

Efficacy of Peptide Receptor Radionuclide Therapy for Esthesioneuroblastoma

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ABSTRACT

Objectives: Esthesioneuroblastoma (ENB) is rare with limited therapeutic options when unresectable or metastatic; however, expression of somatostatin receptors qualifies it for peptide receptor radionuclide therapy (PRRT). We report outcomes of PRRT in ENB from two referral centers.

Methods: Using PRRT databases at two European Neuroendocrine Tumour Society Centers of Excellence, case finding was undertaken between 2004-2018 for patients who had PRRT with recurrent/metastatic ENB deemed unsuitable for further conventional therapies. Evaluations of response using a composite reference standard and for survival were performed.

Results: Of seven patients, four had partial response, two had disease stabilization and one had early progression. Possible side effects include worsening CSF-leaks. Median progression-free survival was 17 months (range, 0-30), and median overall survival was 32 months (range, 4–53).

Conclusions: PRRT shows promising efficacy and moderate survival duration in unresectable locally advanced or metastatic ENB warranting larger cohort studies incorporating measures of quality of life.

INTRODUCTION

Esthesioneuroblastoma (ENB), which is also known as olfactory neuroblastoma, is a rare malignancy (incidence 0.4 per million) accounting for 3–6% of intranasal neoplasms (1,2). The pathology of ENB is intermediate between a pure neural neoplasm, such as neuroblastoma or paraganglioma, and an epithelial tumor with neuroendocrine differentiation (3). The Hyams histological grading system comprises four grades ranging from well-differentiated (I) to least differentiated (IV) (4). The clinical staging system introduced by Kadish and modified by Morita (5,6) is a good predictor of outcomes (5,7,8). Stage A: confined to the nasal cavity; Stage B: extended to para-nasal sinuses; Stage C: further local extension; and Stage D: nodal or distant metastases. A meta-analysis by Dulguerov *et al.* (7) showed that Hyams pathological grade, nodal metastases and response to treatment were prognostic. Late recurrences can occur, with local recurrence rate of 29%, regional recurrence rate of 16%, and distant metastasis rate of 17%. Ten-year survival ranges from 52% to 69% (7,8).

Standard treatment for local disease is surgery followed by radiation, with or without chemotherapy (9). Options for metastatic disease are limited with one meta-analysis suggesting a median clinical follow-up after diagnosis of distant metastatic disease for the cohort of only 9 months (interquartile range [IQR] 5-9 months; range 0.25-224 months), with only 19 patients alive at the last follow up. The 6-month overall survival rate after diagnosis of distant metastases was 63% (95% CI 51%-77%), and a 2-year survival for patients receiving multimodality treatment of 63% (95% CI 43%-92%) (10). A potential molecular target for ENB is overexpression of cell surface somatostatin

receptors (SSRs) (11,12). Somatostatin analogues bind to SSRs with high affinity enabling theranostic applications. Positron emission tomography/computed tomography (PET/CT) with gallium-68 (Ga-68)-labeled somatostatin analogue can be used to image the density of SSR expression at disease sites and therapy can be performed with a companion therapeutic pharmaceutical such as lutetium-177 (Lu-177) DOTATATE for peptide receptor radionuclide therapy (PRRT) (13,14). There is high-level evidence for PRRT in unresectable gastroenteropancreatic neuroendocrine tumors (15,16) but data in rarer forms of neuroendocrine neoplasia are limited, with only very scarce data regarding ENB.

We describe the outcomes of seven patients with recurring/metastatic ENB, who received PRRT with or without radiosensitizing chemotherapy from 2 referral centers, which are now accredited within the European Neuroendocrine Tumour Society (ENETS) Centre-of-Excellence (CoE) Network.

MATERIALS AND METHODS

We retrospectively reviewed seven consecutive patients with ENB, who received PRRT from August 2004 to November 2018. Five patients were treated at the Peter MacCallum Cancer Centre (PMCC, Melbourne, Australia) and two at Hadassah-Hebrew University Medical Center (Jerusalem, Israel). Data was collected until death or most recent available follow-up.

Eligibility criteria were recurrent unresectable or progressive metastatic disease by imaging and/or symptoms despite conventional treatment, high SSR expression on SSR imaging (uptake higher than background liver activity), and adequate renal/haematologic

function. PRRT was administered with reno-protective amino-acid infusion as per unit protocol.

