



# Revision of the Histopathological Examination Following <sup>68</sup>Ga-DOTA-FAPI-04 PET/CT of a Breast Tumor Diagnosed as Invasive Ductal Carcinomatosis

İnvaziv Duktal Karsinoma Tanılı Meme Tümörünün <sup>68</sup>Ga-DOTA-FAPİ-04 PET/BT Sonrası Histopatolojik İncelemesinin Revizyonu

• Nalan Alan Selçuk<sup>1</sup>, • Kaan Akçay<sup>1</sup>, • Gamze Beydağı<sup>1</sup>, • Ömer Sönmez<sup>1</sup>, • Serkan Çelik<sup>2</sup>, • Bala Başak Öven<sup>2</sup>, • Levent Kabasakal<sup>3</sup>

<sup>1</sup>Yeditepe University Faculty of Medicine, Department of Nuclear Medicine, İstanbul, Türkiye

<sup>2</sup>Yeditepe University Faculty of Medicine, Department of Medical Oncology, İstanbul, Türkiye

<sup>3</sup>Istanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Nuclear Medicine, İstanbul, Türkiye

## Abstract

Neuroendocrine tumors (NETs) of the breast represent 1% of breast carcinomas. Histopathological misinterpretation of breast NET is common. We present the case of a female patient who had a breast mass diagnosed as invasive ductal carcinoma initially by histopathological examination. Fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) revealed 2 amebolic hypodense liver lesions. Subsequently, the patient underwent fibroblast activation protein inhibitor (FAPi)-PET/CT, which did not reveal any FAP expression in the liver lesions, but increased FAP expression was observed in the soft tissue mass of the mesenteric root. Consequently, the pathology of the biopsy taken from the nodule in the right breast was revised, and a diagnosis of grade 2 NET was established. The benefit of FAPi-PET/CT on NETs has been previously investigated. Further prospective studies are required to establish the role of FAPi-PET/CT in NET management.

**Keywords:** Fibroblast activation protein, PET/CT, neuroendocrine tumor, <sup>68</sup>gallium DOTATATE

## Öz

Memenin nöroendokrin tümörleri (NET), meme karsinomlarının %1'inden daha azını temsil eder. Meme NET'nin histopatolojik olarak yanlış tanı alması yaygındır. Meme kitlesi histopatolojik inceleme ile başlangıçta invaziv duktal karsinom tanısı alan bir kadın hastayı sunuyoruz. Florodeoksiglukoz pozitron emisyon tomografisi/bilgisayarlı tomografide (FDG PET/BT) 2 amebolik hipodens karaciğer lezyonu saptandı. Akabinde hastaya fibroblast aktivasyon proteini inhibitör (FAPi)-PET/BT tetkikinde karaciğer lezyonlarında FAP ekspresyonu saptanmazken mezenterik kökteki yumuşak doku kitlesinde artmış FAP ekspresyonu izlendi. Bunun üzerine, sağ memedeki nodülden alınan biyopsinin patolojisi revize edildi ve 2. derece NET tanısı konuldu. FAPi-PET/BT'nin NET'ler üzerindeki faydası daha önce literatürde gösterilmiştir. FAPi-PET/BT'nin NET'lerin yönetimindeki rolünün ortaya konması için daha fazla prospektif çalışma gerekmektedir.

**Anahtar kelimeler:** Fibroblast aktivasyon proteini, PET/BT, nöroendokrin tümör, <sup>68</sup>galyum DOTATATE

**Address for Correspondence:** Prof. Nalan Alan Selçuk, Yeditepe University Faculty of Medicine, Department of Nuclear Medicine, İstanbul, Türkiye

**Phone:** +90 216 578 43 53 **E-mail:** nalanselcuk@yahoo.com ORCID ID: orcid.org/0000-0002-3738-6491

**Received:** 15.06.2023 **Accepted:** 01.01.2024 **Epub:** 09.02.2024



Copyright© 2024 The Author. Published by Galenos Publishing House on behalf of the Turkish Society of Nuclear Medicine. This is an open access article under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 (CC BY-NC-ND) International License.

