THE JOURNAL OF DIAGNOSTIC AND THERANOSTIC IMAGING [TheJODTi]

"In Every Frame, We Transform The Care"

Rare Discordance Between 68Ga-DOTATATE and 68Ga-PSMA PET/CT in a Metastatic Ileal Neuroendocrine Tumor: A Case Report and Literature Review

Authors

Fatih Batı[1], Nilüfer Bıçakcı[2]

Affiliations

[1]Department of Nuclear Medicine, Samsun University Faculty of Medicine, Samsun, Türkiye.

[2]Department of Nuclear Medicine, Samsun Education and Research Hospital, Samsun, Türkiye.

Abstract

Background: Somatostatin receptor PET/CT with 68-gallium–labeled tracers (e.g., 68Ga-DOTATATE) is the gold standard imaging modality for well-differentiated neuroendocrine tumors (NETs), whereas 68Ga-PSMA PET/CT is routinely used in prostate cancer. PSMA PET can incidentally localize to other malignancies due to PSMA expression in the tumor neovasculature, but its role in NETs is still unclear.

Case presentation: We present the case of a 40-year-old male with metastatic ileal NET (midgut carcinoid) who had undergone 68Ga-DOTATATE and 68Ga-PSMA PET/CT imaging. DOTATATE PET/CT showed intense radiotracer uptake in the primary ileal tumor and multiple liver metastases (SUVmax ~15), confirming strong somatostatin receptor expression. In striking contrast, PSMA PET/CT demonstrated no abnormal uptake in any of the lesions. The patient had no history of prostate cancer.

Discussion: This case illustrates the rare discordance between DOTATATE and PSMA tracer uptake in NET. Prior literature reports PSMA-avid disease in some NETs (especially pancreatic NETs), which is attributed to PSMA expression in tumor-associated neovasculature. Our midgut NET case showed an absence of PSMA uptake, suggesting heterogeneity in PSMA expression across NET subtypes and tumor microenvironments.

Conclusion: 68Ga-PSMA PET can be negative in DOTATATE-positive midgut NETs, underscoring the importance of somatostatin receptor imaging for disease evaluation and caution against assumptions of universal PSMA avidity in NETs.

Keywords: Ileal neuroendocrine tumor, 68Ga-DOTATATE, 68Ga-PSMA, PET/CT, somatostatin receptor imaging, discordance, theranosti

Received 1 June ; Accepted 19 June; Published 29 June 2025

Corresponding Author: Fatih Batı
Department of Nuclear Medicine, Samsun University Faculty of Medicine, Samsun, Türkiye.
E-mail: fatih.bati@samsun.edu.tr

Cite: Batı F, Bıçakcı N. Rare discordance between 68Ga-DOTATATE and 68Ga-PSMA PET/CT in a metastatic ileal neuroendocrine tumor: a case report and literature review. TheJODTi. 2025;1(1):11-15. https://doi.org/10.5455/TheJODTi.1006.2024

Introduction

Neuroendocrine tumors (NETs) of the gastroenteropancreatic tract are typically visualized using somatostatin receptor (SSTR)-targeted imaging. PET/CT with 68-gallium-labeled somatostatin analogs (such as 68Ga-DOTATATE or 68Ga-DOTATOC) is the standard of care for diagnosing and staging well-differentiated NETs due to their high SSTR expression (1). Prostate-specific membrane antigen (PSMA) PET/CT is an essential imaging modality for prostate cancer. PSMA is also expressed in endothelial cells of tumor-associated neovasculature in many nonprostatic malignancies. This means that PSMA-targeted tracers may incidentally localize to various other tumors, including renal cell carcinoma, hepatocellular carcinoma, and even thyroid or lung cancers, among others (often via neovasculature uptake rather than tumor cell expression) (2).

