The First Application of Ga-68 and Lu-177 Theranostics in the Philippines: A Rare Case of Mediastinal Small Cell Neuroendocrine Carcinoma

Emily Mia C. Acayan, MD, Patricia A. Bautista, MD, Miguel Antonio C. Catangui, MD, and Raquel Marie R. Cabatu-Key, MD

Department of Nuclear Medicine and PET Center, St. Luke's Medical Center, Quezon City, Philippines

ABSTRACT

A 43-year-old female with a surgically unresectable and non-secretory mediastinal small cell neuroendocrine carcinoma was previously given the protein kinase inhibitor Everolimus with intolerable nausea and fatigue. High somatostatin receptor expression of the known tumor was seen on ^{68}Ga-DOTATATE PET/CT scan. She was then given 6.4 GBq of ^{177}Lu-DOTATATE with no adverse events. A follow-up ^{68}Ga-DOTATATE PET/CT scan three months post-treatment showed stable DOTATATE affinity with no evidence of metastasis. This case presents an overview of peptide receptor radionuclide therapy (PRRT), especially for multidisciplinary teams in the Philippines, as ^{68}Ga and ^{177}Lu theranostics is introduced in the country.

Keywords: ^{68}Ga-DOTATATE, ^{177}Lu-DOTATATE, theranostics, Philippines, neuroendocrine carcinoma

For correspondence:
Emily Mia C. Acayan, MD
E-mail: emilyacayan@gmail.com

INTRODUCTION

Neuroendocrine tumors (NETs) account for approximately 0.5% of newly diagnosed carcinomas, with an incidence of 5.86 per 100,000 population [1]. NETs originate from neural crest cells and can develop in different sites of the body [2]. The most frequent primary sites are the gastrointestinal tract and lungs, occurring at 62–67% and 22–27%, respectively [1]. Primary neuroendocrine carcinomas of the mediastinum are extremely rare [3].

NETs are classified into secretory or non-secretory subgroups based on hormone production, or into high-grade, intermediate-grade, or low-grade tumors based on pathology. However, these classifications are not entirely absolute since there is significant heterogeneity in these subgroups that directly affects natural history of disease progression, response to therapeutic agents, and overall survival [2]. Some histologically low-grade tumors can behave like advanced progressive carcinomas and are treated with systemic therapy, whereas other low-grade tumors have slow mitotic rates and are resistant to conventional treatment [1]. Surgical resection, whenever feasible, remains the first option [4]. Somatostatin analogs and/or interferon-α is given for unresectable and symptomatic disease, although tumor regression with these agents is rare. Lastly, Etoposide/platinum-based chemotherapy is used for high-grade or metastatic neuroendocrine carcinomas [2]. Apart from these conventional therapies, peptide receptor radionuclide therapy (PRRT) is now approved by the US FDA and included by the National Cancer Comprehensive Network in the

management options of NETs [5]. We hereby present the first patient referred for PRRT in the Philippines.

CASE REPORT

The patient is a 43-year-old woman who was incidentally found to have an anterior mediastinal mass, for which she underwent left thoracotomy in April and September 2016 at different institutions. She denied endocrinologic or compressive symptoms. Histopathology revealed no malignancy and carcinoid tumor, respectively. However, the tumor was deemed unresectable, and she then received the oral protein kinase inhibitor, Everolimus, from November to December 2016. An ^{18}F-FDG PET/CT done at another institution in July 2017 (Figure 1) showed the anterior mediastinal mass, measuring 6.9 cm x 8.0 cm x 8.0 cm (AP x T x CC), with increased metabolic activity and central area of necrosis, as well as probably metastatic left submandibular lymph nodes.

