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The role of Pet-Ct in neuroendocrine tumors without an identified primary focus: A case report and review

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Abstract

Neuroendocrine tumors are a rare group of heterogeneous tumors, mostly developed in the gastrointestinal and respiratory tract. These tumors show overexpression of somatostatin receptors on the cell membrane, in which type 2 SSTRs are more common. Functional imaging techniques are using for the NETs diagnosis and treatment. In this case a patient with neuroendocrine tumor (NET) without primary focus was admitted to the hospital due to recurrent episodes of cholecystitis. During diagnostic investigation incidentally anechoic foci in the patient's liver were detected and pathological examination of this foci showed that it's a metastasis of neuroendocrine tumor. The patient was previously investigated for the primary focus identification of NET, but no significant outcome was found. Hence, we used SSTR-based PET/CT scan 68Ga-DOTA-peptides, which showed the primary focus of NET in the tail of pancreas. Therefore, we concluded that the PET/CT scan 68Ga-DOTA-TATE showed significant outcome with identification of tumor localization.

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Introduction

Between 9% and 19% of patients with neuroendocrine tumors (NETs) present with metastatic disease with an unknown primary tumor site (Wedin *et al.,* 2024). Localization of the primary tumor is highly relevant in the management of this patient population because complete resection of the primary tumor and metastases is the treatment goal for patients with well-differentiated NET metastases (Huang *et al.,* 2024). Even if the metastases are not completely resectable, debulking surgery can improve symptom control in patients with endocrine symptoms and may improve survival (Ghabra *et al.,* 2024; Søreide *et al.,* 2024).

The standard imaging for staging of NETs includes CT and MRI as well as somatostatin receptor scintigraphy (Marcus *et al.,* 2024). CT and MRI are limited for evaluation of primary small bowel NETs; somatostatin receptor imaging with 111In-octreotide (Octreoscan; Mallinckrodt Pharmaceuticals) also shows limited detectability, with only 37% of small bowel primary NETs detected preoperatively with 111In-octreotide (Marcus *et al.,* 2024). More recently, somatostatin receptor imaging with positron emitters has been developed using 68Ga (a generator product with a half-life of 68 min) and DOTA as chelator. The most widely studied 68Ga-DOTA-octreotide analogs for PET imaging are 68Ga-DOTA-TATE, 68Ga-DOTA-TOC, and 68Ga-DOTA-NOC (Han *et al.,* 2024). All of these radiopharmaceuticals have higher affinity than 111In-octreotide for the somatostatin receptor subtype 2, the primary target in NETs, and are more sensitive than 111In-octreotide in the detection of NET lesions (Di Franco *et al.*, 2024; Raynor and Kempf, 2024). The objective of this study was to evaluate the accuracy of 68Ga-DOTA-TOC and 68Ga-DOTA-TATE PET/CT imaging in the localization of the site of the unknown primary tumor in patients with metastatic.

Case report

In the current study a 72-year-old patient with chronic cholecystitis was investigated, initially an abdominal ultrasound was carried out the results of which showed anechoic foci in the liver. Due to recurrent episodes of cholecystitis a cholecystectomy was performed, while in order to monitor the anechoic foci of the liver the patient underwent regular abdominal US and there were no changes in the anechoic foci of liver. But after 3 years the repeated abdominal US showed an enlargement of this foci, so doctors decided to do a CT scan of the abdominal cavity, which showed three tumors with signs of malignancy in liver segments S1, S2 and S3 with following dimensions 82x66x64 mm, 69x53x50 mm and 17 mm in diameter, respectively also an enlarged lymph nodes in the hilum of the liver were observed. A pathomorphological examination of the suspicious liver lesion revealed low-grade hepatocellular cancer. Therefore, the patient was prescribed chemotherapy, which was unfortunately ineffective and repeated CT scan with contrast showed same level of hypervascularization of the tumor in S3 and tumor in the hilum of liver. As a result, the hyper vascularized tumor in the hilum of liver was surgically removed and immunohistochemical examination of that resected tumor detected metastasis of neuroendocrine tumor in the liver Ki 67 – 15%. So, we resort to PET/CT scan with 18F-FDG which didn't show anything, neither showed PET/CT scan with 68Ga-DOTA-NOC (Fig. 1), but PET/CT scan with 68Ga-DOTA-TATE was informative.