The application of PSMA PET in NETs is of growing interest, but evidence remains limited. A few case reports have documented PSMA-ligand uptake in NET lesions, particularly in pancreatic NETs and high-grade tumors. For example, Vamadevan et al. described a pancreatic NET with intense 68Ga-PSMA uptake on PET/CT(3). Likewise, incidental PSMA PET detection of an unknown NET during a prostate cancer workup has been reported (4). These reports suggest that some NETs can express PSMA (presumably via the tumor neovasculature); however, the frequency and extent of this phenomenon are not well established. In particular, midgut NETs (ileal primaries) were not commonly associated with PSMA uptake. Herein, we present a rare case of metastatic ileal NET imaged using 68Ga-DOTATATE and 68Ga-PSMA-11 PET/CT, demonstrating a striking discordance between the two tracers. These findings underscore the variability of PSMA expression in NETs and highlight the need to better understand its determinants.

Case Presentation

A 40-year-old man was diagnosed with a metastatic ileal NET. The patient initially presented with a vague abdominal pain and flushing. Contrast-enhanced CT revealed an ileal mass and multiple liver lesions, and subsequent liver biopsy confirmed a well-differentiated NET (WHO Grade 2, Ki-67; 5%). For initial staging, the patient underwent 68Ga-DOTATATE PET/CT at an outside institution, which revealed a widespread avid disease. Consequently, treatment with a long-acting somatostatin analog (octreotide LAR, 30 mg monthly) was initiated.

After 12 months of therapy, his clinical symptoms improved and he was referred to our institution for follow-up. 68Ga-PSMA-11 PET/CT was performed as part of the research protocol to explore PSMA expression in NETs. Shortly thereafter, routine follow-up 68Ga-DOTATATE PET/CT was performed to evaluate the patient's response to the ongoing therapy. The 68Ga-DOTATATE study demonstrated a partial metabolic response compared with the initial scan from the previous year. Written informed consent was obtained from all patients for all imaging studies and for the publication of this case report.

Imaging Protocol

All imaging studies were performed on a Philips Gemini TF 16 PET/CT (Philips Healthcare, Cleveland, OH, USA) using a low-dose CT protocol (120 kVp, automated mAs) for attenuation correction and anatomical localization, with PET data acquired in 3D mode at 2 minutes per bed position and reconstructed using OSEM (2 iterations, 21 subsets) with a 4 mm Gaussian post-filter.

For 68Ga-PSMA-11 PET/CT, an activity of 2 MBq/kg (approximately 150–200 MBq total) was administered intravenously, followed by imaging 60 ± 10 min post-injection.

For 68Ga-DOTATATE PET/CT, we administered 2 MBq/kg (up to 200 MBq) intravenously, with imaging 50–75 min after injection. The patient fasted for at least 4 h and was encouraged to hydrate before tracer injection. Long-acting somatostatin analog therapy was withheld for 3–4 weeks before imaging to avoid potential receptor blockade.

All images, both PSMA and SSTR PET/CT, were reconstructed with standardized parameters (OSEM, 2 iterations/21 subsets, 4 mm Gaussian filter) to ensure inter-study comparability, in line with both PSMA and SSTR procedural guidelines.

Imaging Findings

68Ga-PSMA-11 PET/CT performed at our institution demonstrated no pathological uptake of radiotracers in any of the NET lesions. The whole-body maximum intensity projection (MIP) image showed only the normal physiological distribution of the PSMA tracer (e.g., in the salivary and lacrimal glands, liver, spleen, kidneys, and bladder) with no abnormal focal uptake in the abdomen or pelvis (Figure 3, upper row). On axial PET/CT images, the metastatic sites in the liver and primary mesenteric mass were completely indistinguishable from the background activity (Figure 1 and 2, upper panels).

In stark contrast, 68Ga-DOTATATE PET/CT performed shortly after the PSMA scan confirmed the presence of persistent intensely avid disease. The findings were as follows:

- Hepatic Metastases: Approximately 10 focal lesions with intense 68Ga-DOTATATE uptake were identified in both liver lobes. The most prominent of these, a subcapsular lesion in segment IVa, measuring ~1.5 cm with an SUVmax of 16.4, and a central lesion in segment VI measuring ~1 cm with an SUVmax of 14.7 (Figure 1, lower panels).

