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The role of ^{68}Ga-FAPi PET/CT in Staging and Restaging of Breast Cancer Subtypes with Limited ^{18}F-FDG Uptake

Düşük ^{18}F-FDG Tutulumu Gösteren Meme Kanseri Alt Tiplerinde ^{68}Ga-FAPi PET/BT'nin Evreleme ve Yeniden Evrelemedeki Rolü

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Abstract

Objectives: Breast cancer is highly heterogeneous, and certain histopathologic subtypes—particularly invasive lobular carcinoma—exhibit low glucose metabolism that limits ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) performance. Fibroblast activation protein inhibitor (FAPi) imaging with Gallium-68 (^{68}Ga)-FAPi PET/CT has emerged as a promising alternative for such tumors. The aim of this study was to evaluate the efficacy of ^{68}Ga-FAPi PET/CT in staging, restaging, and recurrence detection of breast cancer, with emphasis on subtypes for which ^{18}F-FDG PET/CT has low sensitivity.

Methods: Twenty-nine women with pathologically confirmed breast cancer (mean age 57.7±11.6 years) were prospectively enrolled. Histopathology (available in 24 patients) showed lobular carcinoma in 16, ductal carcinoma in 6, signet ring cell carcinoma in 1, and mucinous carcinoma in 1. All underwent both ^{68}Ga-FAPi and ^{18}F-FDG PET/CT within one week for staging or restaging. Maximum standardized uptake values (SUV_{max}) of primary tumors and metastases were recorded for both tracers and compared using paired t-tests.

Results: In 7/29 patients (24.1%), neither ^{18}F-FDG PET/CT nor ^{68}Ga-FAPi PET/CT detected pathological findings. Disease stage increased in 13/29 (44.8%) after ^{68}Ga-FAPi PET/CT, including 10 patients with no pathologic findings on ^{18}F-FDG PET/CT; nine were upstaged to stage 4 and one to stage 3. Additionally, one patient progressed from stage 1 to 2, one from 2 to 3, and another from 3 to 4. Among patients with lobular carcinoma, 8/16 (50%) were upstaged with ^{68}Ga-FAPi PET/CT. Detection of nodal and distant metastases in lobular carcinoma was higher with ^{68}Ga-FAPi than ^{18}F-FDG. ^{68}Ga-FAPi PET/CT also demonstrated higher SUV_{max} in primary lesions and metastases ($p<0.05$).

Conclusion: ^{68}Ga-FAPi PET/CT provides a significant advantage for staging and restaging breast cancer—especially lobular carcinoma and other low ^{18}F-FDG-avid subtypes—supporting its potential role in clinical decision-making and treatment planning.

Keywords: ^{68}Ga-FAPi PET/CT, invasive lobular carcinoma, breast cancer, staging, restaging

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Öz

Amaç: Meme kanseri oldukça heterojendir ve bazı histopatolojik alt tipler—özellikle invaziv lobüler karsinom—düşük glukoz metabolizması göstererek ^{18}F-florodeoksiglukoz pozitron emisyon tomografisi/bilgisayarlı tomografi (^{18}F-FDG PET/BT) performansını sınırlandırmaktadır. Galyum-68 (^{68}Ga)-FAPi PET/BT ile fibroblast aktivasyon protein inhibitörü (FAPi) görüntüleme, bu tür tümörler için umut vadeden bir alternatif olarak ortaya çıkmıştır. Bu çalışmanın amacı, meme kanserinin evrelenmesi, yeniden evrelenmesi ve nüksünün saptanmasında ^{68}Ga-FAPi PET/BT'nin etkinliğini değerlendirmek ve özellikle ^{18}F-FDG PET/BT'nin duyarlılığının düşük olduğu alt tiplere odaklanmaktır.

Yöntemler: Patolojik olarak meme kanseri tanısı doğrulanmış 29 kadın hasta prospektif olarak çalışmaya dahil edildi. Hastaların ortalama yaşı 57,7±11,6 yıl idi. Histopatolojik değerlendirme 24 hastada mevcut olup, 16 hastada lobüler karsinom, 6 hastada duktal karsinom, 1 hastada taşlı yüzük hücreli karsinom ve 1 hastada müsinöz karsinom saptandı. Tüm hastalara evreleme veya yeniden evreleme amacıyla bir hafta içinde ^{68}Ga-FAPi ve ^{18}F-FDG PET/BT uygulandı. Primer tümörlerin ve metastazların maksimum standardize tutulum değerleri (SUV_{maks}) her iki izleyici için kaydedildi ve eşleştirilmiş t-testleri kullanılarak karşılaştırıldı.

