Original Article

Mol Imaging Radionucl Ther 2025;34:31-37 *DOI:10.4274/mirt.galenos.2024.50470*

Impact of ^{68}Ga-FAPi PET/CT on Staging or Restaging Digestive System Tumors in Patients with Negative or Equivocal ^{18}F-FDG PET/CT Findings

Negatif veya Şüpheli ^{18}F-FDG PET/BT Bulguları olan Digestif Sistem Tümörlü Olguların Evrelenmesi ve Yeniden Evrelenmesinde ^{68}Ga-FAPi PET/BT'nin rolü

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Abstract

Objectives: This study aimed to evaluate the potential efficacy of ^{68}Ga-fibroblast activation protein inhibitor (FAPi) positron emission tomography/computed tomography (PET/CT) for detecting, staging, and restaging digestive system malignancies that are ^{18}F-fluorodeoxyglucose (^{18}F-FDG) negative or show equivocal ^{18}F-FDG uptake.

Methods: We conducted a prospective analysis of 30 patients with pathologically confirmed primary tumors or metastases of the digestive system. Participants underwent ^{68}Ga-FAPi PET/CT and ^{18}F-FDG PET/CT imaging for staging or restaging purposes within the same week. The efficacy of ^{68}Ga-FAPi PET/CT was assessed by comparing its ability to detect lesions and influence disease staging with that of ^{18}F-FDG PET/CT.

Results: ^{68}Ga-FAPi PET/CT imaging was performed in 30 patients with ^{18}F-FDG-negative or indeterminate lesions. Of the 30 patients, 23 had gastric cancer and 7 had colorectal cancer. Among all patients, histopathological diagnosis of signet ring cell carcinoma was present in 15 (50%) patients. Primary tumor or local recurrence was detected in 19 (63%) patients, lymph node metastasis in 8 (27%) patients, visceral metastasis in 4 (13%) patients, peritoneal metastasis in 14 (47%) patients, and bone metastasis in 3 (10%) patients on ^{68}Ga-FAPi PET/CT images. All patients underwent histopathological confirmation on ^{68}Ga-FAPi PET/CT images. The disease stage was upgraded in 20 patients (67%) after ^{68}Ga-FAPi PET/CT imaging. Of the 20 patients, 12 had no evidence of recurrence or metastasis on ^{18}F-FDG PET/CT.

Conclusion: Based on our study, ^{68}Ga-FAPi PET/CT alters the disease stage in the majority of gastrointestinal malignancies with negative or equivocal ^{18}F-FDG PET/CT findings. ^{68}Ga-FAPi PET/CT appears to be effective in both staging and restaging of gastrointestinal malignancies, such as signet-ring cell carcinomas of the stomach that frequently show low ^{18}F-FDG -avidity.

Keywords: ^{68}Ga-FAPi PET/CT imaging, tumor microenvironment, gastrointestinal malignancies

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Received: 02.10.2024 **Accepted:** 23.12.2024 **Publication Date:** 07.02.2025

Cite this article as: Selçuk NA, Beydağı G, Akçay K, Demirci E, Görmez A, Öven BB, Çelik S, Şen F, Kapar Ö, Kabasakal L. Impact of 68Ga-FAPi PET/CT on staging or restaging digestive system tumors in patients with negative or equivocal 18F-FDG PET/CT findings. Mol Imaging Radionucl Ther. 2025;34:31-37.

Öz

Amaç: Bu çalışmanın amacı, ^{18}F-florodeoksiglukoz (^{18}F-FDG) negatif veya şüpheli ^{18}F-FDG tutulumu gösteren digestif sistem malignitelerinin evrelenmesi ve yeniden evrelenmesi için ^{68}Ga-Fibroblast Aktivasyon Proteini İnhibitörü (FAPi) pozitron emisyon tomografisi/bilgisayarlı tomografinin (PET/BT) potansiyel etkinliğini değerlendirmektir.