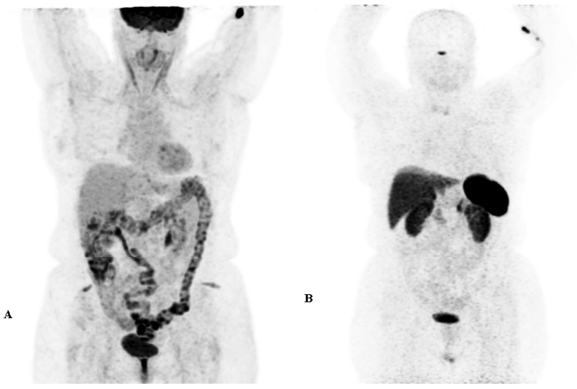

Fig. 1. (A). PET/CT scan with 18F-FDG and 68Ga-DOTA-NOC. (B) The PET/CT scan with 68Ga-DOTANOC. In both examination no tumor localization was detected

Ultrasound and CT scan reports

Initially the patient was examined by using ultrasound examination; the results revolved anechoic foci in the liver. CT scan analysis in 2021 showed S2, S3, S4, three tumor formations. The patient was treated with chemotherapy – hepatic artery chembolization with Doxorubicin. In order to check dynamic of the chemotherapy patient underwent recurrent CT scan with contrast which showed the same level of hypervascularization of the tumor in S3 and tumor in the hilum of liver. On 09/27/2021 surgeon decided to remove the tumor in S3 and tumor in the hilum of the liver and do the drainage of the abdominal cavity.

Histology examination and PET-CT scan analysis

The resected tumors were sent to histological investigation, pathologist was unable to confirm the final diagnosis (is it metastasis of neuroendocrine tumor or is its low-grade hepatocellular cancer). Therefore, they send resected tumor to immunohistochemical investigation which confirm it was a neuroendocrine tumor metastasis in the liver Ki 67 – 15%. So they resort to PET/CT scan with 18F-FDG and 68Ga-DOTA-NOC which revealed nothing. While using PET/CT scan 68Ga-DOTA-TATE detected tumors (Fig. 2 & 3).

Once the focus of hyper fixation was detected (Fig. 2 and Fig. 3), surgeons removed these tumors by: corporocaudal resection of the pancreas with preservation of the spleen (Fig. 3b) and Para tumoral resection of liver metastasis S4a (Fig. 3a). Additionally patient was treated by biotherapy. The resected tumors on histochemical examination revealed neuroendocrine pancreatic tumor, G1, Ki67 <1% with liver metastasis. The final diagnosis was - Malignant neoplasm of the tail of the pancreas T2N0M1 (hep) G2, metastasis in the liver Ki67-15%. PET/CT with 68Ga-DOTA-peptides plays an important role not only in assessing the prevalence of NEO, but also in the search for a primary focus.