Bulgular: Yirmi dokuz hastanın 7'sinde (%24,1) nüks ve metastaz saptanmadı. ^{68}Ga-FAPi PET/BT sonrasında 29 hastanın 13'ünde (%44,8) hastalık evresi yükseldi; bunların 10'unda ^{18}F-FDG PET/BT'de patolojik bulgu yoktu. Bu hastaların dokuzu evre 4'e, biri ise evre 3'e yükseltildi. Ayrıca bir hastada evre 1'den 2'ye, bir hastada evre 2'den 3'e ve bir hastada evre 3'ten 4'e evre artışı saptandı. Lobüler karsinomlu hastalar arasında 16 hastanın 8'inde (%50) ^{68}Ga-FAPi PET/BT ile evre yükseldi. Lobüler karsinomda nodal ve uzak metastazların saptanması ^{68}Ga-FAPi ile ^{18}F-FDG'ye kıyasla daha yüksekti. Ayrıca ^{68}Ga-FAPi PET/BT, primer lezyonlarda ve metastazlarda daha yüksek SUV_{maks} değerleri gösterdi ($p<0,05$).

Sonuç: ^{68}Ga-FAPi PET/BT, meme kanserinin evrelenmesi ve yeniden evrelenmesinde—özellikle lobüler karsinom ve düşük ^{18}F-FDG tutulumu gösteren diğer alt tiplerde—önemli bir avantaj sağlamaktadır. Bu bulgular, ^{68}Ga-FAPi PET/BT'nin klinik karar verme ve tedavi planlamasında potansiyel bir role sahip olduğunu desteklemektedir.

Anahtar Kelimeler: ^{68}Ga-FAPi PET/BT, invaziv lobüler karsinom, meme kanseri, evreleme, yeniden evreleme

Introduction

Breast cancer is the most common malignancy among women and represents a significant public health issue due to its high incidence and mortality rates (1). This heterogeneous disease exhibits considerable variability in biological behavior, histopathological characteristics, and treatment response (2). Accurate staging and restaging are critical components in the diagnosis and management of breast cancer. ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) is a key modality in breast cancer management, contributing to diagnosis, staging, restaging, treatment assessment, and prognostic evaluation. While ^{18}F-FDG PET/CT demonstrates high diagnostic accuracy, particularly for metastases, its sensitivity is limited for detecting small tumors (<1 cm), peritoneal micrometastases, and lymph node metastases (3). Moreover, its diagnostic efficacy is limited in certain histopathological subtypes, such as lobular carcinoma, which typically demonstrates low metabolic activity (4). These limitations underscores the need for more sensitive and effective imaging modalities in these patients. Studies have demonstrated that PET/CT performed with Gallium-68 (^{68}Ga)-labeled fibroblast activation protein inhibitor (FAPi) a new theranostic candidate, provides superior sensitivity and specificity in detecting primary and metastatic breast cancer lesions compared to ^{18}F-FDG PET/CT, offering improved diagnostic accuracy and staging precision (5,6).

FAPi targets fibroblast activation protein, which is highly expressed in the tumor stroma, providing effective imaging even in cases with low ^{18}F-FDG uptake. ^{68}Ga-FAPi PET/CT has been shown to outperform conventional methods in detecting primary tumors and metastatic lesions with low ^{18}F-FDG affinity. In particular, it is thought to offer enhanced sensitivity for histological subtypes such as lobular carcinoma, for identifying lymph node metastases and distant metastases.

The aim of this study was to evaluate the efficacy of ^{68}Ga-FAPi PET/CT in staging, restaging, and recurrence detection of breast cancer patients, particularly in tumors such as lobular carcinoma, in which the diagnostic value of ^{18}F-FDG is limited.