Yöntem: Çalışma, patolojik olarak doğrulanmış primer tümörleri veya sindirim sistemi metastazları olan 30 hastada prospektif olarak gerçekleştirildi. Hastalara aynı hafta içerisinde evreleme veya yeniden evreleme amacıyla ^{68}Ga-FAPi PET/BT ve ^{18}F-FDG PET/BT görüntülemesi gerçekleştirildi. ^{68}Ga-FAPi PET/BT'nin etkinliği, lezyonları tespit etme yeteneği ve hastalığın evresini değiştirme potansiyeli açısından ^{18}F-FDG PET/BT ile karşılaştırılarak değerlendirildi.

Bulgular: ^{18}F-FDG-negatif veya şüpheli lezyonlara sahip 30 hastada ^{68}Ga-FAPi PET/BT görüntülemesi gerçekleştirildi. Hastaların 23'ü mide, 7'si kolorektal kanser tanısı almıştı. Tüm hastalar arasında, 15 hastada (%50) patolojik tanı olarak taşlı yüzük hücreli karsinom vardı. ^{68}Ga-FAPi PET/BT görüntülerinde, 19 hastada (%63) primer tümör veya lokal nüks, 8 hastada (%27) lenf nodu metastazı, 4 hastada (%13) visseral metastaz, 14 hastada (%47) peritoneal metastaz ve 3 hastada (%10) kemik metastazı tespit edildi. Tüm hastalarda ^{68}Ga-FAPi PET/BT görüntülemesinin ardından en az bir lezyondan histopatolojik doğrulama yapıldı. ^{68}Ga-FAPi PET/BT görüntülemesinden sonra 20 hastanın (%67) hastalık evresi yükseldi. Bu 20 hastanın 12'sinde ^{18}F-FDG PET/BT'de nüks veya metastaz tespit edilmedi ve ^{18}F-FDG PET/BT tamamen negatifti.

Sonuç: Çalışmamıza göre, ^{68}Ga-FAPi PET/BT, negatif veya şüpheli ^{18}F-FDG PET/BT bulguları olan digestif sistem malignitelerde hastalığın evresini önemli oranda değiştirmektedir. ^{68}Ga-FAPi PET/BT, özellikle mide taşlı yüzük hücreli karsinomları gibi düşük ^{18}F-FDG-afinitesi gösteren digestif sistem malignitelerin evreleme ve yeniden evrelemesinde etkili görünmektedir.

Anahtar kelimeler: ^{68}Ga-FAPi PET/BT görüntüleme, tumor mikroçevre, gastrointestinal malignancies, digestif sistem tümörleri

Introduction

The World Health Organization (WHO) reclassified digestive system tumors in 2020 and emphasized the importance of molecular pathology in clinical practice (1). According to the WHO, approximately 5 million new cases and 3.6 million deaths from digestive system cancers will occur worldwide in 2020, and the incidence of various types of digestive system cancers is gradually increasing (2,3). Most cancers of the digestive tract have a poor prognosis and differ in clinical presentation because of the involvement of multiple organs (4,5). Therefore, early diagnosis and accurate evaluation are of great clinical importance in the treatment of these tumors.

Malignancies in the digestive system are investigated using standard imaging techniques, such as biomarkers, ultrasound, and endoscopic procedures (6,7). However, these techniques have numerous drawbacks, including the inability to accurately determine the stage and metastasis of cancers of the digestive system. ^{18}F-FDG positron emission tomography/computed tomography (PET/CT) is currently used as a standard imaging method in the clinical applications of oncology, for preoperative systemic evaluation, and for determining tumor stage. However, it may be inadequate for imaging certain types of cancer, such as signet-ring cell cancers, mucinous-serous adenocarcinomas, and peritoneal tumors, which have low glucose metabolism (8,9,10). Another important factor affecting the sensitivity to ^{18}F-FDG PET/CT is the size of the tumor (11). In addition, the physiological uptake of ^{18}F-FDG through the gastrointestinal tract may lead to false-positive results, limiting the use of ^{18}F-FDG-PET/CT (12). Therefore, the search for new tumor diagnostic methods has always been an important issue.