## Introduction

Metastatic neuroendocrine tumors (NETs) are exceedingly rare in breast cancer, representing less than 1% of all breast carcinomas (1,2). A study examining 18 cases of NETs metastasizing to the breast revealed that 62% of these tumors originated from the gastrointestinal tract and 28% from the lungs. Notably, 44% of these tumors were initially misdiagnosed as primary breast carcinoma (1). We present a rare case of metastatic NET initially reported as invasive ductal carcinoma (IDC), which was demonstrated through [<sup>68</sup>Ga]gallium-fibroblast activation protein inhibitor (<sup>68</sup>Ga-FAPI) positron emission tomography/computed tomography (PET/CT) and [<sup>68</sup>Ga]Ga-DOTATATE PET/CT imaging.

## Case Report

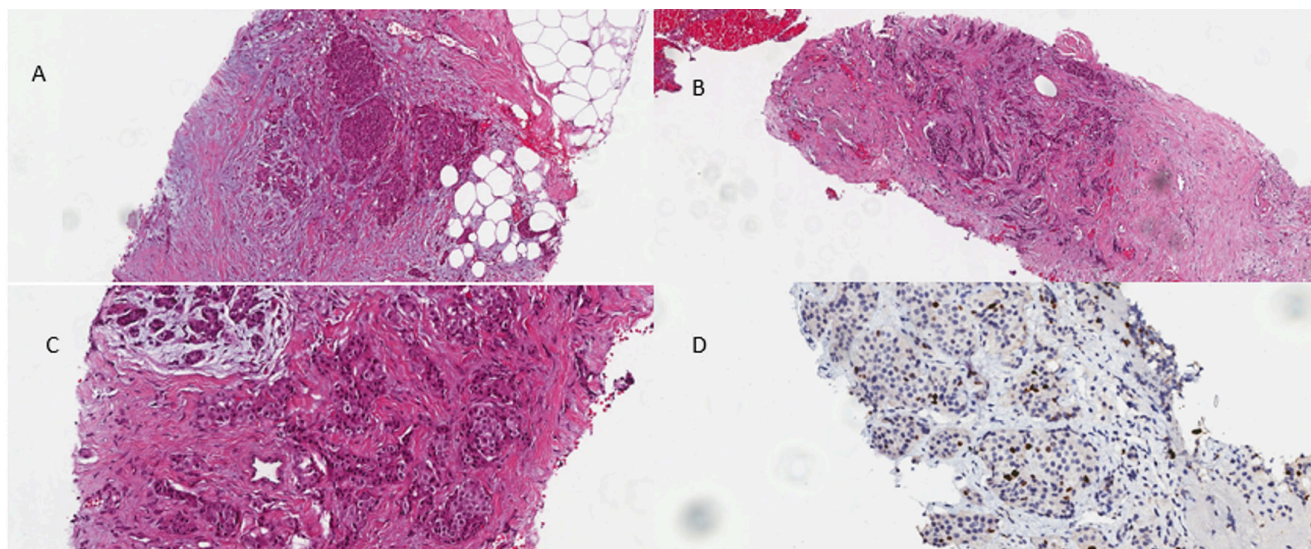
A 59-year-old female patient presented with a 1-year history of nausea, vomiting, and flushing. During a physical examination, a breast mass was detected, which led to a tru-cut biopsy. Histopathological analysis initially indicated IDC (Figure 1). She was subsequently referred to our clinic for staging. Fluorodeoxyglucose (FDG) PET/CT revealed a slightly hypermetabolic 7-mm nodule in the right breast and two hypodense, ametabolic liver lesions (Figure 2A). Considering the ametabolic nature of these liver lesions, lobular carcinoma was suspected, prompting [<sup>68</sup>Ga]Ga-DOTA-FAPI-04 PET/CT. This imaging did not demonstrate any FAP expression in the liver lesions, but increased FAP expression was observed in the mesenteric root soft tissue