Materials and Methods

Patients

This single-center prospective clinical study enrolled 29 female patients (mean age 57.7±11.6 years) with pathologically confirmed breast cancer. All patients underwent both ^{18}F-FDG and ^{68}Ga-FAPi PET/CT imaging within one week for staging or restaging. The inclusion criteria were as follows: I) histologically confirmed invasive breast carcinoma (primary staging or restaging), II) a prior ^{18}F-FDG PET/CT performed within the clinical work-up, III) ^{18}F-FDG PET/CT that showed: a) no abnormal ^{18}F-FDG uptake (^{18}F-FDG-negative), b) low-grade, equivocal, or clinically non-explanatory ^{18}F-FDG uptake, insufficient to account for clinical suspicion, rising tumor markers, or abnormalities on other imaging modalities, IV) a clinical expectation that ^{68}Ga-FAPi PET/CT might clarify disease extent or reveal additional metastatic sites not visualized on ^{18}F-FDG PET/CT, V) age ≥18 years and ECOG performance status <3.

Exclusion criteria were: I) ^{18}F-FDG PET/CT demonstrating clear and disseminated ^{18}F-FDG positive metastatic (stage IV) disease, for which ^{68}Ga-FAPi PET/CT was not expected to provide further diagnostic benefit and would only add unnecessary radiation exposure, II) ^{18}F-FDG-avid primary breast cancers in which staging was already conclusive based on ^{18}F-FDG PET/CT findings, III) history of a second primary malignancy.

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

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

^{68}Ga-DOTA-FAPi-46 (used in 19 patients) and ^{68}Ga-DOTA-FAP-2286 (used in 10 patients) were prepared using a modular-based fully automated synthesizer (GRP V4, Scintomics GmbH, Germany). The use of two FAP-targeting ligands was related to radiopharmaceutical availability and logistical changes in the local radiochemistry workflow. The imaging acquisition protocol, scanner, reconstruction parameters, and interpretation criteria were kept consistent throughout the study. The study was not designed as a head-to-head comparison of these two ligands. Briefly, the ^{68}Ga obtained from the ^{68}Ge/^{68}Ga generator (iThemba LABS) was sent to the reaction vial containing DOTA-FAPi-46 or DOTA-FAP-2286. After completion of the labelling process, the reaction solution was purified using an extraction cartridge and then subjected to sterile filtration to prepare the final patient dose. The total synthesis time was 25 minutes. The radiochemical purity and radiolabeling efficiency of ^{68}Ga-DOTA-FAPi-46 and ^{68}Ga-DOTA-FAP-2286 were determined by combining a radioactive detector with reversed-phase high-pressure liquid chromatography. ^{68}Ga-FAPi with a radiochemical purity of ≥95% was administered to patients.

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

Whole-body ^{18}F-FDG PET/CT and ^{68}Ga-FAPi PET/CT scans were performed using a PET scanner (Discovery PET/CT 710, General Electric Medical Systems, Milwaukee, WI, USA) with high resolution, time-of-flight function, and LYSO crystal and integrated with 64-slice CT scanner. The average activity of ^{18}F-FDG was 425±64 MBq (range: 340-548 MBq) [11.5±1.7 mCi (range: 9.2-14.8 mCi)], ^{68}Ga-FAPi was 243±57 MBq (range: 122-312 MBq) [6.6±1.5 mCi (range: 3.3-8.4 mCi)]. Patients were positioned supine on the PET scanner bed 60 minutes after intravenous injection of radiopharmaceuticals. CT and PET images were acquired from the vertex region to mid-thigh. ^{68}Ga-FAPi PET/CT scans were performed within 7 days after ^{18}F-FDG PET/CT.

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

The presence of primary breast lesions and metastatic lesions, as well as changes in disease stage, on ^{18}F-FDG and ^{68}Ga-FAPi PET/CT scans were noted. Uptake in the tumor was measured by maximum standardized 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.

The final disease status of PET-positive and PET-negative findings was determined using a predefined composite reference standard. Histopathological confirmation was used whenever clinically available. For lesions without histopathological confirmation, a ^{68}Ga-FAPi PET/CT-positive finding was accepted as true-positive only when all of the following criteria were fulfilled: anatomical/radiological correlation on diagnostic contrast-enhanced CT and/or magnetic resonance imaging (MRI); compatible findings on follow-up or correlative imaging performed at least 6 months after the index PET/CT, including ^{68}Ga-FAPi PET/CT, ^{18}F-FDG PET/CT, CT, and/or MRI; and confirmation by multidisciplinary tumor board assessment. Follow-up imaging findings were interpreted together with the clinical course and treatment status. PET findings were not used as the sole reference standard. All images were reviewed by consensus by three senior nuclear medicine physicians for confirmation.