Responses were assessed at 3 months post-PRRT. Clinical response was measured subjectively by the referring physician. Imaging response was measured using a composite reference of both molecular and anatomic imaging, with the former assessed by the number and intensity of lesions (using a modified Krenning score related to tomographic rather than planar imaging) and the latter as defined by Response Evaluation Criteria in Solid Tumors (RECIST 1.1). Progression-free survival (PFS) was calculated from PRRT initiation to tumor progression or death from any cause, and defined by symptomatic or imaging progression. Overall survival (OS) was defined from PRRT initiation to death from any cause. Toxicity was defined by Common Terminology Criteria for Adverse Events (CTCAE 5.0).

All patients provided written informed consent for PRRT under compassionate use authority. Retrospective analysis and reporting of results were granted a patient-consent waiver by the ethical committees of PMCC and Hadassah-Hebrew University Medical Center.

RESULTS

Database review identified seven patients who were treated with PRRT (4 men, 3 women, 39–77 years). All patients had Kadish Stage D disease; Hyams Grade was II in four patients.

Four patients had high-volume and three had small to moderate-volume disease, with either locally advanced or metastatic disease. All had prior (sometimes repeated) conventional multi-modality treatment including surgery, chemotherapy and radiation therapy. One had a remarkable response and remained relatively asymptomatic early in the course of disease; three had favorable partial responses (PRs) both clinically and by imaging; two had disease stabilization by imaging (one patient had marked clinical response with complete resolution of headaches); and one had locoregional recurrence involving the retropharyngeal region that progressed shortly after PRRT. Details of disease course and therapy are presented in tables 1 and 2, as well as examples of multi-modality scans presented in figures 1-4.

Five patients died, four secondary to ENB. The median PFS was 17 months (range, 0–30), and the median OS was 32 months (range, 4–53). Two patients are still alive at 33 and 11 months of follow-up.

Toxicity of PRRT was generally mild but included one case each of transient grade 4 neutropenia (in the context of prior chemotherapy), grade 2 thrombocytopenia and a transient grade 1–2 pancytopenia. These were likely multifactorial related to multiple previous therapies, as hemotoxicity of PRRT is known to usually be transient and of low-grade (16). One patient developed worsening of his pre-existing tumor-related cerebrospinal fluid (CSF) leak, secondary to measurable shrinkage of tumor that extended intracranially through the dura.

DISCUSSION

Treatment of unresectable recurrent or metastatic ENB remains challenging with limited therapeutic options. High SSR expression in some of these tumors makes a theranostics approach using PRRT a therapeutic option. Outside this series, there are only three single ENB cases treated with PRRT reported in the literature with dates ranging from 2015-2018 (17-19). Our first patient was treated in 2008 at the PMCC. Our series encompasses complicated and heterogeneous clinical presentations and disease courses. For most patients, PRRT was able to achieve favourable clinical and imaging responses despite progression after conventional therapies. Treatment was generally well tolerated without significant toxicity.

The single patient with progressive disease in our series may have had a particularly poor outcome for several reasons. External beam radiation therapy in our experience diminishes subsequent local PRRT response, possibly secondary to radiation induced vasculopathy with eventual compromise to lesional blood flow or selection for radioresistant disease clones (20). This may partly explain the poor response despite high SSR expression. Additionally, patients with ENB who develop retropharyngeal nodal metastasis are known to have a poorer prognosis (18,19,21).

ENB is a rare entity and collecting data is challenging. Although a very limited series, this is, to our knowledge, the only study to report outcomes of PRRT in a consecutive cohort of patients. A further limitation is the retrospective nature of the study with non-uniform PRRT protocols and prior therapies reflecting different institutional practices. Furthermore, variability in administered activity, number of cycles, and

variable use of radiosensitising chemotherapy reflecting personalized treatment regimens may limit generalizability of results.

CONCLUSION

PRRT with radiolabeled somatostatin analogues appears to be a safe and effective option for unresectable, locally extensive, or metastatic ENB. Case selection depends on symptoms, somatostatin receptor expression, disease volume, and prior intervention. In our limited series, PRRT improved symptoms and provided promising disease control and encouraging survival duration. Further prospective studies incorporating formal quality of life assessments and standardized response assessment are warranted.

No potential conflicts of interest relevant to this article exist.

KEY POINTS

Question: Is PRRT an effective therapy method in unresectable metastatic ENB?

Pertinent Findings: This study was a retrospective review case series. PRRT shows promising efficacy and moderate survival duration in unresectable locally advanced or metastatic ENB warranting larger cohort studies incorporating measures of quality of life.

Implications: Potential use of PRRT in treatment of ENB patients.