PET/CT imaging methods based on fibroblast activation protein (FAP) expressed by cancer-associated fibroblasts (CAFs) in cancer tissues have recently been developed. FAP was first demonstrated in malignant sarcoma cells in 1988 (13). FAP is a type 2 transmembrane serine protease consisting of 760 amino acids with endopeptidase and dipeptidyl peptidase activities (14). It is expressed on the surface of CAFs, which are also found in many tumor tissues. The current FAP inhibitors (FAPi) are peptidomimetic quinoline derivatives that bind to FAP with high affinity and can be used for PET imaging by binding to the ^{68}Ga (15).

CAFs differ from other fibroblasts in that they express higher levels of FAP in the tumor microenvironment. Therefore, FAP is expressed at a very low level in healthy tissues, which allows ^{68}Ga-FAPi PET/CT to provide low background uptake. The low background uptake of ^{68}Ga-FAPi PET/CT provides technical advantages, such as higher tumor detection sensitivity. The requirement for supportive stroma in tumor tissue larger than 1-2 mm in size and the fact that the stromal volume is higher than the cancer cell volume provide an advantage for ^{68}Ga-FAPi PET/CT (16).

Studies comparing ^{18}F-FDG PET/CT with ^{68}Ga-FAPi PET/CT have demonstrated the contribution of ^{68}Ga-FAPi PET/CT in the staging of digestive system tumors (17). However, there is limited information on the success of ^{68}Ga-FAPi PET/CT in ^{18}F-FDG-negative patients. The aim of this study was to detect ^{18}F-FDG-negative or equivocal ^{18}F-F-FDG lesions using ^{68}Ga-FAPi PET/CT and to evaluate the contribution of ^{68}Ga-FAPi PET/CT to the clinical staging or restaging of digestive tumors.

Materials and methods

Patients

This single-center prospective clinical trial was conducted between September 2020 and March 2024, a total of 30 patients with digestive tumors enrolled for ^{18}F-FDG PET/CT with the indication of staging or restaging who met the following inclusion criteria were offered a ^{68}Ga-FAPi PET/CT: (a) low ^{18}F-F-FDG affinity in the metastasis sites of tumor on ^{18}F-FDG PET/CT; (b) an elevation in tumor markers without any focal findings on ^{18}F-FDG PET/CT; (c) presence of an indeterminate finding on ^{18}F-FDG PET/CT; (d) the presence of a lesion in the CT component of ^{18}F-FDG PET/CT that does not exhibit ^{18}F-FDG avidity; (e) patients with stage 1-3 disease diagnosed on ^{18}F-FDG PET/CT. The term indeterminate finding was assigned to areas exhibiting uptake indistinguishable from the background that could not be identified as abnormal.

The exclusion criteria were as follows: (a) aged 18 years; (b) having two or more primary diseases; (c) patients identified as stage 4 on ^{18}F-FDG -PET/CT; (d) pregnant or suspected of being pregnant; (e) inability to remain still during the scan (20-30 minutes).

Informed consent was obtained from all patients. This prospective study was approved by the Yeditepe University Clinical Research Ethics Committee (decision no: 1576, date: 02.03.2022).

Preparation and Quality Control of ^{68}Ga-FAPi

^{68}Ga-DOTA-FAPi-04 was prepared using a modular-based fully automated synthesizer (GRP V4, Scintomics GmbH, Germany). Briefly, the ^{68}Ga obtained from the ^{68}Ge/^{68}Ga generator (iThemba LABS) was sent to the reaction vial containing DOTA-FAPi-04. After completion of the labeling process, the reaction solution was purified with an extraction cartridge and subjected to sterile filtration to prepare the final patient dose. The total synthesis time was 20-25 minutes. The radiochemical purity and radiolabeling efficiency ^{68}Ga-FAPi were determined by combining a radioactive detector with reversed-phase high-pressure liquid chromatography (retinitis pigmentosa-high-performance liquid chromatography). ^{68}Ga-FAPi with a radiochemical purity of ≥ 95% was administered to patients.