For lesion-site-based detection analysis, the number of patients positive at each metastatic site was determined using a composite reference standard derived from all available patient data. This included histopathological confirmation when available, contrast-enhanced CT, MRI when clinically performed, other conventional imaging findings, follow-up imaging, tumor marker evolution, clinical course, and multidisciplinary consensus. Therefore, detection rates were not calculated solely from ^{18}F-FDG PET/CT and ^{68}Ga-FAPi PET/CT findings, but were correlated with the parameters mentioned above.

Statistical Analysis

Statistical analyses 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 for non-normally distributed measurements. The SUV_{max} of the primary tumor areas, axillary lymph nodes and metastases on the ^{18}F-FDG and ^{68}Ga-FAPi PET/CT images were recorded and statistically compared using the paired t-test. Chi-square test was used to evaluate the staging accuracy of ^{18}F-FDG PET/CT

and ^{68}Ga-FAPi PET/CT. A p value of less than 0.05 was considered statistically significant.

Results

Pathology reports from previous surgeries/biopsies were available for all patients; however, a documented histopathological subtype was available in 24 patients: lobular carcinoma in 16, ductal carcinoma in 6, signet-ring cell carcinoma in 1, and mucinous carcinoma in 1. In 5 patients, the pathology reports did not include a documented histopathological subtype. Thirteen patients (44.8%) were enrolled for staging purposes, and 16 (55.2%) were enrolled for restaging purposes.

^{68}Ga-FAPi PET/CT demonstrated positive positive findings in 22 patients, whereas ^{18}F-FDG PET/CT revealed positive findings in only 12 patients. In seven patients (24.1%), neither ^{18}F-FDG PET/CT nor ^{68}Ga-FAPi PET/CT detected any pathological findings. Among these patients, two were undergoing initial staging, while five were undergoing restaging. No pathological findings were detected in these patients by other imaging modalities or during follow-up.

On ^{68}Ga-FAPi PET/CT, the most frequently detected metastatic site was bone (41.4%, n=12), followed by axillary lymph nodes (34.5%, n=10), primary tumor lesions (34.5%, n=10), distant lymph nodes (24.1%, n=7), visceral metastases (20.7%, n=6), and peritoneal metastases (17.2%, n=5) (Table 1).

The detection of lymph nodes and distant metastases was higher with ^{68}Ga-FAPi PET/CT than with ^{18}F-FDG PET/CT (Table 2). Furthermore, ^{68}Ga-FAPi PET/CT showed a higher SUV_{max} in primary tumor foci and metastases ($p<0.05$) (Table 3). The mean SUV_{max} of primary lesions was significantly higher on ^{68}Ga-FAPi PET/CT than on ^{18}F-FDG PET/CT, 15.08±4.30 vs. 2.30±1.98, respectively, $p<0.001$. Axillary lymph node metastases also demonstrated significantly higher uptake on ^{68}Ga-FAPi PET/CT, with SUV_{max} of 23.54±16.46 compared with 5.30±11.22 on ^{18}F-FDG PET/CT, $p=0.032$. For distant lymph node, visceral, peritoneal, and bone metastases, no ^{18}F-FDG SUV_{max} comparison was possible because these sites were not detected on ^{18}F-FDG PET/CT in our cohort. The mean SUV_{max} on ^{68}Ga-FAPi PET/CT were 14.07±6.50 for distant lymph node metastases, 10.66±4.50 for visceral metastases, 9.94±2.15 for peritoneal metastases, and 16.32±9.31 for bone metastases.

In 5 out of 13 patients (38.4%) referred for staging, the disease stage was higher on ^{68}Ga-FAPi PET/CT compared to ^{18}F-FDG PET/CT. Following ^{68}Ga-FAPi PET/CT, one patient was upstaged from stage 1 to stage 2, one from stage 2 to stage 3, and another from stage 3 to stage 4 according to the American Joint Committee on Cancer 8th edition. ^{68}Ga-FAPi PET/CT also revealed stage 4 disease in two patients where no findings were observed on ^{18}F-FDG PET/CT. All patients who were upstaged to stage 4 (a total of 3 patients) were found to have bone

Table 1. Patient characteristics (n=29)

