310	213.000	0.4
3˚	03/2021	206.8	12.1	3280	253.000	0.3
4˚	05/2021	212.5	14.5	4570	250.000	0.5
1 m	06/2021	------	13.8	3050	214.000	0.5

differentiation [3]. The olfactory epithelium is constituted by a neurosensory epithelium, composed of three types of cells: basal type, olfactory neurosensory cells, and the sustentacular supporting cells. The basal cell layer has a compartment with totipotent cells that give the tissue the ability to regenerate after aggression [17], it is from this layer of cells that esthesioneuroblastoma is believed to originate [4].

When well differentiated, esthesioneuroblastoma is not difficult to identify due to its histopathological characteristics, but when undifferentiated, an immunohistochemical analysis is necessary to differentiate this tumor from other tumors that can originate in the same region, such as melanoma, rhabdomyosarcoma, extramedullary plasmacytomas, sinus carcinoma, and sinus neuroendocrine carcinoma. There are no specific markers to differentiate these tumors, and the radiological image does not usually have any particularity that determines their diagnosis, but a potential molecular target is the overexpression of somatostatin receptors (SSTR) [13] [14], as ENB is considered a part of the neuroendocrine family of tumors.

In 2018, a European study [18] investigated the immunohistochemical expression of SSTR2A and SSTR5 in a cohort of 40 ENBs. In addition, tissue microarrays containing 40 high-grade sinonasal carcinomas as well as 6 sinonasal lymphomas, 3 rhabdomyosarcomas, and 3 Ewing sarcomas were evaluated. Thirty cases (75%) were immunopositive for SSTR2A and 3 (7.5%) for SSTR5. Among the 30 SSTR2A-positive ENBs, 19 tumors (63.3%) scored 2+ and 11 (36.7%) scored 3+. All SSTR5-positive ENBs scored 2+. Neither sinonasal carcinomas nor sinonasal small round blue cell neoplasms expressed SSTR2A or SSTR5. The frequent expression of SSTR2A provided a rationale for radio-receptor diagnosis and therapy with SST analogs in ENBs [18].

Most people affected by this disease have symptoms such as unilateral nasal obstruction and nasal discharge, followed by epistaxis (not observed in the case reported here), and the interval between the onset of symptoms and diagnosis is usually 6 months [7] [17].

In Broich's meta-analysis, about 1000 reports of this disease were gathered since the discovery of the tumor in 1924, with most of these cases reported from the 1990s, possibly related to the greater technical capacity to perform the diagnosis of this pathology [17].

Previous reports on the therapeutic management of ENB are also uncommon, but the preferred approach to tumors without metastases is based on surgery followed by radiotherapy [7] [8] [9] [10] [11]. Curiously, less than 10% of cases are diagnosed with nodal metastases, we believe that this occurs because the disease manifests signs and symptoms at an early stage due to its proximity to noble and/or visible structures. Salvage surgery after recurrence is possible between 33% - 50% [7] [17]. Platin-based chemotherapy treatment is reserved for relapsed or metastatic diseases, usually based on small series of cases [12].

A retrospective review [9] described all diagnosed cases of ENB registered in Denmark between 1978 and 2000. They obtained access to 40 verified cases, thirty-seven of those cases were treated with curative intent (surgery or surgery followed by radiotherapy). One patient died before receiving any therapy and only two patients received palliative treatment with radiochemotherapy. In those patients, regimens that contained cyclophosphamide, doxorubicin, vincristine, and cisplatin were the most frequently used chemotherapeutic agents [9].

According to published meta-analyses [2] [19] 5-year survival is estimated to be 45% for advanced or relapsed diseases. The recurrence is common, occurring even after 10 years (with a local recurrence rate of 29% and a distant metastasis rate of 17%), and for those patients the treatment options are scarce [2] [19]. When the usual therapies are exhausted, there is a lack of data in the literature on other treatment options for metastatic and relapsed patients.

Taking this information into account and combined with the knowledge that ENB over-expressed somatostatin receptors [13] [14] [18], treatment with analogs of somatostatin emerges as an appropriate option to be considered.

PET-DOTATOC radiolabeled somatostatin analogs can be used to image the presence and the density of somatostatin receptors expression, and subsequent therapy to target these receptors can be performed with analogs of somatostatin or ^{177}Lutetium-Dotatate [20] [21].

For advanced low-grade NETs, treatment with ^{177}Lutetium-Dotatate is already a standard of care. In 2008 Kwekkeboom *et al.* described the results of a single group trial of ^{177}Lutetium-Dotatate treated patients with gastroenteropancreatic NETs, achieving a progression-free survival of 33 months [22]. After this, Strosberg *et al.* published the NETTER-1 trial, a phase 3 randomized multicentric trial that evaluated the efficacy and safety of ^{177}Lutetium-Dotatate in patients with advanced somatostatin-receptor positive midgut NETs [21]. The study demonstrated a longer progression-free survival and a higher response rate than a high dose of octreotide alone among those patients, and now this is considered standard therapy for relapsed low-grade NETs [21].

There is only one ongoing clinical trial, named DOMINO-START [23], that is recruiting patients with primary or recurrent head and neck tumors (including ENB) to determine the diagnostic utility of 68Ga-DOTATATOC PET/MRI in the diagnosis and management of patients with SSTR-positive head and neck cancers (ClinicalTrials.gov Identifier: NCT04081701) [23]. This study hopefully will

give additional information on possible tumors to be treated in a near future with PRRT.

Data on the use of ^{177}Lutetium-Dotatate as a treatment option for patients with ENB is very limited14. Only four publications were reported using PRRT as a possible treatment for advanced disease detailed in **Table 3** and described [13] [14] [15] [16].

