Philippine Journal of Gastroenterology

Intra-arterial peptide receptor radionuclide therapy in a Filipino male with predominantly hepatic metastases in a known primary gastric neuroendocrine tumor: A case report*

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Abstract

Significance: Neuroendocrine tumors (NETs) express Somatostatin receptors (SSTR) which allow for diagnostic imaging using Gallium-68 DOTA-0-Tyr3-Octreotate (DOTATATE) Positron Emission Tomography-Computed Tomography (PET-CT) and Peptide Receptor Radioligand Therapy (PRRT) using Lutetium-177 (Lu-177) DOTATATE. Standard intravenous PRRT (IV-PRRT) is an established treatment modality for well-differentiated neuroendocrine tumors. However, this may be limited in large bulky masses. Thus, the intra-arterial route has been utilized in other countries. This is the first recorded use of intra-arterial PRRT (IA-PPRT) administration in the country.

Clinical Presentation: This is a case report of a 59-year-old man, with known gastric neuroendocrine neoplasm, Grade II, presenting with persistent large SSTR-expressing hepatic lesions. He is a post-pyloroantral segment resection patient with trans-arterial chemoembolization in 2017. He had chemotherapy in 2018, with 4 cycles of IV-PRRT from 2018 to 2019 and 2 fractions of tomotherapy in 2022.

Management: The patient was referred again for PRRT due to progressive metastatic hepatic lesions. IA-PRRT was done in October 2023 followed by IV-PRRT in February 2024. There were no gastrointestinal adverse events or hematologic or nephrologic toxicities during the course of his admissions. The post-treatment scan of the IV-PRRT demonstrated a decrease in intensity of the hepatic lesions reflecting the response to the IA-PRRT. A follow-up Ga-68 DOTATATE PET-CT scan in February 2025 showed a decrease in size and SSTR-overexpression, consistent with good and sustained treatment response from the IA-PRRT and IV-PPRT.

Recommendation: Intra-arterial PRRT is a non-conventional alternative means of administering Lu-177 DOTATATE. While there is sufficient data for IV-PRRT, further dosimetric studies are needed to quantify tumoral and critical organ absorbed dose. There is also a need to monitor long-term hematologic risks of IA-PRRT.

Keywords: Neuroendocrine tumor, Lutetium-177 DOTATATE, Intra-arterial, PRRT

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* This study has been registered and approved by the St. Luke's Institutional Scientific Review Committee (ISRC) and Institutional Ethics Review Committee (IERC). It has also been presented at the 2024 Annual Meeting of KSNM & ARCCNM in Seoul, Korea on 1-2 November 2024.

Introduction

NETs are neoplasms derived from neuroendocrine cells and are commonly seen in the gastrointestinal tract (48%), lungs (25%), and pancreas (9%).[1] Often diagnosed late in the disease, neuroendocrine liver metastasis (NELM) occurs in 40-80% of patients at the initial diagnosis which has been associated with decreased overall survivability.[2] The 2022 WHO classification subclassified neuroendocrine neoplasms into well-differentiated neuroendocrine tumors and poorly-differentiated neuroendocrine carcinomas (NECs) based on their degree of proliferation, as indicated by the Ki67% index value and mitotic count values; with higher values corresponding to higher tumor grading and poorer prognostication.[3,4] NETs retain the expression of SSTRs, which enables the diagnostic evaluation and treatment options through the use SSTR analogs such as DOTATATE PET-CT and PRRT, respectively.[4]

Lu-177 is a beta (β-) and gamma (γ) emitter, which allows for simultaneous therapeutic use and diagnostic imaging. Lu-177, bound to DOTATATE, allows for the specific targeted delivery of radiotoxicity to the SSTR overexpressing tumoral cells. The radiopharmaceutical's low linear energy transfer and short tissue penetration range (1.6 mm_{max}) make it ideal for treating small tumor lesions (<2 cm).[5,6,7]

The NETTER-1 trial demonstrated better progression-free survival (PFS) and overall survivability (OS) with a combination of octreotide long-acting release (LAR) and four cycles of Lu-177 DOTATATE versus high-dose octreotide LAR for advance midgut NETs (hazard ratio for disease progression or death with Lu-177 DOTATATE vs. control: 0.21; 95% CI, 0.13 to 0.33; P<0.001). Mild gastrointestinal symptoms (Grade 1 to Grade 2) were common, with less than 10% presenting with significant hematologic toxicities (Grade 3 to Grade 4) and with no significant renal toxicities. The findings led to the approval and inclusion of PRRT in the National Comprehensive Cancer Network (NCCN) guidelines as an alternative first-line treatment for metastatic midgut GEP NETs.[8,9,10,11]

Despite the favorable PFS and OS, the objective response rate remains modest in those with bulky NELM. A retrospective post-hoc of the NETTER-1 trial showed that patients with lesions >3 cm had a lower median PFS of 13.3 months compared to those with <3 cm lesions who had a median PFS of 27.4 months.[12] This may suggest that standard IV-PRRT may be less effective for larger hepatic lesions, thus alternative routes of administration may be considered.