^{68}Ga-FAPi and ^{18}F-FDG PET/CT Imaging

Whole-body imaging of ^{68}Ga-FAPi and ^{18}F-FDG PET/CT was performed using a PET scanner (Discovery PET/CT 710, General Electric Medical Systems, Milwaukee, WI, USA) with integrated 64-slice CT, high resolution, time-of-flight function, and LYSO crystal. After intravenous injection of radiopharmaceuticals with an average activity of 240±60 MBq (range: 122-312 MBq), patients were fixed supine on the bed of the PET scanner 60 minutes after injection. CT and PET images were acquired from the vertex region to mid-thigh. ^{68}Ga-FAPi PET/CT was performed within 7 days after ^{18}F-FDG PET/CT.

Evaluation of ^{68}Ga-FAPİ PET/CT and ^{18}F-FDG PET/CT Images

Activity uptake in the tumor was measured by maximum standard uptake value (SUV_{max}) using circular regions of interest drawn around the lesions with focal uptake in transaxial slices and automatically adapted to a 3D voxel area within the 60% iso-contour. All images were reviewed by three senior nuclear medicine physicians who reached consensus for confirmation.

Statistical Analysis

Statistical analysis were performed using SPSS software (version 25.0; IBM Inc.). Descriptive analyses were conducted to assess the characteristics of the patients and their tumors. The mean and standard deviation were calculated for normally distributed measurements, and the median and range were calculated for non-normal measurements. Diagnostic parameters were calculated using a simple matrix method. Using the sample size, 95% Confidence Intervals were also calculated. Pearson's chi-square test was used to compare ^{68}Ga-FAPi PET/CT and ^{18}F-FDG PET/CT. McNemar's test was used to evaluate the staging accuracy of ^{68}Ga-FAPi PET/CT and ^{18}F-FDG PET/CT. A P-value of less than 0.05 was considered statistically significant.

Results

A total of 30 patients were included in the study. Of all patient group for 14 (47%) patients, ^{68}Ga-FAPi PET/CT was performed for restaging because of suspected progressive disease, whereas the 16 (53%) patients with new diagnoses underwent PET imaging for primary staging. The mean age of the patients was 52.7±12.0 (range: 35-77 years). Of the 30 patients, 23 had gastric (77%), and 7 had colorectal (23%). Among all patients, histopathological diagnosis of signet ring cell carcinoma was present in 15 (50%) patients. The demographic characteristics of patients are presented in Table 1.

In half of the patients (n=15), ^{18}F-FDG PET/CT findings were completely negative, while others had equivocal findings. ^{68}Ga-FAPi PET/CT was performed in these patients due to suspicion of potential oversight in staging and evaluation, prompted by clinical progression and/or elevated tumor markers, such as CA 19-9 and CEA. Primary tumor or local

Table 1. Patient characteristics (n=30)	
Characteristic	**Value**
Age, mean ± SD	52.7±12.0
Gender, % (n)	
Female	57% (17)
Male	43% (13)
Primary tumor sites, % (n)	
Gastric	77% (23)
Signet-ring cell	47% (14)
Colorectal	23% (7)
Signet-ring cell	3% (1)
Metastasis sites on ^{68}Ga-FAPi PET/CT, % (n)	
Primary location/local recurrence	63% (19)
Lymph node	27% (8)
Visceral metastasis	13% (4)
Peritoneal metastasis	47% (14)
Bone	10% (3)
Metastasis sites on ^{18}F-FDG PET/CT, % (n)	
Primary location/local recurrence	43% (13)
Lymph node	10% (3)
Visceral metastasis	-
Peritoneal metastasis	-
Bone	-
Indication for imaging, % (n)	
Staging	53% (16)
Restaging	47% (14)

SD: Standard deviation, PET/CT: Positron emission tomography/computed tomography

recurrence was detected in 19 (63%) patients, lymph node metastasis in 8 (27%) patients, visceral metastasis in 4 (13%) patients, peritoneal metastasis in 14 (47%) patients, and bone metastasis in 3 (10%) patients on ^{68}Ga-FAPi PET/CT images. For ^{18}F-FDG PET/CT, primary tumor or local recurrence was detected in 13 (43%) patients and lymph node metastasis in 3 (10%) patients. Otherwise, visceral, peritoneal, and bone metastases could not be detected on ^{18}F-FDG PET/CT (Table 1). ^{68}Ga-FAPi PET/CT demonstrated a higher detection rate for primary lesions at 96%, compared to 71% with ^{18}F-FDG PET/CT.