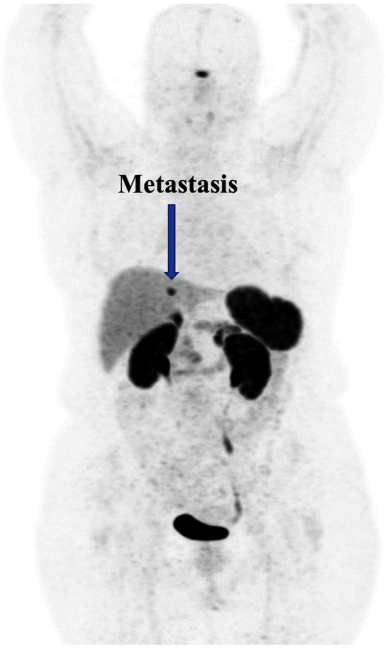

Fig. 2. The PET-CT scan with 68Ga-DOTATATE detect the Metastasis of NET

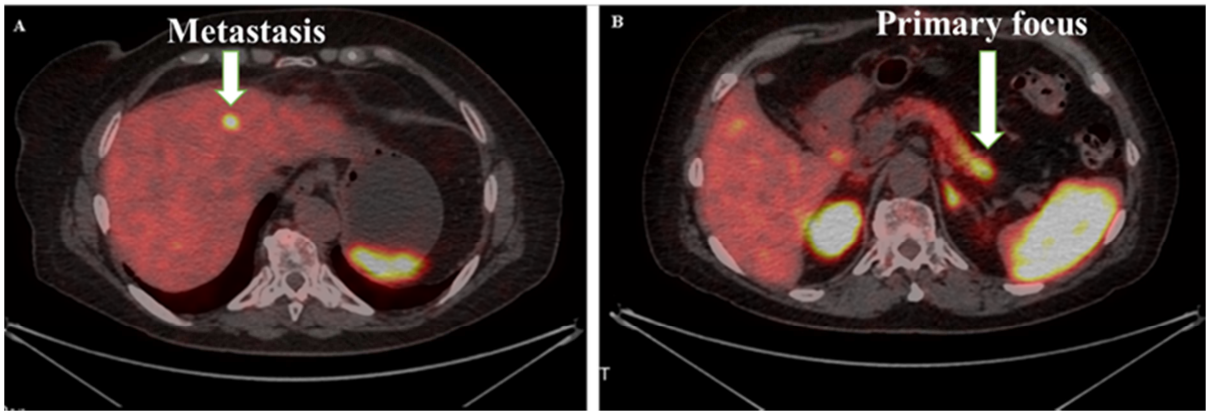

Fig. 3. (A). Picture of the focus of pathological accumulation (metastasis) of 68Ga-DOTA-TATE in S4 liver with dimensions of 14mm with SUV=8.5. (B). Focal hyper fixation (primary focus) of 68Ga-DOTA-TATE in the distal parts of the tail of the pancreas with dimensions of 28*17mm with SUV=6.9

In patients with NET (Neoendocrine tumor) G2, PET/CT is advisable with 18F-FDG and 68Ga-DOTA-peptides. In a recent study with PET/CT with the two above-mentioned Radiopharmaceuticals, the overall sensitivity was 94.0%, regardless of the degree of differentiation and proliferative activity of the tumor process, as well as the localization of the focus. The F-18 FDG PET/CT can provide forecast information regarding both overall survival and disease-free survival. The European Society for Neuroendocrine Tumors (ENETS) recommends surgical excision of the primary tumor in highly differentiated grade 1/2 NET with liver metastases, as well as possible resection of liver metastases, regardless of the location of the primary tumor. (anterior, middle and posterior intestine), which leads to an overall 5-year survival rate of 60-80 % compared to 30 % 5-year survival in non-resected liver metastases.[11] IHC determination of SSTR facilitates the choice of Radiopharmaceutical drugs(RFD) for PET/C if we want to choose appropriate RFD we should rely on tumor proliferation index (Table 1).

Table 1. Detail of tumor proliferation index

	G1	G2	G3
Ki67 Index (%)	<3	3-20	>20
18F-FDG	-	+	+
68Ga-DOTA peptides	+	+	-

Discussion

Neuroendocrine neoplasms are different types of tumors that can develop in any organs, so their clinical manifestations are different in each case (Arrivi *et al.,* 2024). In some instances a neuroendocrine tumor can be clinically silent and symptoms arise only after metastatic spreading of tumor (Arrivi *et al.,* 2024). In addition, it can be difficult to find the site of original tumor, due to small size of the last. Generally for tumor diagnosis conventional imaging techniques like CT and MRI scan are usually required. As long as these diagnostic techniques detect a space-occupying lesion, they are unable to show distinguishing features for various type of neuroendocrine tumors (Ditonno *et al.,* 2024). A multiple attempts has been tried to identify the carcinoid tumor by using functional imaging. The 18F-FDG PET/CT has been conducted in patients with carcinoids, which showed low sensitivity of this functional imaging technique in diagnosis of tumors, due to low metabolic rate in well-differentiated NET's (Ambrosini *et al.,* 2024; Sugawara *et al.,* 2024). In another study 7 patients with pulmonary carcinoid were studied and only one patient's 18F-FDG PET showed pathological radiotracer uptake, the remaining was visually negative or showed incorrect results. Gallium-68 labeled DOTA-TOC is a radiotracer PET for locating NET that express somatostatin receptors, particularly SSR2 and SSR3 (Pishdad *et al.,* 2024). This radiologic investigation showed significant role not only in the diagnosis of NET, but also in the diagnosis of primary lung tumor, meningiomas, thyroid and prostatic malignancies, due to high resolution of PET/CT (Pishdad *et al.,* 2024). Even though of a lot of advantages DOTA-TOC PET/CT has a disadvantage -hypothetically it can show false-positive rate in non-tumor organs (hypophysis, pancreas and granulomatous disease). However, this technique still is a big forward step in the diagnosis of oncological diseases. In a recent study where 18 patients with pulmonary NET assessed using PET/CT with 68-Ga-DOTA-TATE, revealed that the vast majority of carcinoid showed increased radiotracer uptake (Has Simsek *et al.,* 2024). In our study PET/CT scan with 68Ga-DOTA-TATE in the 72-years-old asymptomatic patient with neuroendocrine tumor metastasis in the liver played a crucial role in the identification of the primary localization of neoendocrine tumor in comparison to other radiotracer used in functional imaging.

Conclusion

Neuroendocrine tumor without a primary focus is a serious problem in oncology and radiology. This is due to the difficulties of determining the location of the primary tumor using traditional technologies such as CT and MRI. Though, due to the presence of special receptors on the NET, functional imaging helps to identify the primary neoplasm. The first step in functional imaging of NET is the use of PET with 18F-FDG and one of the radiotracers of 68Ga-DOTA-

peptides (DOTATOC, DOTATATE, DOTANOC), however sometimes using only one type of peptide may not always help in diagnosis. Therefore, the use of various peptides is justified since some neuroendocrine tumors sometimes contain receptors that are more tropic to certain types of peptides.