Chromogranin A was elevated at 135.48 ng/mL (normal value < 100) in September 2017. Slide review in October 2017 disclosed a different diagnosis, which is small cell neuroendocrine carcinoma (CD 56 positive and chromogranin positive). The patient refused further treatment with Everolimus. She was referred to our institution for possible peptide receptor radionuclide therapy (PRRT). A ^{68}Ga-DOTATATE PET/CT was done in February 2018 (Figure 2) to evaluate somatostatin receptor density in the tumor. The mass was intensely DOTATATE-avid (Krenning 4), still with central portions of necrosis and with interval increase in size to 7.6 cm x 7.9 cm x 8.5 cm. The left submandibular lymph nodes have resolved, consistent with the patient's history of upper respiratory tract infection at

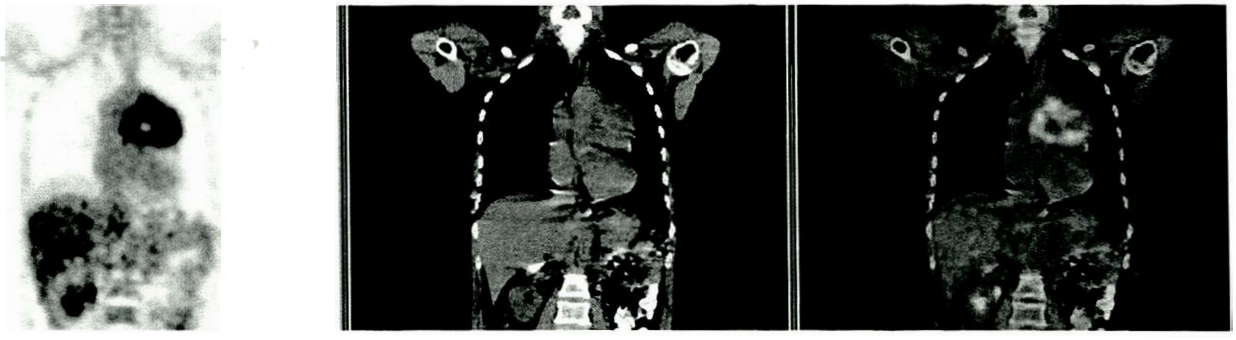

Figure 1. ^{18}F-FDG PET-CT dated July 2017.

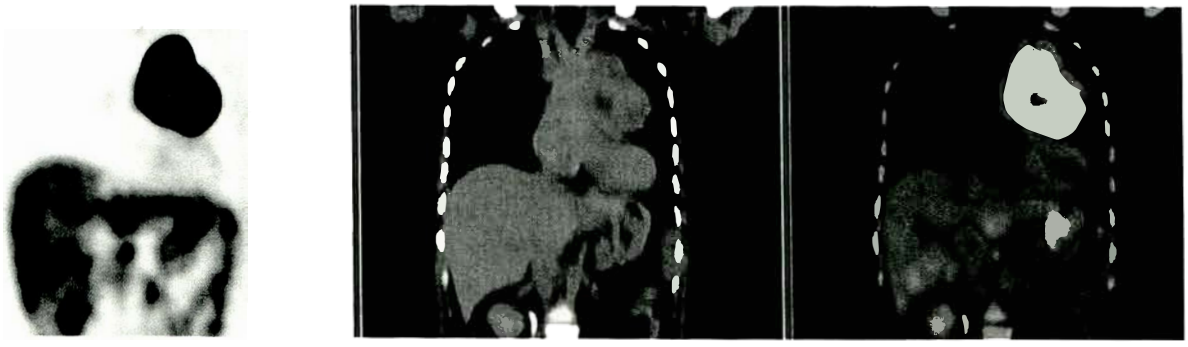

Figure 2. ^{68}Ga-DOTATATE PET-CT dated February 2018.

the time of the ^{18}F-FDG PET/CT.

Given the significant overexpression of somatostatin receptors in the periphery of the mass, she was then admitted and given 6.4 GBq ^{177}Lu-DOTATATE in May 2018 after thorough pre-therapy assessment and patient education. Post-PRRT scan with SPECT-CT done two days after showed similar intensity and distribution of the ^{177}Lu-DOTATATE as the ^{68}Ga-DOTATATE in the PET/CT scan (Figure 3).

Follow-up ^{68}Ga-DOTATATE PET/CT in August 2018 (Figure 4A) showed slight interval increase in size of the mass to 9.4 cm x 8.2 cm x 8.7 cm but stable DOTATATE avidity (Krenning 4). No metastatic lesions were seen.