At least one lesion in all patients was confirmed histopathologically after ^{68}Ga-FAPi PET/CT imaging. In one patient, although peritoneal fluid sampling was negative, ^{68}Ga-FAPi PET/CT revealed signs consistent with peritoneal carcinomatosis. Since the findings of peritoneal carcinomatosis were confirmed radiologically in the patient's subsequent follow-up visits, clinical follow-up confirmed that the cytology result was false negative. In one patient, despite the presence of a primary tumor on CT and/or magnetic resonance imaging (MRI), both ^{68}Ga-FAPi and ^{18}F-FDG PET/CT findings were negative.

Although no findings were detected in 15 patients on ^{18}F-FDG PET/CT, ^{68}Ga-FAPi PET/CT identified 2 patients (7%) as stage 2, 1 patient (3%) as stage 3, and 9 patients (30%) as stage 4 (Table 2). While there was clinical suspicion in 2 patients, no evidence of recurrence or metastasis was found in ^{18}F-FDG and ^{68}Ga-FAPi PET/CT as well as CT and/or MRI. A patient diagnosed with signet ring cell carcinoma of the stomach who presented for staging showed false-negative results on both ^{18}F-FDG and ^{68}Ga-FAPi PET/CT. We found that 12 of 15 patients with negative ^{18}F-FDG PET/CT

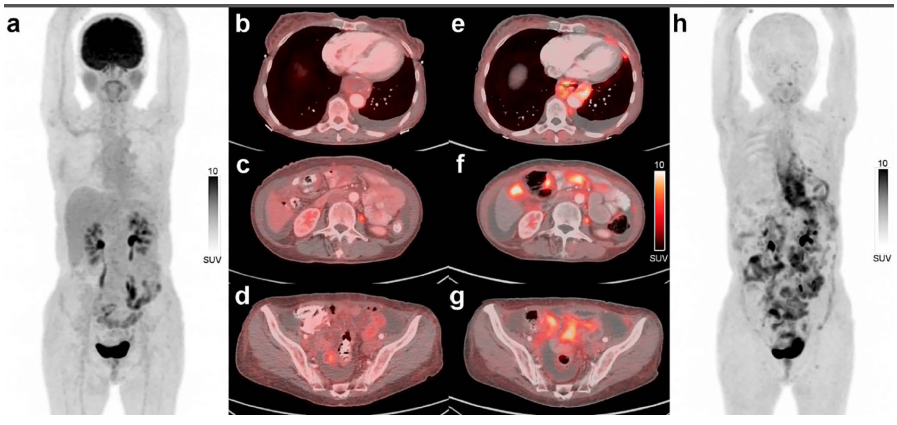

Figure 1. A 63-year-old female patient was diagnosed with gastric adenocarcinoma. Subsequent abdominal magnetic resonance imaging revealed an increase in peritoneal effusion. ^{18}F-FDG-PET/CT did not reveal any malignant lesions that would explain the effusion (a-d). In contrast, the ^{68}Ga-FAPi PET/CT scan revealed widespread peritoneal metastases. These findings observed on the ^{68}Ga -FAPi PET/CT scan (e-h) were later confirmed by histopathologic examination.