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References

Ambrosini V, Caplin M, Castaño JP, Christ E, Denecke T, Deroose CM, Dromain C, Falconi M, Grozinsky-Glasberg S, Hicks RJ, Hofland J. 2024. Use and perceived utility of [18F] FDG PET/CT in neuroendocrine neoplasms: A consensus report from the European Neuroendocrine Tumor Society (ENETS) Advisory Board Meeting 2022. Journal of Neuroendocrinology **36(1)**, e13359.

Arrivi G, Specchia M, Pilozzi E, Rinzivillo M, Caruso D, Santangeli C, Prosperi D, Ascolese AM, Panzuto F, Mazzuca F. 2024. Diagnostic and Therapeutic Management of Primary Orbital Neuroendocrine Tumors (NETs): Systematic Literature Review and Clinical Case Presentation. Biomedicines **12(2)**, 379.

Di Franco M, Zanoni L, Fortunati E, Fanti S, Ambrosini V. 2024. Radionuclide Theranostics in Neuroendocrine Neoplasms: An Update. Current Oncology Reports **2024**, 1-13.

Ditonno F, Franco A, Manfredi C, Veccia A, Valerio M, Bukavina L, Zukowski LB, Vourganti S, Stenzl A, Andriole GL, Antonelli A. 2024. Novel non-MRI imaging techniques for primary diagnosis of prostate cancer: micro-ultrasound, contrast-enhanced ultrasound, elastography, multiparametric ultrasound, and PSMA PET/CT. Prostate Cancer Prostatic Disease **27(1)**, 29-36.

Ghabra S, Ramamoorthy B, Andrews SG, Sadowski SM. 2024. Surgical Management and Long-Term Evaluation of Pancreatic Neuroendocrine Tumors. Surgical Clinics **104(4)**, 891-908.

Han S, Ryu J, Song SW, Kim JS, Ryu JS, Oh M. 2024. 68Ga-DOATATOC Brain PET/CT Imaging in a case of Dural Metastasis from Synovial Sarcoma. Nuclear Medicine and Molecular Imaging **2024**, 1-7.

Has Simsek D, Guzel Y, Denizmen D, Sanli Y, Buyukkaya F, Kovan B, Komek H, Isik EG, Ozkan ZG, Kuyumcu S. 2024. The inferior performance of [68Ga] Ga-FAPI-04 PET/CT as a diagnostic and theranostic biomarker in [177Lu] Lu-DOTATATE refractory well-differentiated neuroendocrine tumors. European Journal of Nuclear Medicine and Molecular Imaging **51(3)**, 828-40.

Huang J, Liu H, Yang D, Xu T, Wang J, Li J. 2024. Personalized treatment of well-differentiated gastric neuroendocrine tumors based on clinicopathological classification and grading: A multicenter retrospective study. Chinese Medical Journal **2024**, 10-1097.

Marcus C, Muzahir S, Subramaniam RM. 2024. Quarter Century PET/Computed Tomography Transformation of Oncology: Neuroendocrine Tumors. PET Clinics **19(2)**, 187-196.

Pishdad R, Treglia G, Mehta A, Santhanam P. 2024. Somatostatin receptor imaging of thyroid tissue and differentiated thyroid cancer using gallium-68-labeled radiotracers—a review of clinical studies. Endocrine **18**, 1-10.

Raynor WY, Kempf JS. 2024. Somatostatin Receptor PET Imaging of Physiologic and Benign Processes: Implications for Image Interpretation, Avoiding Pitfalls, and Clinical Applications. Applied Radiology **2**, 53.

Søreide K, Stättner S, Hallet J. 2024. Surgery as a Principle and Technical Consideration for Primary Tumor Resection of Small Bowel Neuroendocrine Tumors. Annals of Surgical Oncology **31(2)**, 1125-1137.

Sugawara H, Kikkawa N, Ito K, Watanabe H, Kaku S, Akai H, Abe O, Watanabe SI, Yatabe Y, Kusumoto M. 2024. Is 18F-fluorodeoxyglucose PET recommended for small lung nodules? CT findings of 18F-fluorodeoxyglucose non-avid lung cancer. British Journal of Radiology **97(1154)**, 462-468.

Wedin M, Janson ET, Wallin G, Sundin A, Daskalakis K. 2024. Prevalence of metastases outside the liver and abdominal lymph nodes on 68Ga-DOTATOC-PET/CT in patients with small intestinal and pancreatic neuroendocrine tumours. Journal of Neuroendocrinology **36(5)**, e13391.