- Primary Mesenteric Mass: A conglomerate of mass lesions was identified in the mesentery, adjacent to the small bowel loops. At the L2 vertebral level, the largest component measured approximately 6 cm, with an exceptionally high SUVmax of 30.1. This was contiguous with other masses at the L1 level (~3.5 cm, SUVmax 22.4) and L3 level (~2.5 cm, SUVmax 27.3). The two larger masses exhibited central areas of diminished uptake, suggesting necrosis (Figure 2, lower panel).

● Other Findings: Physiologic uptake was noted in both adrenal glands (right SUVmax 8.2, left SUVmax 10.2) and the prostate (SUVmax 5.0).

Compared with the patient's initial staging scan from the outside institution, the lesions showed a partial reduction in 68Ga-DOTATATE avidity, consistent with a partial metabolic response to somatostatin analog therapy.

Collectively, these imaging results confirm a true and striking discordance: the patient's well-differentiated ileal NET lesions were highly 68Ga-DOTATATE-avid, but entirely 68Ga-PSMA-negative. A direct side-by-side comparison of the representative liver metastases clearly illustrated this discrepancy (Figure 1).

No suspicious findings on the PSMA scan were suggestive of any other malignant tumor (such as prostate cancer). These imaging results confirm a true discordance: ileal NET lesions are highly DOTATATE-avid but entirely PSMA-negative.