PET/CT: Positron emission tomography/computed tomography, SUV: Standard uptake value, FAPİ: Fibroblast activation protein inhibitor

results (80%) experienced an increase in disease stage after undergoing ^{68}Ga-FAPi PET/CT. Additionally, 8 of 15 patients with initially staged 1-3 on ^{18}F-FDG PET/CT (53%) showed an elevation in their primary disease stage when assessed with ^{68}GaFAPi PET/CT. Notably, a discrepancy in staging between ^{68}Ga-FAPi and ^{18}F-FDG PET/CT was observed in 67% of patients, leading to significant alterations in their oncologic treatment plans (Table 2). Our findings indicate that staging with ^{68}Ga-FAPi PET/CT is statistically more effective than ^{18}F-FDG PET/CT (Pearson chi-square value of 27.18; p=0.007).

The mean SUV_{max} values of the primary tumors in gastric and colorectal cancer were 14.8±5.8 (range: 5.5-21.8) and 9.5±4.2 (range: 5.3-13.6), respectively. Notably, all peritoneal metastases were negative on ^{18}F-FDG PET/CT, whereas they exhibited significant uptake on ^{68}Ga-FAPi PET/CT, with a mean SUV_{max} value of 10.5±4.9 (range: 3.6-21.8) (Figure 2).

A histopathological diagnosis of signet ring cell cancer was made in 15 patients (50%). Among these, 14 patients (47%) had gastric signet ring cell cancer, and 1 patient (3%) had colonic signet ring cell malignancy (Table 1). In patients with signet ring cell cancer, 45% of primary lesions (5/11) and 80% of lymph node metastases (4/5) were negative on ^{18}F-FDG PET/CT, whereas all these lesions demonstrated increased uptake on ^{68}Ga-FAPi PET/CT. Additionally, peritoneal metastases were identified in 4 patients using ^{68}Ga-FAPi PET/CT, whereas these lesions were negative on ^{18}F-FDG PET/CT. The mean SUV_{max} for primary lesions was 13.4±5.2 (range: 5.5-17.0) on ^{68}Ga-FAPi PET/CT and 6.8±2.1 (range: 3.8-10.1) on ^{18}F-FDG PET/CT. For peritoneal metastases, the mean SUV_{max} on ^{68}Ga-FAPi PET/CT was 10.6±3.6 (range: 5.9-14.5) (Figure 2).

Discussion

In this study, ^{18}F-FDG-positive cases were excluded because they were already well documented. Our study highlights the diagnostic superiority of ^{68}Ga-FAPi PET/CT over ^{18}F-FDG PET/CT in staging digestive system malignancies, particularly when ^{18}F-FDG PET/CT results are equivocal or negative. The pivotal role of ^{68}Ga-FAPi PET/CT is attributed to its targeted imaging of CAFs, which are prominently expressed in the stromal components of gastrointestinal tumors. This expression pattern significantly enhances tumor detection sensitivity, highlighting the critical role of stromal involvement in gastrointestinal cancer pathology.

^{18}F-FDG PET/CT and CT demonstrate suboptimal lesion detectability, primarily due to the mucinous types of gastric cancer and signet ring cell carcinoma, which constitute the majority of cases in this study and typically manifest as small, diffusely growing patterns characterized by a scarcity of tumor cells (12). Some lesions exhibit low expression of tumor glucose transporters but high levels of dephosphorylation, resulting in lessened accumulation of ^{18}F-FDG PET/CT (18,19). Furthermore, in contrast to the relatively high physiological uptake of ^{18}F-FDG PET/CT in the gastrointestinal tract, the low background uptake of ^{68}Ga-FAPi PET/CT in the abdominopelvic cavity contributes to the superior performance of ^{68}Ga-FAPi PET/CT (20,21).

As with the clinical presentation of gastrointestinal cancers, imaging characteristics and workflows can exhibit substantial variability, resulting in unequal diagnostic efficacy among different imaging modalities (22). The findings of this study indicate that ^{68}Ga-FAPi PET/CT holds considerable promise for detecting disease extent in gastrointestinal cancer, a conclusion that is consistent with other published reports (23,24,25). Many other studies have shown that ^{68}Ga-FAPi PET/CT is superior to other modalities, such as MRI, CT, and ^{18}F-FDG PET/CT, in digestive tract malignancies. However, very few studies have investigated the effect of ^{68}Ga-FAPi PET/CT. The current study is one of the few studies that emphasizes stage changes after ^{68}Ga-FAPi PET/CT performed for staging or restaging of gastrointestinal tumors correlated with biopsy. The results demonstrated that ^{68}Ga-FAPi PET/CT changed disease staging in approximately 67% of cases with ^{18}F-FDG-negative or equivocal lesions. This is a significant finding for accurate staging and the application of correct treatment algorithms.