DISCUSSION

NETs generally overexpress somatostatin receptors (SSTRs), especially SSTR2. DOTA-conjugated

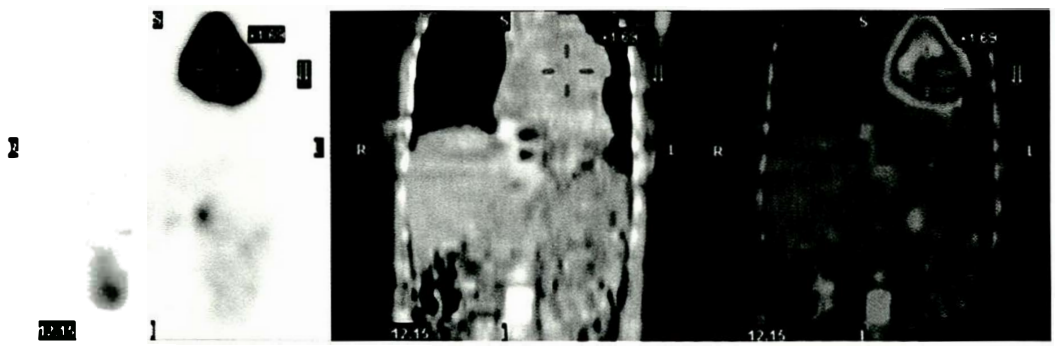

Figure 3. Post-PRRT Scan with SPECT-CT dated May 2018.

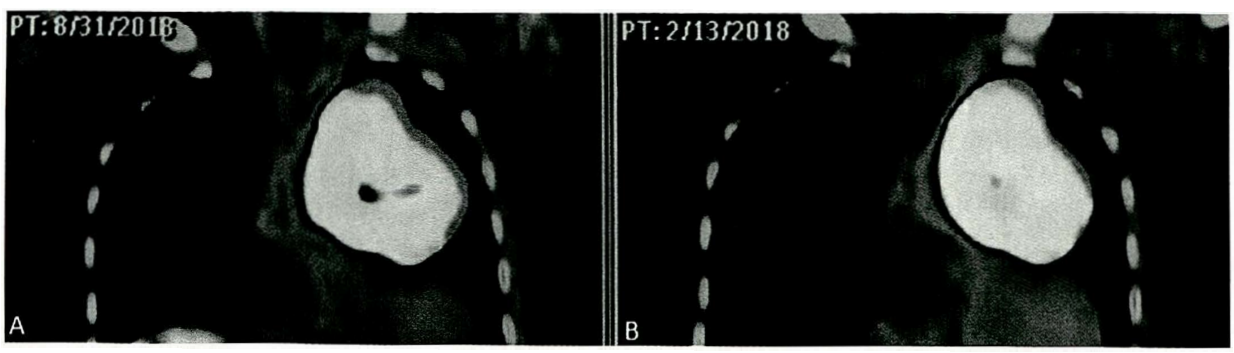

Figure 4. Comparison of ^{68}Ga-DOTATATE PET-CT scans dated [A] August 2018 and [B] February 2018.

peptides all have affinity for SSTR2. DOTATATE is predominantly affinitive to SSTR2. DOTANOC also has good affinity for SSTR2 and SSTR3, while DOTATOC also shows some affinity to SSTR5 [7]. Well differentiated or low-grade tumors have high uptake in SSTR-based imaging, such as ^{68}Ga-DOTATATE PET/CT, and decreased to absent tracer uptake in ^{18}F-FDG PET/CT. Conversely, poorly differentiated or high-grade tumors have high uptake in ^{18}F-FDG PET/CT and decreased to absent tracer uptake in SSTR-based imaging [4]. Our patient's ^{68}Ga-DOTATATE PET/CT in February 2018 (Figure 2) showed higher tracer uptake in the known mediastinal tumor compared to the ^{18}F-FDG PET/CT. Given this finding, it can be inferred that the tumor is most likely grade 2 or intermediate-

grade, although neuroendocrine carcinoma is typically classified as grade 3 [8]. A complete histopathologic picture including the tumor's histologic grade and Ki-67 index would have been ideal. Despite limited histopathologic data, the evidence of high ^{68}Ga-DOTATATE affinity to SSTRs allowed for therapy using ^{177}Lu-DOTATATE [9].

This first PRRT in the country went smoothly from the flawless production of the ^{177}Lu-DOTATATE to the patient's relatively unremarkable hospital stay. Our patient's tumor is non-secretory; hence, she experienced no side effects except for mild and transient warm feeling in the mediastinum, and she was discharged two days after PRRT. Our patient's follow-up ^{68}Ga-DOTATATE PET/CT three months after PRRT (Figure 4A) showed stable DOTATATE activity in the known mediastinal tumor with no evidence of metastasis. Absence of metastasis 28 months after initial diagnosis is already considered favorable, taking into account the poor survival of mediastinal primary small cell neuroendocrine carcinoma [10].