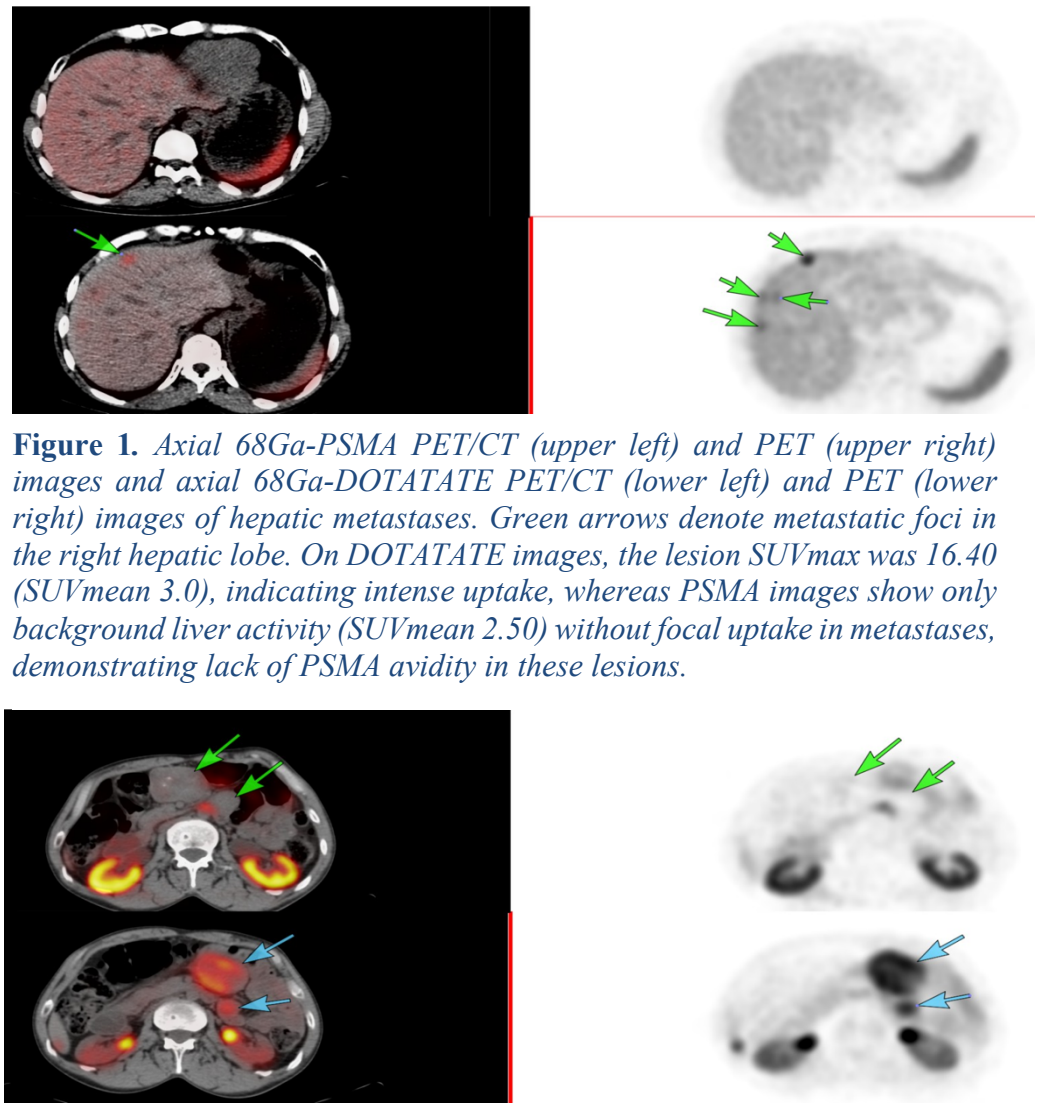

Figure 1. *Axial 68Ga-PSMA PET/CT (upper left) and PET (upper right) images and axial 68Ga-DOTATATE PET/CT (lower left) and PET (lower right) images of hepatic metastases. Green arrows denote metastatic foci in the right hepatic lobe. On DOTATATE images, the lesion SUVmax was 16.40 (SUVmean 3.0), indicating intense uptake, whereas PSMA images show only background liver activity (SUVmean 2.50) without focal uptake in metastases, demonstrating lack of PSMA avidity in these lesions.*

Figure 2. *Axial 68Ga-PSMA PET/CT (upper left) and PET (upper right) images and axial 68Ga-DOTATATE PET/CT (lower left) and PET (lower right) images of the primary ileal neuroendocrine tumor (blue arrow, measuring 50 × 60 mm) in the middle-left quadrant. A small adjacent mesenteric lymph node is seen abutting the primary lesion (blue arrow). The ileal mass shows minimal PSMA avidity (green arrow, SUVmax 1.70) but intense DOTATATE uptake (blue arrow, SUVmax 30.0), confirming strong somatostatin receptor expression despite absent PSMA expression.*

Discussion

This case demonstrates a rare imaging discordance in a metastatic midgut NET: the patient's tumors were strongly 68Ga-DOTATATE–positive yet 68Ga-PSMA–negative. Typically, well-differentiated NETs uniformly express somatostatin receptors, making SSTR-targeted imaging (and therapy) the cornerstone of management (5). In contrast, PSMA-targeted imaging is not routinely used in NETs; however, there is biological