In our study, all patients had histopathological confirmation after ^{68}Ga-FAPi PET/CT images. ^{68}Ga-FAPi PET/CT findings of one patient were compatible with peritoneal carcinomatosis, although the peritoneal fluid sample was negative. However, on clinical radiological follow-up, these

Table 2. Stage changes according to both ^{18}F-FDG PET/CT and ^{68}Ga-FAPi PET/CT

Staging/re-staging (n=30)	Negative	Stage 1	Stage 2	Stage 3	Stage 4	Equal	Upstage
Staging with ^{18}F-FDG-PET/CT	15 (50%)	5 (17%)	7 (23%)	3 (10%)	-	10 (33%)	-
Staging with ^{68}Ga-FAPi PET/CT	3 (10%)*	3 (10%)	4 (13%)	5 (17%)	15 (50%)	10 (33%)	20 (67%)

*A patient diagnosed with signet ring cell carcinoma of the stomach who presented for staging showed false-negative results on both [^{18}F]FDG PET/CT and ^{68}Ga-FAPi PET/CT. In the other two patients who had negative ^{68}Ga-FAPi PET/CT results, no lesions consistent with malignancy were detected by other radiological methods or during follow-up, indicating true negative resultsPET/CT: Positron emission tomography/computed tomography, FAPi: Fibroblast activation protein inhibitor

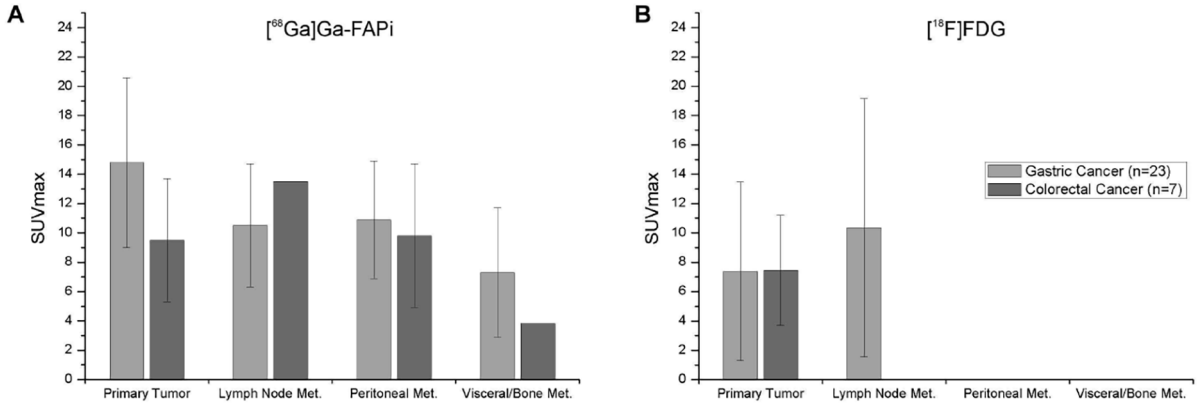

Figure 2. SUV_{max} values from ^{68}Ga-FAPi PET/CT and ^{18}F-FDG PET/CT, categorized by primary malignancy diagnosis and metastasis location, are presented
SUV_{max}: Maximum standard uptake value, PET/CT: Positron emission tomography/computed tomography

findings confirmed that the pathology result was false negative. In another patient, despite the presence of a tumor, the ^{68}Ga-FAPi and ^{18}F-FDG PET/CT findings were negative.