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Figure 1: Patient 1

Locally extensive disease involving the sinuses and orbit with brain metastases. Partial Response to PRRT after 3 Induction cycles of ¹⁷⁷Lutetium DOTATATE. ⁶⁸Ga- DOTATATE pre (left) and post PRRT (right); and CT, fused, and post therapy SPECT scans (in the middle).

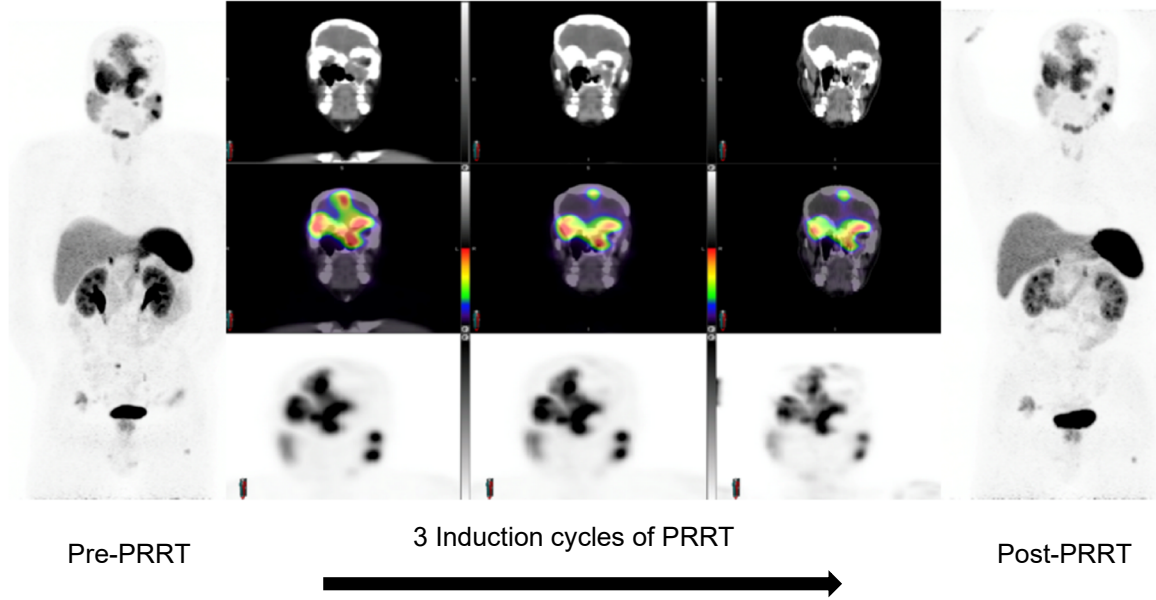


Figure 2: Patient 1

Contrast Enhanced T1 weighted MRI sections of the head, brain metastases and local disease. Subsequent progression with orbital, maxillary, and base of skull extension.

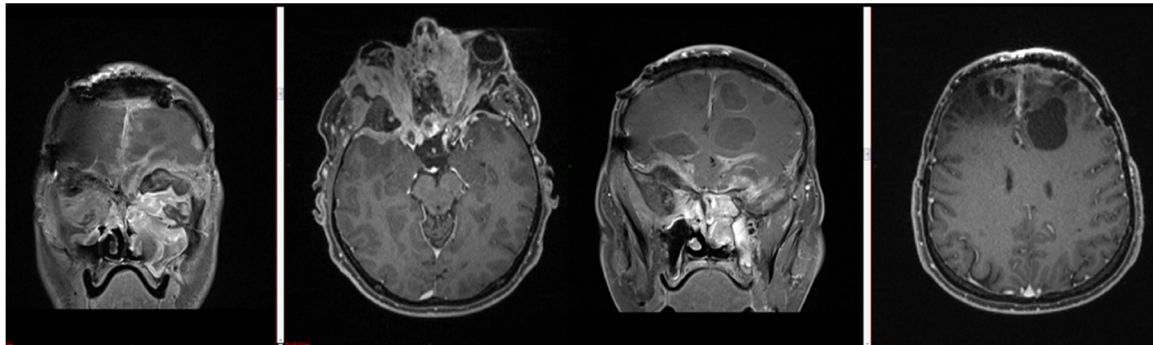


Figure 3: Patient 2

Multiple time points Ga-DOTATATE scans: Multiple metastatic skeletal deposits involving both axial and appendicular skeleton. Remarkable response to PRRT after 3 cycles of ¹⁷⁷Lutetium DOTATATE.