Characteristic	Value
Age, mean ± SD	57.7±11.6
Gender	
Female	29
Male	-
Histopathological subtype	Available in 24 patients
Lobular carcinoma	16
Ductal carcinoma	6
Signet ring cell carcinoma	1
Mucinous carcinoma	1
Primary surgery before scanning % (n)	
Yes	62.1% (18/29)
No	37.9% (11/29)
Lesion localization detected on ^{68}Ga-FAPi PET/CT, % (n)	
Primary lesion	34.5% (10/29)
Axillary lymph node metastasis	34.5% (10/29)
Distant lymph node metastasis	24.1% (7/29)
Visceral metastasis	20.7% (6/29)
Peritoneal metastasis	17.2% (5/29)
Bone metastasis	41.4% (12/29)
Indication for imaging, % (n)	
Staging	44.8% (13/29)
Restaging	55.2% (16/29)

SD: Standard deviation, ^{68}Ga-FAPi PET/CT: Gallium-68 fibroblast activation protein inhibitor positron emission tomography/computed tomography

Table 2. Lesion detection rates for ^{18}F-FDG and ^{68}Ga-FAPi PET/CT scans

Lesion site	Number of positive patients*	^{18}F-FDG	^{68}Ga-FAPi
Primary lesion	11	8 (72.7%)	10 (90.9%)
Axillary LN metastasis	10	6 (60%)	10 (100%)
Distant LN metastasis	7	0	7 (100%)
Visceral metastasis	7	0	6 (85.7%)
Peritoneal metastasis	5	0	5 (100%)
Bone metastasis	12	0	12 (100%)

*: Number of positive lesion-sites were determined based on all known information about the patients, ^{18}F-FDG: ^{18}F-fluorodeoxyglucose, ^{68}Ga-FAPi PET/CT: Gallium-68 fibroblast activation protein inhibitor positron emission tomography/computed tomography, LN: Lymph nodes

Table 3. SUV_{max} of ^{18}F-FDG PET/CT and ^{68}Ga-FAPi PET/CT according to lesion location

Lesion site	^{18}F-FDG	^{68}Ga-FAPi	p
Primary lesion	2.30±1.98	15.08±4.30	<0.001
Axillary LN metastasis	5.30±11.22	23.54±16.46	0.032
Distant LN metastasis	N/A	14.07±6.50	-
Visceral metastasis	N/A	10.66±4.50	-
Peritoneal metastasis	N/A	9.94±2.15	-
Bone metastasis	N/A	16.32±9.31	-

^{68}Ga-FAPi PET/CT: Gallium-68 fibroblast activation protein inhibitor positron emission tomography/computed tomography, LN: Lymph nodes, ^{18}F-FDG: ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography, SUV_{max}: Maximum standardized uptake value

metastases, as detected by ^{68}Ga-FAPi PET/CT, highlighting its superior sensitivity in identifying metastatic lesions compared to ^{18}F-FDG PET/CT.

Of the 21 patients referred to our clinic for restaging due to elevated tumor markers or suspected recurrence on conventional imaging during follow-up, ^{18}F-FDG PET identified recurrence in 8 patients, while ^{68}Ga-FAPi PET/CT detected recurrence in 16 patients (Figure 1). In 5 patients, no lesion was identified by either modality.

False-negative findings were observed in two patients: one had no uptake in the primary tumor, and the other had mucinous carcinoma with lung metastasis; these lesions were undetected by both ^{18}F-FDG PET/CT and ^{68}Ga-FAPi PET/CT.

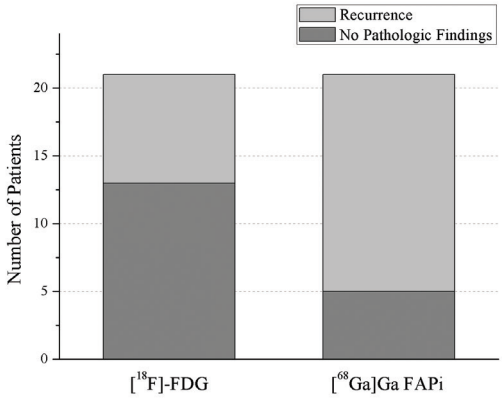

Figure 1. Recurrence detection numbers with ^{18}F-FDG and ^{68}Ga-FAPi PET/CT (n=21) in the restaging cohort. Among 16 patients referred for restaging, ^{18}F-FDG PET/CT identified recurrence in 3 patients, whereas ^{68}Ga-FAPi PET/CT detected recurrence in 11 patients. In 5 patients, no pathological finding was detected with either modality.
^{68}Ga-FAPi PET/CT: Gallium-68-fibroblast activation protein inhibitor positron emission/computed tomography, ^{18}F-FDG: ^{18}F-fluorodeoxyglucose