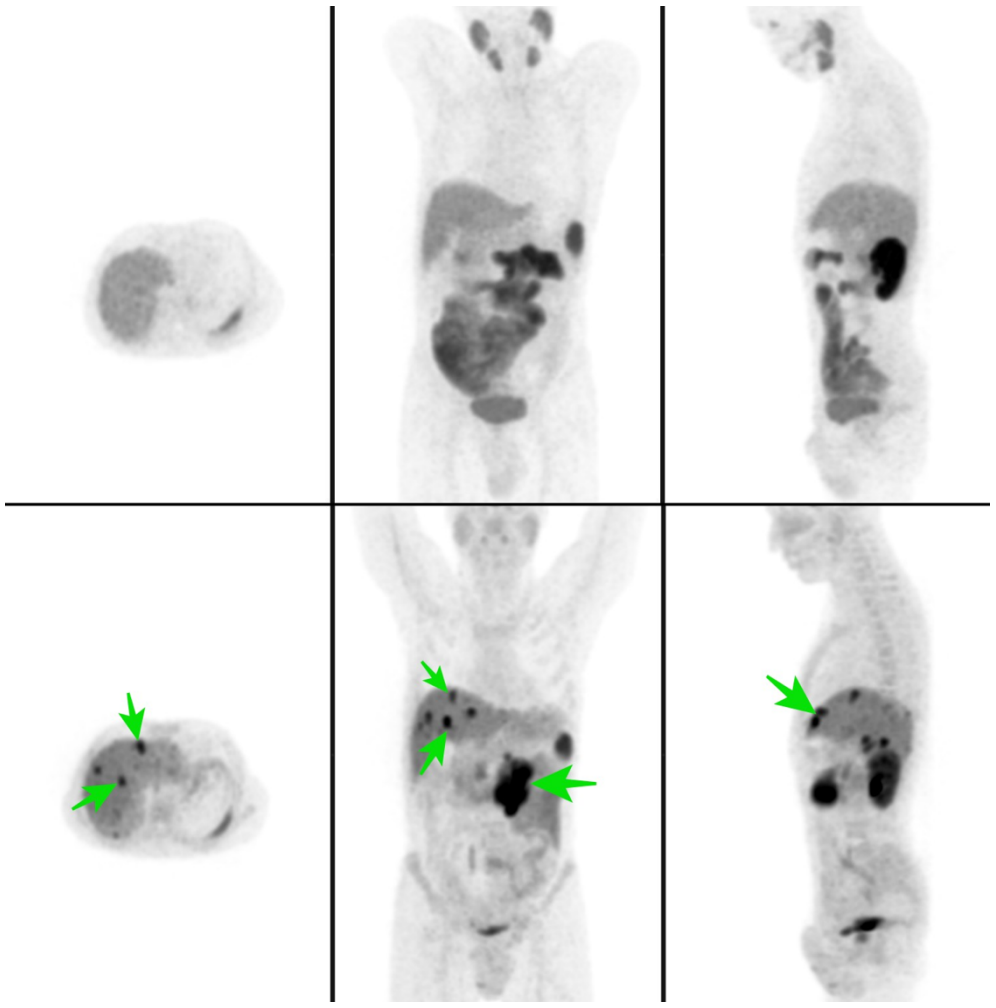

Figure 3. *Maximum-intensity-projection (MIP) PET images from 68Ga-PSMA-11 (upper row) and 68Ga-DOTATATE (lower row) studies in the same patient, shown in axial (left), coronal (middle), and sagittal (right) planes. The PSMA-11 MIP (upper panels) demonstrates only physiologic tracer distribution without focal uptake in the ileal or hepatic regions. The DOTATATE MIP (lower panels) shows intense uptake in the primary ileal neuroendocrine lesion (green arrow; SUVmax 30.0) and multiple liver metastases (green arrows; highest SUVmax 16.40).*

plausibility for PSMA uptake in NET lesions, as endothelial cells of the tumor neovasculature across many solid tumors are known to express PSMA. NETs are often highly vascular tumors, and increased neoangiogenesis can lead to some degree of PSMA expression in the tumor microenvironment, especially in aggressive or metastatic cases (6). Despite this theoretical expectation, evidence of PSMA-PET positivity in NETs is limited to scattered reports in the literature.

Our findings are in contrast with those of several published cases in which NET lesions showed PSMA avidity. Chen et al. (2023) reported a case of a 53-year-old patient with a pancreatic NET (grade 2) in whom 68Ga-PSMA PET/CT revealed intense PSMA-avid liver metastasis. In this case, the liver lesion was positive on both 68Ga-PSMA and 68Ga-DOTATATE imaging, indicating substantial PSMA expression, whereas the primary pancreatic tumor was PSMA-positive on PET (and 18F-FDG avid) (7). Similarly, Vamadevan et al. (2016) documented a PSMA-avid pancreatic NET metastasis identified on PSMA PET (3), and Morales et al. (2020) described an incidentally discovered NET during PSMA scanning for prostate cancer (the primary NET was later found in the small bowel) (4). These reports suggest that PSMA-PET can sometimes detect NET lesions, particularly in pancreatic tumors or possibly more aggressive tumors. In striking distinction, our patient's midgut NET lesions showed no uptake on PSMA-PET despite clear visualization on DOTATATE PET. To the best of our knowledge, this represents one of the few documented instances of a completely PSMA-negative gastroenteropancreatic NET despite widespread SSTR-positive disease.