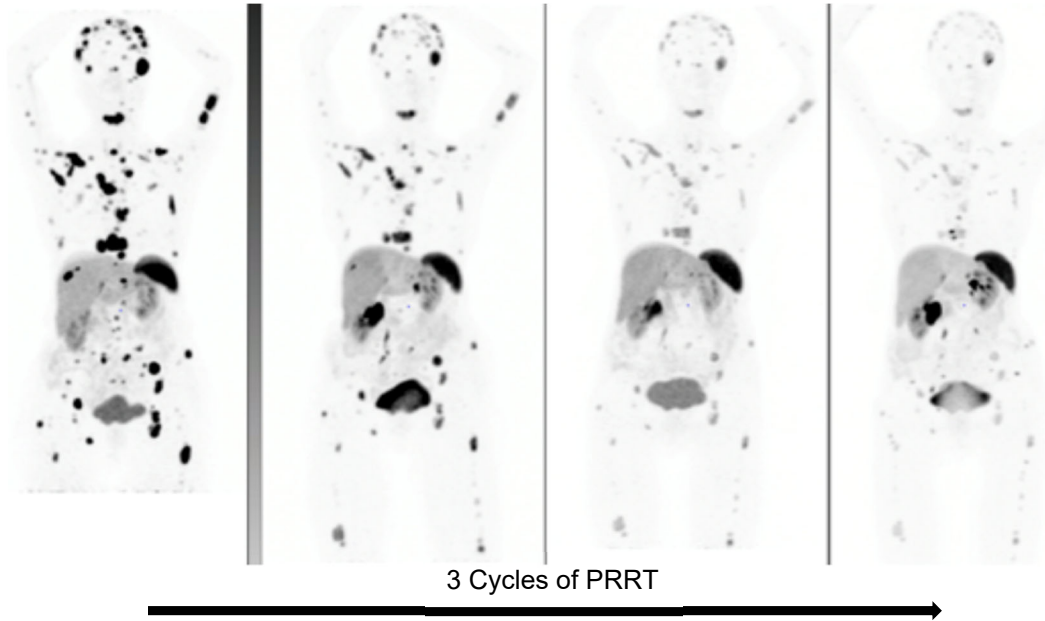


Figure 4: Patient 2

Multiple time points FDG PET/CT: Concordant remarkable response to PRRT after 3 cycles of ¹⁷⁷Lutetium DOTATATE. No disease discordance.

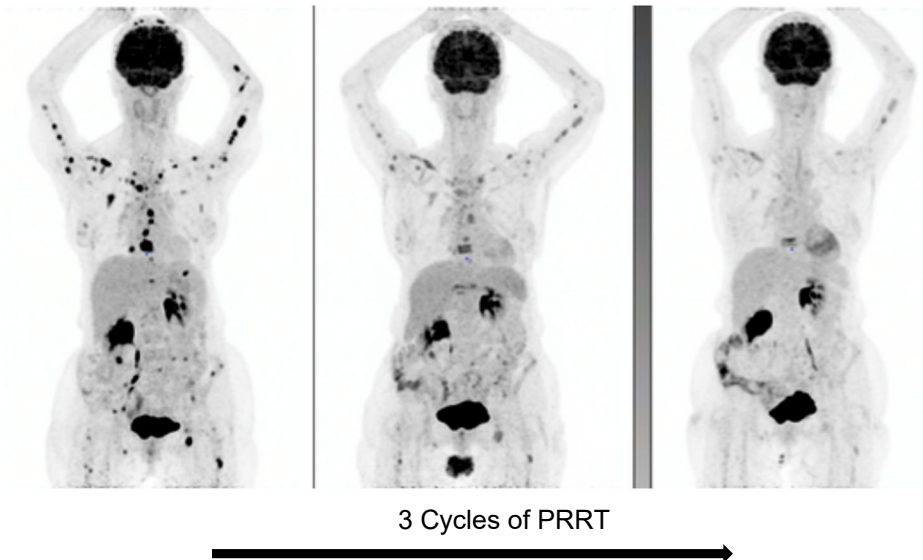


Table 1: Demographics and baseline data.