IA-PPRT has emerged as a potential strategy to increase tumoral activity, especially in patients with liver-dominant disease. A systematic review reported that intra-arterial administration had an overall higher objective response rate of 53 to 69% compared to standard PRRT administration of 18%, with none of the studies demonstrating adverse events outside of what is expected with IV-PRRT.

Case Presentation

The following case report describes the first documented IA-PRRT for metastatic hepatic lesions in a primary gastric neuroendocrine tumor in the Philippines. The present discussion further evaluates various modes of administration of PRRT in the management of NETs.

The patient is a 59-year-old male, a known case of neuroendocrine neoplasm of the stomach, Grade II, presenting with persistent large SSTR-expressing hepatic lesions. He had pyloroantral segment resection (September 2017), trans-arterial chemoembolization (October 2017), and chemotherapy (December 2017 to April 2018). A baseline Ga-68 DOTATATE PET- CT scan in 2018 showed SSTR-overexpressing lesions in the pancreatic head and liver. The patient underwent four cycles of IV-PRRT from November 2018 to September 2019, in which the patient achieved stable to slight interval

regression of the disease. The patient then underwent two fractions of tomotherapy in 2022.

A repeat Ga-68 DOTATATE PET-CT scan was done in July 2023 which showed resolution of the lesions in the pancreatic head. There was also relatively stable Standard Uptake Value Maximum (SUVmax) in the hepatic lesions (SUVmax 64.1, previously 61.4), however, with an overall interval increase in size, and number, indicative of progressive disease based on the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) criteria (Figure 1).

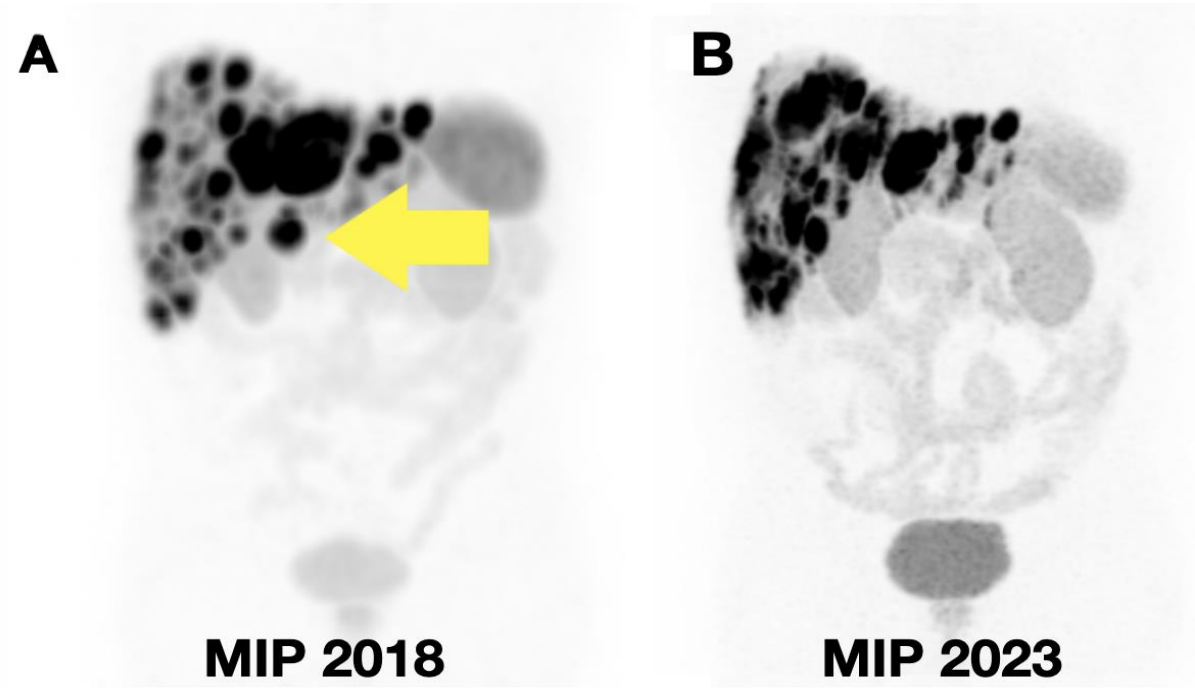

Figure 1: Maximum Intensity Projections (MIP) of the Ga-68 DOTATATE PET-CT scans. (A) 2018 prior to the first IV-PRRT showing multiple DOTATATE-avid lesions in the liver and pancreas (yellow arrowhead). (B) Ga-68 DOTATATE PET-CT scan in July 2023 prior to the IA-PRRT.