^{68}Ga-FAPi PET/CT showed more peritoneal implants and lymph node metastases than ^{18}F-FDG PET/CT, which led to upstaging based on the tumor-node-metastasis system. In addition, ^{68}Ga-FAPi PET/CT detected more primary lesions than ^{18}F-FDG PET/CT in individuals diagnosed with digestive system malignancy, with detection rates of 96% and 71%, respectively. These results are consistent with literature (17,21). Recent research has also highlighted the promising potential of ^{68}Ga-FAPi PET/CT in guiding the clinical management of pancreatic and gastric cancer (26,27). Koerber et al. (25) have shown that ^{68}Ga-FAPi PET/CT resulted in changes in treatment classified as high, intermediate, and low in 19%, 33%, and 29% of patients, respectively. In our study, we observed that 80% (12/15) of patients with no detectable uptake in the primary tumor and/or metastasis sites on ^{18}F-FDG PET/CT showed increased uptake on ^{68}Ga-FAPi PET/CT. In addition, we demonstrated that of the patients identified by ^{18}F-FDG PET/CT at any stage (stage 1, 2, 3), 53% showed an increase in the primary disease stage when examined by ^{68}Ga-FAPi PET/CT. In summary, 67% of patients showed a difference in staging between ^{68}Ga-FAPi PET/CT and ^{18}F-FDG PET/CT, leading to significant changes in their oncologic treatment strategies.

In agreement with the literature, we found a higher SUV_{max} on ^{68}Ga-FAPi PET/CT than on ^{18}F-FDG PET/CT in primary tumors (17). However, it is worth noting that we did not include patients with high ^{18}F-FDG uptake in our study. The lesions of the patients in our study had either no ^{18}F-FDG uptake or very low uptake outside the primary lesion, which could not be distinguished from the background. Therefore, our patients were expected to have a higher SUV_{max} on ^{68}Ga-FAPi PET/CT. In our study, higher uptake was observed in primary lesions of gastric cancer (SUV_{max}: 14.8) than in colorectal cancer (SUV_{max}: 9.5) on ^{68}Ga-FAPi PET/CT.

The role of ^{18}F-FDG-PET/CT in signet ring cell carcinoma is of limited diagnostic value in terms of both primary lesions and metastases. Peritoneal metastases are often overlooked in ^{18}F-FDG PET/CT. This is because these tumors are mucin-rich, do not consume glucose, and express low levels of glucose transporters (28,29). In addition, the peritoneal implants are usually small and can be missed even with diagnostic tools such as CT and/or MRI. In this context, previous studies have shown that ^{68}Ga-FAPi PET/CT is extremely sensitive in signet ring cell carcinomas (30,31). In our study, 45% of primary lesions (5/11) and 80% of lymph node metastases (4/5) of patients with signet ring cell carcinoma were negative on ^{18}F-FDG PET/CT. Of these patients, 4 had peritoneal metastasis, which could not be detected by ^{18}F-FDG PET/CT. The average SUV_{max} was 13.4 for the primary tumor and 10.6 for the peritoneal metastasis.

Conclusion

In conclusion, ^{68}Ga-FAPi PET/CT is superior for staging and restaging indications in digestive system tumors, especially in patients with ^{18}F-FDG-negative or equivocal lesions, such as signet ring cell carcinoma. The strength of our study lies in its ability to stage cases in which ^{18}F-FDG PET/CT fails to resolve using ^{68}Ga-FAPi PET/CT and in corroborating these findings with biopsy results in all patients. The ^{68}Ga-FAPi

PET/CT modality is a promising imaging modality for the diagnosis and management of FDG-negative GI tumors. The use of this method has the potential to introduce new applications for tumor staging or restaging. Future studies should explore the longitudinal impact of ^{68}Ga-FAPi PET/CT-guided treatment decisions on patient outcomes, potentially establishing this modality as a standard component of gastrointestinal cancer management protocols.

Ethics

Ethics Committee Approval: This prospective study was approved by the Yeditepe University Clinical Research Ethics Committee (decision no: 1576, date: 02.03.2022).

Informed Consent: Informed consent was obtained from all patients.

Footnotes

Authorship Contributions

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

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

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

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