mass and right breast nodular lesion (Figure 2B). Maximum standardized uptake value of uptake in the mesenteric root was 16. Upon retrospective re-evaluation of the patient's clinical findings, the mesenteric root soft tissue mass, as demonstrated by [<sup>68</sup>Ga]Ga-DOTA-FAPI-04 PET/CT, along with symptoms such as nausea, vomiting, and flushing, were consistent with a diagnosis of NET. Based on these findings, the histopathological examination was repeated, and the diagnosis was revised to NET (Figure 3). In addition to revising the primary pathological sample, histopathological examination of biopsies obtained from the mesentery and liver confirmed the diagnosis of grade 2 NET. Consequently, [<sup>68</sup>Ga]Ga-DOTATATE PET/CT was performed. Imaging revealed a soft tissue mass in the mesenteric root with increased somatostatin receptor (SSTR) expression, multiple SSTR-positive bone, liver, and lymph node metastases, and metastatic SSTR-positive nodules in both breasts (Figure 2C).

Informed consent was obtained from the patient for all modalities.

## Literature Review and Discussion

Although the FAPI uptake pattern of NETs is not exactly established, heterogeneous uptake has been reported (3). In addition to that, [<sup>68</sup>Ga]Ga-FAPI PET/CT's utility in primary and metastatic NETs was previously demonstrated in case reports (4,5,6,7). Despite the high FAP expression of the primary tumor (mass in mesenteric root) in our case, the absence of FAPI uptake by liver and bone metastases was remarkable. In this case, <sup>18</sup>F-FDG PET/CT was requested



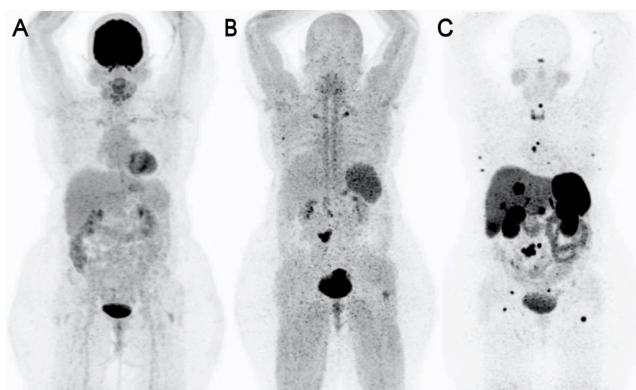
**Figure 1.** (A, B): Neoplastic cells are arranged in small and large nests, small groups with irregular borders, trabecula and occasional single cells in desmoplastic and collagenous stroma. Hematoxylin and eosin x100. (C): Neoplastic cells are oval-polygonal with amphophilic-granular cytoplasm, round-oval nuclei with occasional hyperchromasia and small nucleoli. Hematoxylin and eosin x200. (D): Ki67 proliferation index in the neoplasia is 10%; Ki67 x200

for the preoperative staging of breast cancer. However, the  $^{18}\text{F}$ -FDG PET/CT scan revealed a mildly FDG-avid nodule in the right upper outer quadrant of the breast. In addition, soft tissue mass in the mesenteric root and hypodense nodules in the right hepatic lobe were FDG-negative. Concurrently, magnetic resonance imaging of the liver interpreted these liver nodules as suggestive of metastases. In the literature, there is a substantial amount of data suggesting that  $^{68}\text{Ga}$ ]Ga-FAPI PET/CT, because of the absence of background liver activity, can better detect metastatic lesions (8). Therefore, we performed  $^{68}\text{Ga}$ ]Ga-FAPI PET/CT to evaluate the possibility of lobular breast

carcinoma and its metastasis in the liver. However,  $^{68}\text{Ga}$ ]Ga- $^{68}\text{Ga}$ ]Ga-FAPI PET/CT images did not show uptake in the liver lesions. Instead, an additional FAPI-avid mass within the mesenteric root that was inseparable from the bowel loops was detected in the abdominal region, along with multiple metastatic nodules in both breast lobes, raising the suspicion that the primary tumor might not be in the breast but rather in the abdominal mass, possibly a NET. As a result, a biopsy was recommended to the lesion in the mesenteric root and revealed a diagnosis of G2 NET. Afterwards  $^{68}\text{Ga}$ ]Ga-DOTATATE PET was performed for staging of NET.  $^{68}\text{Ga}$ ]Ga-DOTATATE imaging revealed SSTR positivity in the breast, abdominal, and liver lesions. Additional multiple bone metastases were detected.