The divergent tracer uptake patterns observed can be explained by the differences in tumor biology and microenvironments. In non-prostatic tumors, PSMA expression is predominantly located in the neovasculature endothelium rather than in tumor cells (2). The degree of PSMA PET uptake in NET lesions likely depends on the extent and characteristics of tumor angiogenesis. Pancreatic NETs may induce more robust or PSMA-expressing neovasculature, especially in metastatic sites such as the liver, which could explain the PSMA-avid liver metastases noted in literature (7). In contrast, midgut (ileal) NETs, often slow-growing and highly SSTR-positive, may have a different angiogenic profile, with relatively limited PSMA expression (8). Moreover, intrapatient heterogeneity can play a role; even within the same individual, one NET metastasis might show PSMA uptake, while the other does not. Winter et al. (2023) illustrated this heterogeneity in a complex case in which a patient had both prostate cancer and a duodenal NET, and NET liver metastasis demonstrated very high PSMA uptake, whereas NET primary and lymph node metastases were PSMA-negative (9). The authors emphasized that the expression of PSMA in tumors can be highly variable, context-dependent, and influenced by factors such as the metastatic site, local neoangiogenic activity, and organ-specific microenvironment. Our case reinforces this point on an interpatient level: despite similar SSTR expression, a midgut NET may lack the PSMA expression that some pancreatic NETs or other tumors exhibit.

Another consideration is tumor grade and differentiation. Well-differentiated NETs (G1/G2) tend to be SSTR-positive and often relatively indolent, whereas poorly differentiated neuroendocrine carcinomas (G3) may lose SSTR expression but show increased glucose metabolism on 18F-FDG PET. It is conceivable that high-grade or biologically aggressive NETs could also demonstrate higher PSMA expression, given their greater angiogenic and proliferative activities (10). However, our patient's NET was well-differentiated (G2) and remained strongly DOTATATE-avid, correlating with a good response to somatostatin analog therapy. In this context, the lack of PSMA uptake suggests that PSMA-targeted imaging or therapy (such as 177Lu-PSMA radioligand therapy) would likely not benefit this patient. In contrast, for rare NET patients with PSMA-avid lesions, PSMA-targeted approaches could potentially serve as an alternative or adjunct, for example, in cases where SSTR-based therapies have failed (11). Identifying PSMA expression in NETs may also provide prognostic information or indicate tumor heterogeneity that warrants biopsy confirmation.

Our case highlights the importance of not assuming cross-tracer positivity without evidence. A negative PSMA PET in a patient with NET should be interpreted in light of the known biology; the absence of PSMA uptake does not contradict the presence of NET disease (as shown by the positive DOTATATE scan), but rather indicates that this NET's neoangiogenesis did not express the PSMA target. This finding underscores the need for histopathological validation of unexpected imaging findings. Additionally, it contributes to the growing body of knowledge that PSMA expression in NETs is heterogeneous and likely dependent on the tumor subtype, differentiation, and tumor microenvironment (12). Further research, including immunohistochemical studies of PSMA in tissues from the midgut versus pancreatic NETs, would be valuable to elucidate the mechanisms underlying this variability.

Conclusion

We report the unique case of a 40-year-old man with metastatic ileal (midgut) neuroendocrine tumor who demonstrated complete discordance between 68Ga-DOTATATE and 68Ga-PSMA PET/CT findings. The patient's NET lesions were strongly DOTATATE-positive but showed no uptake on PSMA PET. This rare imaging finding highlights that not all NETs express PSMA, especially in non-pancreatic subtypes, and that PSMA-targeted imaging can yield false-negative results in well-differentiated NETs of the midgut. Clinicians should be aware that 68Ga-PSMA PET/CT, which is useful in many oncological settings, has limited utility for detecting NETs that lack significant PSMA expression. Conversely, somatostatin receptor PET/CT remains the primary functional imaging modality for gastroenteropancreatic NETs, and should be used for disease evaluation in these patients. Finally, this case underscores the broader principle of tumor heterogeneity in molecular imaging, and the necessity of correlating imaging results with histology and established imaging standards. Ongoing comparative studies and case reports will further clarify the PSMA expression spectrum in NETs and help optimize imaging strategies for uncommon tumors.