International data on the efficacy and safety of PRRT [11] are encouraging but documentation of local experience is essential, especially now, while we are just starting to utilize ^{68}Ga and ^{177}Lu theranostics in the Philippines. There is a need to develop proper referral systems across different institutions and among different subspecialties involved in the management of NETs. Creation of a comprehensive clinical database of patients being treated with ^{177}Lu-DOTATATE will be most helpful for future research purposes.

CONCLUSION

PRRT with ^{177}Lu-DOTATATE is a viable treatment option for mediastinal small cell neuroendocrine carcinoma, provided there is proof of SSTR affinity using its theranostic partner ^{68}Ga-DOTATATE. The usefulness of theranostics in the management of NETs can be maximized through proper referral systems and conscientious treatment of patients by competent nuclear medicine physicians, and must be documented in the local setting as we are in the early phase of its implementation.

REFERENCES

1. Oronsky B, Ma PC, Morgensztern D, Carter CA. Nothing but NET: a review of neuroendocrine tumors and carcinomas. Neoplasia. 2017 Dec;19(12):991-1002.
2. Chauhan A, Yu Q, Ray N, Farooqui Z, Huang B, Durbin EB, Tucker T, Evers M, Arnold S, Anthony LB. Global burden of neuroendocrine tumors and changing incidence in Kentucky. Oncotarget. 2018 Apr 10;9(27):19245-19254.
3. Dwivedi AN, Goel K, Tripathi S, Garg S, Rai M. Primary neuroendocrine mediastinal tumor presenting with carcinoid syndrome and left supraclavicular lymphadenopathy: clinico-radiological and pathological features. J Cancer Res Ther. 2013 Apr-Jun;9(2):278-80.
4. Thapa P, Parghane R, Basu S. 177Lu-DOTATATE peptide receptor radionuclide therapy in metastatic or advanced and inoperable primary neuroendocrine tumors of rare sites. World J Nucl Med. 2017 Jul-Sep;16(3):223-228.
5. Shah MH, Goldner WS, Halfdanarson TR, Bergsland E, Berlin JD, Halperin D, et al. NCCN guidelines insights: neuroendocrine and adrenal tumors, version 2.2018. J Natl Compr Canc Netw 2018;16:693-702.
6. Raphael MJ, Chan DL, Law C1, Singh S. Principles of diagnosis and management of neuroendocrine tumours. CMAJ. 2017 Mar 13;189(10):E398-E404.
7. Virgolini I, Ambrosini V, Bomanji JB, Baum RP, Fanti S, Gabriel M, Papathanasiou ND, Pepe G, Oyen W, De Cristoforo C, Chiti A. Procedure guidelines for PET/CT tumour imaging with 68Ga-DOTA-conjugated peptides: 68Ga-DOTA-TOC, 68Ga-DOTA-NOC, 68Ga-DOTA-TATE. Eur J Nucl Med Mol Imaging. 2010 Oct;37(10):2004-10.
8. Kim JY, Hong SM, Ro JY. Recent updates on grading and classification of neuroendocrine tumors. Ann Diagn Pathol. 2017 Aug;29:11-16.
9. Bodei L, Mueller-Brand J, Baum RP, Pavel ME, Hörsch D, O'Dorisio MS, O'Dorisio TM, Howe JR, Cremonesi M, Kwekkeboom DJ, Zaknun JJ. The joint IAEA, EANM, and SNMMI practical guidance on peptide receptor radionuclide therapy (PRRNT) in neuroendocrine tumours. Eur J Nucl Med Mol Imaging. 2013 May;40(5):800-16.
10. Takanami I, Imamura T, Yamamoto Y, Yamamoto T, Kodaira S. Long survival in small-cell (neuroendocrine) carcinoma of the mediastinum. Scand J Thorac Cardiovasc Surg. 1996;30:179–80.
11. Mittra ES. Neuroendocrine tumor therapy: 177Lu-DOTATATE. Am J Roentgenol. 2018 Aug;211(2):278-285.