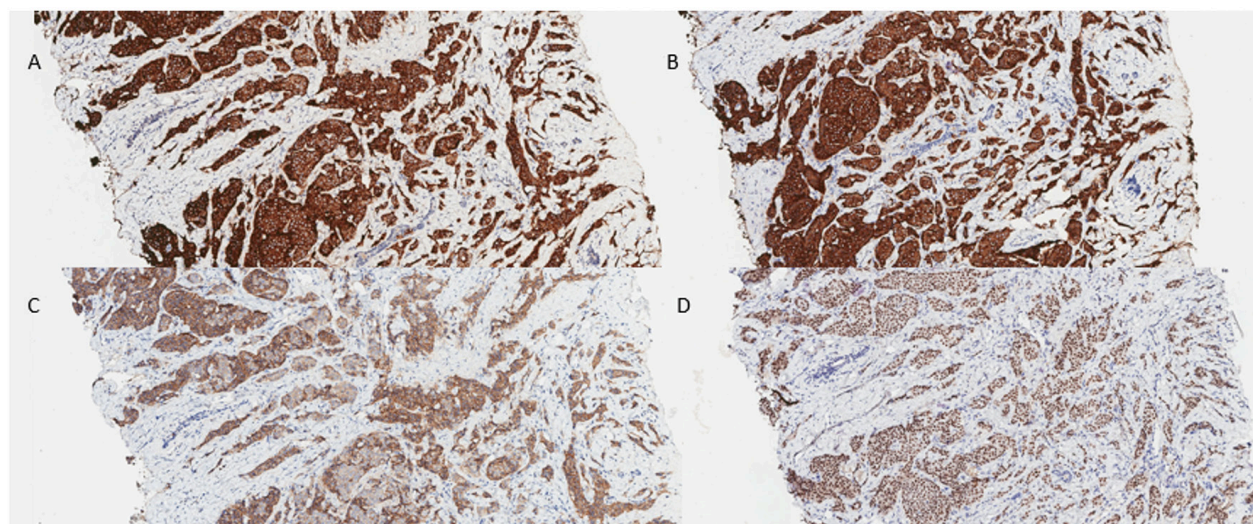
In this case, following these three imaging modalities, the patient's clinical diagnosis and stage changed significantly. Initially referred to our clinic for preoperative staging of breast cancer, the patient was ultimately diagnosed with metastatic NET, leading to the initiation of systemic treatment. NET metastases in the breast are quite rare, and biopsy alone may not be sufficient. In such cases, molecular imaging techniques such as  $^{68}\text{Ga}$ ]Ga-FAPI and  $^{68}\text{Ga}$ ]Ga-DOTATATE can be beneficial.

The images of PET/CTs using 3 different tracers all showed multiple foci of increased uptake of radiopharmaceutical in the abdomen and breast, in which  $^{68}\text{Ga}$ ]Ga-FAPI PET/CT displayed the highest tumor-to-background ratio. However,  $^{68}\text{Ga}$ ]Ga-DOTATATE PET/CT detected more metastatic lesions and liver and bone metastases, which were missed by both  $^{18}\text{F}$ -FDG and  $^{68}\text{Ga}$ ]Ga-FAPI PET/CT.