In 2015 the first published case reports a 51-year-old male patient with a recurrent metastatic ENB [15]. He underwent 3 cycles of ^{177}Lutetium-Dotatate over 4 months (no side effects have been described in this paper) which helped alleviate his symptoms and improved his quality of life. However, the disease progressed and the patient died a few months after treatment. In this report, Makis suggest that the PRRT could play a role in the management of ENB [15].

A paper published in 2016 [14] described a case more similar to the one portrayed in our report. A 74-year-old female with numerous recurrences and treatments over the past 10 years of diagnosis. The patient was treated with ^{177}Lutetium-Dotatate for 4 cycles, achieving disease control with partial response and an apparent decrease in the rate of progression after 1 year and 7 months

Table 3. Cases reported using ^{177}Lutetium-Dotatate as a possible treatment for recurrent or metastatic ENB.

Author	No. of Patients	Treatment received	Imaging Response	Adverse Events	Follow up
This study	1	4 cycles of Lu-Dotatate and 4 cycles of Octreotide in 2020 followed by 20 cycles of octreotide maintenance	Partial	Fatigue, hyporexia, dysgeusia, Grade 1 alopecia	18 months (alive with disease controlled)
Hasan [13]	7	4 cycles of Lu-Dotatate and 111In-Octreotide in 2008.			
		In 2010 5FU and Lu-Dotatete	Partial	Transient phlebitis	38 months
		3 cycles of Lu-Dotatate with 5FU in 2010 and 4 cycles of Lu-Dotatate in 2011	Partial	Grade 2 thrombocytopenia	53 months
		2 cycles of Lu-Dotatate in 2012	Progression	Pneumonia, Grade 4 neutropenia	4 months
		4 cycles of Lu-Dotatate with etoposide in 2017	Stable	None	33 months (alive)
		3 cycles of Lu-Dotatate in 2017	Partial	Recurrence of cerebrospinal fluid leak	20 months
		4 cycles in 2015 and 3 salvage cycles in 2017 of Lu-Dotatate	Partial	Weakness, transient grade 2 pancytopenia	32 months
Sabongi [14]	1	3 cycles of Lu-Dotatate and 4 cycles of octreotide in 2010	Partial	Not described	(alive)
Makis [15]	1	4 cycles of 111In-Octreotide followed by 3 cycles of Lu-Dotatate	Partial	Not described	5 months
Schneider [16]	1	4 cycles of Lu-Dotatate in 2016 And after relapse another 4 cycles	Partial	Not described	13 months

of follow-up [14].

In 2020, Hasan published the unique series of 7 patients with unresectable or metastatic ENB who received PRRT. Of these patients, 1 had a complete response and remained asymptomatic; 3 had a partial response, 2 achieved disease control and 1 progressed soon after the end of the treatment16. As of the date of publication by Hasan, one patient was still alive after 11 months of follow-up and the longest progression-free survival was 30 months [13].

Schneider [16] was the first to describe the neuroradiological and neuropathological changes associated with PRRT in a patient with metastatic ENB [15]. The female patient received 4 cycles of ^{177}Lutetium-Dotatate in 2016 with partial response observed in the PET-DOTATOC (1 lesion localized in the central nervous system). After 3 months, the disease has progressed, the patient underwent surgical resection and a neuropathological analysis was performed, confirming strong diffuse staining (SSTR2 stain positivity) in viable tumor cells associated with radiation necrosis. Shortly thereafter, another four cycles of ^{177}Lutetium-Dotatate were performed and a new PET-DOTATOC showed the metastasis was mostly stable after PRRT, suggesting that prolonged maintenance treatment, could be an option [16].

Inconsistencies were observed regarding the number of cycles of ^{177}Lutetium-Dotatate performed and regarding the concomitant use of octreotide in all reported cases, as well as little or no information regarding the intensity of uptake (SUV) of the targeted lesions in those reports. In our study, the patient received four cycles of ^{177}Lutetium-Dotatate like the other five patients described in other series, but our case is the first reported in which maintenance with octreotide was given after PRRT and also with detailed information about SUV uptake of the lesions and response [13] [14] [15].

There is a clear relation between SUV uptake (minimum, maximum, and mean) with the selection of patients for PRRT, which can explain differences in response and should be used to select patients for PRRT. Previous studies showed that low SUVmax on 68Ga-DOTATATOC PET-CT independently predicts early failure on somatostatin receptor analog monotherapy in patients with well-differentiated grade 1 - 2 NET [24].

Our case is the first to document the SUV of the lesions before and after therapy. As shown, all the lesions had a high SUV before therapy, ranging from 8.3 to 28.7, with most of the lesions with an SUV above 10. This high uptake could explain the excellent response presented by our patient and should guide better responses to PRRT in ENB as previously documented in low-grade NET.

The patient reported here at 12 months out of treatment (18 months of follow-up) had partial and long-term disease control and, in addition, managed to maintain quality of life without significant toxicities (only grade 1). In addition, the presence of direct central nervous system invasion is an adverse prognostic factor in every tumor, and the ability to cross the blood-brain barrier and allow a response in the meningeal area was also unexpected due to the high tumor volume presented by the patient, reinforcing the role of PRRT with ^{177}Lutetium-Dotatate

as a safe and active strategy for those patients with ENB expressing somatostatin receptors in the PET-DOTATOC.

Evaluation of somatostatin receptors by PET-CT Ga-DOTATOC should be explored and treatment with ^{177}Lutetium-Dotatate followed by maintenance with octreotide proved to be very tolerable and achieved the objective of disease control for metastatic/relapsed cases when the traditional treatment options have already been exhausted. Multicentric prospective studies with PRRT should be performed and are already planned to confirm this strategy as this is an unmet need for relapsed ENB.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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