Due to the SSTR-positive hepatic lesions, the patient was advised to undergo IA-PRRT. A 4-phase dynamic CT scan and liver volumetric analysis (Figure 2) were performed to determine the appropriate dosage based on the tumor volume in each hepatic lobe.

The dynamic CT scan of the liver showed vari-sized enhancing masses in both hepatic lobes with the largest measuring up to 4.4 x 5.2 x 5.5 cm. The pancreas showed homogeneous enhancement with no discrete mass.

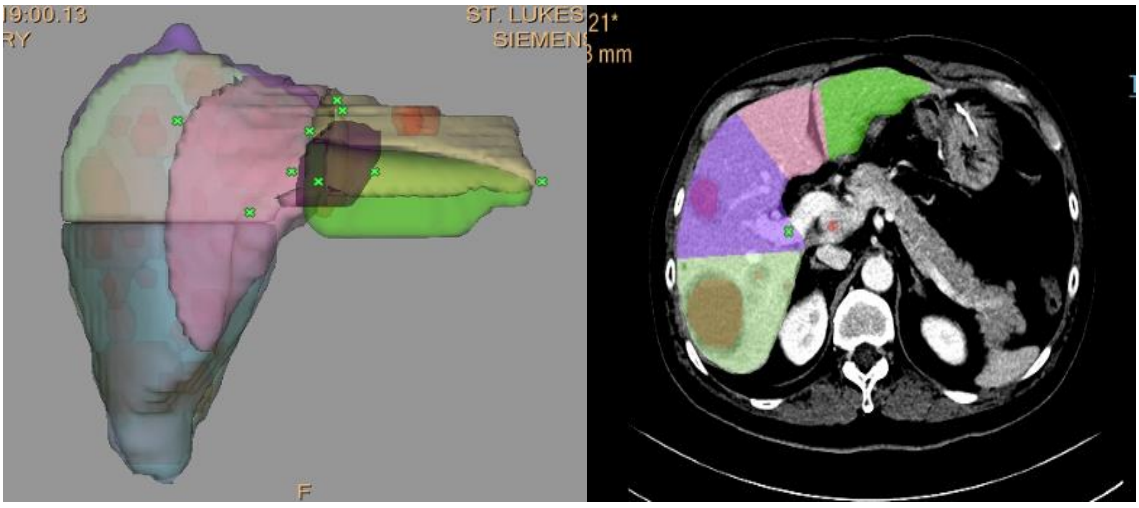

Figure 2: Liver volumetric study. 3D render and axial view.

The liver volumetric study showed a functional volume of 1117 cc in the right lobe and 449 cc in the left lobe. The total volume of the hepatic metastatic lesions in both lobes was approximately 245 cc or 13% of the total liver volume.

Intra-Arterial Administration

Percutaneous right transfemoral access using a 5F Terumo Yashiro catheter was established to the right and left hepatic arteries. A super selective transcatheter contrast examination using 2.7F Terumo Progreat showed multiple tumor staining masses scattered in both hepatic lobes. Administration of the radiopharmaceutical was subsequently done with a total of 7.89 GBq of Lu-177 DOTATATE, 6.75 GBq, and 1.14 GBq to the right and left hepatic lobes, respectively. A 24-hour post therapy scan demonstrated adequate localization of Lu-77 DOTATATE in the hepatic lesions.

The patient was discharged with adequate hemostasis, effective pain management, no gastrointestinal symptoms and without significant hematologic or renal toxicities.

Four months later, IV-PRRT was administered, and a 24-hour post-therapy scan showed a decrease in intensity of the hepatic lesions, demonstrating the treatment effect from the IA-PPRT.

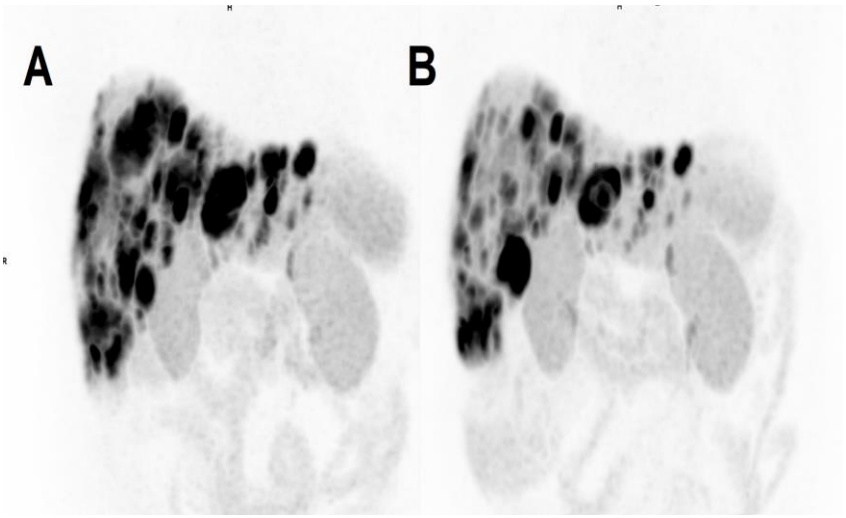

Figure 3: Maximum Intensity Projections (MIP) of the Ga-68 DOTATATE PET-CT scans. (A) July 2023 (B) February 2025.