Ethical Approval: *All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.*

Conflict of Interests: *The authors declare that there is no conflict of interest in this article.*

Competing interests: *The authors declare that they have no competing interests.*

Financial Disclosure: *The authors declare that they have received no financial support for this article.*

References

1. Ebner R, Sheikh GT, Brendel M, Ricke J, Cyran CC. ESR Essentials: role of PET/CT in neuroendocrine tumors—practice recommendations by the European Society for Hybrid, Molecular and Translational Imaging. Eur Radiol. 2024 Oct 10;35(4):1903–12.

2. de Galiza Barbosa F, Queiroz MA, Nunes RF, Costa LB, Zaniboni EC, Marin JFG, et al. Nonprostatic diseases on PSMA PET imaging: a spectrum of benign and malignant findings. Cancer Imaging. 2020 Dec 14;20(1):23.

3. Vamadevan S, Shetty D, Le K, Bui C, Mansberg R, Loh H. Prostate-Specific Membrane Antigen (PSMA) Avid Pancreatic Neuroendocrine Tumor. Clin Nucl Med. 2016 Oct;41(10):804–6.

4. Morales MI, Erhard A, Lozano MD, Quincoces G, Richter JA, Rodríguez-Fraile M. Diagnóstico incidental de tumor neuroendocrino con 68Ga-PSMA PET/TC: a propósito de un caso. Rev Esp Med Nucl Imagen Mol. 2020 Mar;39(2):102–3.

5. Bozkurt MF, Virgolini I, Balogova S, Beheshti M, Rubello D, Decristoforo C, et al. Guideline for PET/CT imaging of neuroendocrine neoplasms with 68Ga-DOTA-conjugated somatostatin receptor targeting peptides and 18F–DOPA. Eur J Nucl Med Mol Imaging. 2017 Aug 25;44(9):1588–601.

6. Van de Wiele C, Sathekge M, de Spiegeleer B, De Jonghe PJ, Debruyne PR, Borms M, et al. PSMA expression on neovasculature of solid tumors. Histol Histopathol. 2020 Sep;35(9):919–27.

7. Chen S, Lin Z, Wang C, Miao W. 68Ga-PSMA PET/CT in Hepatic Metastasis From Pancreatic Neuroendocrine Tumor. Clin Nucl Med. 2023 Nov;48(11):991–3.

8. Salas Fragomeni RA, Amir T, Sheikhbahaei S, Harvey SC, Javadi MS, Solnes LB, et al. Imaging of Nonprostate Cancers Using PSMA-Targeted Radiotracers: Rationale, Current State of the Field, and a Call to Arms. Journal of Nuclear Medicine. 2018 Jun;59(6):871–7.

9. Winter E, Zschäbitz S, Kratochwil C. Liver metastasis of a neuroendocrine tumor demonstrates intense uptake in PSMA-PET—but not its lymph-node metastasis and primary-tumor. Eur J Nucl Med Mol Imaging. 2023 Jun 13;50(7):2226–7.

10. Shen Z, Zhang X, Li Q, Wang R. Comparison of 18F-FDG PET/CT and 18F-DOTATATE PET/CT in the diagnosis of multiple metastases in rectal neuroendocrine neoplasms. Radiol Case Rep. 2024 Sep;19(9):3757–62.

11. Nesari Javan F, Aryana K, Askari E. Prostate Cancer With Neuroendocrine Differentiation Recurring After Treatment With 177Lu-PSMA. Clin Nucl Med. 2021 Sep;46(9):e480–2.

12. Bakht MK, Beltran H. Biological determinants of PSMA expression, regulation and heterogeneity in prostate cancer. Nat Rev Urol. 2025 Jan 8;22(1):26–45.