	Age at Diagnosis/ Age Pre PRRT /Sex	Presentation at Diagnosis/ pre PRRT	PRRT Indication	Hyams Grade	Kadish-Morita Stage/ Dulguerov TNM staging* Pre-PRRT	Baseline Modified Krenning Score**/FDG PET
Patient 1	31Y/54Y/M	Epistaxis/ proptosis, epiphora	Clinical and imaging progression	NA	Stage D T4N1M1	3/NA
Patient 2	72Y/73Y/F	Anosmia, nasal obstruction/ asymptomatic	Imaging progression	Grade 2	Stage D T2N1M1	4/Positive Concordant
Patient 3	55Y/65Y/M	Nasal obstruction/ Dysphagia	Clinical and imaging progression	Grade 2	Stage D T2N1M1	2-3/Positive Concordant
Patient 4	39Y/39Y/F	Anosmia, nasal obstruction, epistaxis/ severe scalp pain	Clinical and imaging progression	Grade 2	Stage D T4N1M1	3/Positive Concordant
Patient 5	48Y/48Y/M	Anosmia, nasal obstruction/ partial vision loss	Clinical and imaging progression	Grade 2	Stage D T4N0M1	3/Positive Concordant
Patient 6	40Y/48Y/M	Epistaxis, nasal obstruction/ chest pain, coughing	Clinical and imaging progression	NA	Stage D T4N1M1	4/Positive Concordant
Patient 7	67Y/77Y/F	Swelling, Anosmia, nasal obstruction/ asymptomatic	Imaging progression	NA	Stage D T4N1M1	4/Positive but less than on Ga-TATE

* Previously described (5,6,7)

**Score 0 = no uptake; 1 = very low uptake; 2 = uptake equal or less than liver; 3 = uptake greater than liver; 4 = uptake greater than spleen (22)

Table 2: Peptide Receptor Radionuclide Therapy (PRRT) Details and outcomes:

	Induction/ Maintenance PRRT	Total Cumulative Activity	PRRT Related Clinical /Blood Adverse Events	3 Months Post PRRT Clinical/ Imaging (Ga- 68 DOTATATE scan) Response	Further Follow up/ Disease Course	Overall Clinical/ Imaging Response to PRRT	PFS	Overall survival
Patient 1	4 cycles between Sep. 2008 and Feb 2009 of Indium (In)-111 octreotide and Lutetium (Lu)-177 octreotate with 5 FU*/ One cycle March 2010 of In octreotide with 5 FU	13.9 GBq** In-111 octreotide 24.7 GBq Lu-177 octreotate	Transient phlebitis/ None	Improvement in bilateral proptosis/ Partial response	Eventual progression with near complete blindness/ denied any further intervention. Nov. 2011: Succumbed to his illness.	Partial/ Partial	17 Months	38 Months
Patient 2	3 cycles between May and Sep.2010 of In and Lu octreotate with 5FU/ 4 cycles between Dec 2011 and July 2014 of Lu and Yttrium (Y)-90 octreotate	15.2 GBq In-111 octreotate 33.5 GBq Lu-177 octreotate 1.1 GBq Y-90 octreotate	None/ Grade 2*** Thrombocytopenia	No significant complaints/ Minimal improvement	Remarkable response after maintenance cycles/ Oct.2014: Died of Coronary artery disease	Stable/ Partial	30 Months	53 Months
Patient 3	2 cycles between Nov 2012 and Jan 2013 of In and Lu octreotate	13 GBq Lu-177 octreotate 12.6 GBq In-111 octreotate	Pneumonia / Grade 4 Neutropenia	Progression/ Marked progression by FDG PET/CT scan	No more PRRT offered, failed further chemotherapy/ May 2013, succumbed to his illness, eventually succumbed to his illness.	Progression/ Progression	0 Months	4 Months
Patient 4	4 cycles between Jan. and July 2017 of Lu octreotate with etoposide	24.9 GBq Lu-177 octreotate	None/None	Complete resolution of scalp pain/ Stable disease	On going response	Complete/ Stable	No progression	Alive (33 Months)
Patient 5	3 cycles between Nov. 2017 and Feb. 2018 of Lu and Y octreotate	22.0 GBq Lu-177 octreotate 3.2 GBq Y-90 octreotate	Recurrence of CSF leak/None	NA	Marked clinical improvement with ceasing CSF leak. Local tumor regression by imaging.	Partial/ Partial	17 Months	20 Months

Patient 6	4 cycles between Feb and July 2015 of Lu octreotate/ 3 salvage cycles between Jan and April 2017 of Lu	53.3 GBq Lu-177 octreotate	Weakness and SOB/ Transient G1-2 pancytopenia	Improvement in bilateral proptosis/ Partial response	Eventual progression after 8 months/ June 2018: succumbed to his illness	Partial/ Partial	20 months	32 months
Patient 7	3 cycles between June and Aug. 2018 Lu	22.1 GBq Lu-177 octreotate	Mild hair loss/None	No significant complaints/ Minimal improvement	On going response	Stable/ Partial	No progression	Alive (11 Months)

* 5 FU=5-Fluorouracil

** GBq= Gigabecquerel

*** CTCAE 5.0 (Common Terminology Criteria for Adverse Events)