A repeat Ga-68 DOTATATE PET-CT scan was done one year after, which showed overall regression in size and number of the hepatic lesions, the largest currently measuring 2.6 x 3.2 x 2.6 cm, previously 4.4 x 5.2 x 5.5 cm, as well as an interval decrease of SSTR-overexpression in the hepatic lesions (SUVMax 54.1, previously 64.1) (Figure 3).

Discussion

Intra-arterial PRRT is a non-conventional means of administering Lu-177 DOTATATE in those with extensive hepatic disease. It may directly enhance tumoral activity through selective delivery via the hepatic artery, reducing systemic circulation and early excretion, potentially also reducing non-tumoral toxicity compared to standard intravenous administration.[14, 15]

Several studies compared intra-arterial versus intra-venous administration of Lu-177 DOTATATE. Vonken et al. demonstrated an overall mean with 398% increased target lesion accumulation for the intra-arterial Lu-177 administration in the management of salvage meningiomas.[16] Thakral et al. compared two separate groups receiving IA and IV PRRT which showed a significantly higher hepatic tumoral activity of IA (4.18 ± 5.6) compared to IV (2.68 ± 2.89) administration, as well as reduction in the non-tumoral liver parenchymal activity in IA (0.17 ± 0.062) versus IV (0.23 ± 0.062).

In the LUTIA Trial conducted by Ebbers et al. in patients with bi-lobal liver metastases, received IA-PRRT through either the left or right hepatic artery, with the contralateral liver lobe receiving the treatment via the second pass effect or the systemic circulation, the study showed a 17% increase via intra-arterial administration compared to the contralateral lobe. The study demonstrated an insignificant tumoral increase, however, with a relatively safe profile. Most common adverse events were limited to mild to moderate fatigue and nausea. Grade 3 to 4 lymphocytopenia was limited. The study mentioned several limitations, including a small sample size, heterogeneity in tumor grading, size, and degree of SSTR expression in the lesions.[17]

Some studies used different radionuclides such as In-111 DTPA-octreotide and In-111 DOTATOC. However, direct comparison to Lu-177 DOTATATE may be difficult due to varied affinity to different target receptors, administered activity, and radiation characteristics. These studies, however, demonstrated up to 1.9 - 4.5x fold in tumor absorbed dose when administered intra-arterially.[18, 19]

Due to the predominance of hepatic metastasis in the patient, intra-arterial administration was considered. The follow-up Ga-68 DOTATATE PET-CT scan provided imaging evidence of good response to IA-PRRT and IV-PRRT with overall reduction in size and SSTR-overexpression in the hepatic lesions. It has been over seven years since the diagnosis and the initiation of multiple treatment modalities including Lu-177 DOTATATE to the patient. To date, there have been no significant adverse events or hospitalizations reported. The patient remains asymptomatic with no jaundice, weight loss or loss of appetite, and has excellent functional capacity and normal liver function tests. Due to the sustained treatment response, he and his physician-wife prefers surveillance as the current management.

There are some limitations of the treatment modality including the limited accessibility of Lu-177 DOTATATE itself, being available only in few tertiary hospitals in the Philippines, the need for advanced theranostic quantification software, as well as the requirement of the specialized expertise in nuclear medicine theranostics and interventional radiology. Future studies using dosimetric analysis and the cost-effectiveness of this approach may be done.

Conclusion

This case report highlights the applicability of IA-PRRT for hepatic-predominant NET metastasis. The approach led to favorable tumor response with minimal toxicity. Further research and clinical trials are needed to establish IA-PRRT in clinical practice when compared to standard intravenous administration.

Conflict of Interest

The authors declare no conflicts of interest.

Patient Consent Statement

The authors attest to having secured all necessary patient consent documentation. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that no patient identifiers will be disclosed in this journal and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed. Patient consent has been obtained for publication.

The study abides by the Principles of the Declaration of Helsinki and is conducted along the Guidelines of the International Conference on Harmonization - Good Clinical Practice (ICH-GCP), E6 (R2), other ICH-GCP 6 (as amended), and National Ethical Guidelines for Health and Health-Related Research.[20, 21]

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