**Figure 2.** Cancer integrin imaging with  $^{68}\text{Ga}$ ]Ga-Trivehexin PET/CT for a patient with breast cancer and neuroendocrine neoplasm: a case both  $^{18}\text{F}$ -FDG PET/CT and  $^{68}\text{Ga}$ ]Ga-DOTATATE positive but integrin  $\alpha\beta 6$  negative lesion on  $^{68}\text{Ga}$ ]Ga-Trivehexin PET

PET/CT: Positron emission tomography/computed tomography,  $^{18}\text{F}$ -FDG:  $^{18}\text{F}$ -fluorodeoxyglucose



**Figure 3.** (A): Neoplastic cells are positive for chromogranin A; chromogranin A x100. (B): Neoplastic cells are positive for synaptophysin; synaptophysin x100. (C): Neoplastic cells are positive for CD56; CD56 x100. (D): Neoplastic cells are positive for CDX2; CDX2 x100

In this study, both modalities led to a complete change in the patient's histopathological diagnosis and, concurrently, a shift in the treatment algorithm.

### Ethics

**Informed Consent:** Informed consent was obtained from the patient for all modalities.

### Authorship Contributions

Surgical and Medical Practices: N.A.S., S.Ç., B.B.Ö., Concept: N.A.S., S.Ç., B.B.Ö., L.K., Design: N.A.S., L.K., Data Collection or Processing: K.A., G.B., Ö.S., Analysis or Interpretation: N.A.S., L.K., Literature Search: K.A., G.B., Ö.S., Writing: N.A.S., K.A., G.B., Ö.S., S.Ç., B.B.Ö., L.K.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study received no financial support.

### References

- Perry KD, Reynolds C, Rosen DG, Edgerton ME, Albarracín C, Gilcrease MZ, Sahin AA, Abraham SC, Wu Y. Metastatic neuroendocrine tumour in the breast: a potential mimic of in-situ and invasive mammary carcinoma. *Histopathology* 2011;59:619-630.
- Adams RW, Dyson P, Barthelme L. Neuroendocrine breast tumours: breast cancer or neuroendocrine cancer presenting in the breast? *Breast* 2014;23:120-127.
- Kreppel B, Gonzalez-Carmona MA, Feldmann G, Küppers J, Moon ES, Marinova M, Bundschuh RA, Kristiansen G, Essler M, Roesch F, Gaertner FC. Fibroblast activation protein inhibitor (FAPI) positive tumour fraction on PET/CT correlates with Ki-67 in liver metastases of neuroendocrine tumours. *Nuklearmedizin* 2021;60:344-354.
- Kömek H, Gündoğan C, Can C. 68Ga-FAPI PET/CT Versus 68Ga-DOTATATE PET/CT in the Evaluation of a Patient With Neuroendocrine Tumor. *Clin Nucl Med* 2021;46:e290-e292.
- Cheng Z, Zou S, Cheng S, Song S, Zhu X. Comparison of 18F-FDG, 68Ga-FAPI, and 68Ga-DOTATATE PET/CT in a Patient With Pancreatic Neuroendocrine Tumor. *Clin Nucl Med* 2021;46:764-765.
- Wang H, Du Z, Huang Q, Ren S, Guan Y, Xie F, Lu L, Zhu W. The superiority of [<sup>68</sup>Ga]Ga-FAPI-04 over [<sup>18</sup>F]-FDG in a case of neuroendocrine tumour with hepatic metastasis. *Eur J Nucl Med Mol Imaging* 2021;48:3005-3006.
- Ergül N, Yılmaz B, Cin M, Çermik TF. 68Ga-DOTA-FAPI-04 PET/CT in Neuroendocrine Carcinoma of the Liver With Elevated AFP Level: Comparison With 18F-FDG PET/CT. *Clin Nucl Med* 2022;47:e29-e31.
- Giesel FL, Kratochwil C, Schlittenhardt J, Dendl K, Eiber M, Staudinger F, Kessler L, Fendler WP, Lindner T, Koerber SA, Cardinale J, Sennung D, Roehrich M, Debus J, Sathekge M, Haberkorn U, Calais J, Serfling S, Buck AL. Head-to-head intra-individual comparison of biodistribution and tumor uptake of <sup>68</sup>Ga-FAPI and <sup>18</sup>F-FDG PET/CT in cancer patients. *Eur J Nucl Med Mol Imaging* 2021;48:4377-4385.