Discussion

Although ^{18}F-FDG PET/CT is a highly valuable method for the diagnosis and staging of breast cancer, it may yield negative findings in several histopathological subtypes of breast tumors, particularly in invasive lobular carcinoma and certain subtypes of ductal carcinoma (7). In such cases, both the diagnosis of the primary tumor and the staging of the disease can be compromised. ^{68}Ga-FAPi PET/CT stands out due to its low background uptake and high uptake in these tumor types (8). Recent studies have found that ^{68}Ga-FAPi PET/CT demonstrates generally high tumor uptake in breast cancer and shows a higher metastasis detection rate compared with ^{18}F-FDG PET/CT, particularly for bone and peritoneal metastases (9,10).

In our study, the lesion detection capabilities of both modalities across different regions are presented in Table 2. The reported detection rates were calculated using this composite reference standard. Accordingly, distant lymph node metastases were present in 7 patients and were detected by ^{68}Ga-FAPi PET/CT in all 7 patients. Visceral metastases were present in 7 patients and were detected by ^{68}Ga-FAPi PET/CT in 6 patients. Peritoneal metastases were present in 5 patients and were detected by ^{68}Ga-FAPi PET/CT in all 5 patients. These findings suggest that ^{68}Ga-FAPi PET/CT may provide additional diagnostic value in lesion sites that are often difficult to detect with ^{18}F-FDG PET/CT in low-^{18}F-FDG-avidity breast cancer subtypes. According to these results, ^{68}Ga-FAPi was found to be highly effective, with detection rates of 100% for distant lymph nodes, 85.7% for visceral organ metastases, and 100% for peritoneal metastases. In contrast, ^{18}F-FDG PET/CT was unable to detect these lesions. In the literature, the detection rates of ^{18}F-FDG PET/CT for lobular breast carcinoma have been reported to vary between 50% and 90% (11). However, in our study, these rates were significantly lower. The key point emphasized in this study is that this group of tumors, for which ^{18}F-FDG has limited diagnostic value and often fails to detect, can be visualized with the novel molecular agent ^{68}Ga-FAPi.

While primary tumors and axillary lymph nodes can often be detected with the help of the CT component of ^{18}F-FDG PET/CT, distant lymph node, visceral organ, and peritoneal metastases are frequently missed in this patient group. In our study, the detection rates for axillary lymphadenopathy did not differ significantly between the two imaging modalities for staging. However, the number of lesions detected with ^{68}Ga-FAPi PET/CT was higher compared to ^{18}F-FDG PET/CT. Regarding the ability to detect the primary tumor, no significant difference was observed between the two modalities. The absence of a significant difference

between the two imaging modalities in detecting the primary tumor may be attributed to the limited sample size. On the other hand, the SUV_{max} of the primary tumors were found to be higher with ^{68}Ga-FAPi PET/CT. SUV_{max} for all localizations were significantly higher with ^{68}Ga-FAPi compared to ^{18}F-FDG (Table 3). Elboga et al. (12) performed a retrospective analysis involving 48 patients with invasive breast cancer, demonstrating that ^{68}Ga-FAPi PET/CT identified more primary breast lesions and additional metastatic lesions with greater uptake values compared to ^{18}F-FDG PET/CT. The effectiveness of ^{18}F-FDG PET/CT was notably reduced in the invasive lobular carcinoma subtype, emphasizing the necessity for a more efficient imaging modality, especially for this specific patient group in their study. Similarly, Ballal et al. (13) observed increased radiotracer uptake using ^{68}Ga-DOTA.SA.FAPi in lymph nodes corresponding to CT findings in the axillary region, where no uptake was detected with ^{18}F-FDG PET/CT. The findings of this prospective study highlight the significant impact of ^{68}Ga-FAPi PET/CT imaging on accurate staging of breast cancer, particularly in cases with lobular carcinoma.

According to our results, disease upstaging was observed in 44.8% of patients, emphasizing the diagnostic superiority of ^{68}Ga-FAPi PET/CT compared to ^{18}F-FDG PET/CT. This demonstrates the enhanced sensitivity of ^{68}Ga-FAPi PET/CT in detecting previously undetected metastases or disease extent. Notably, 50% of patients with lobular carcinoma were upstaged after ^{68}Ga-FAPi PET/CT imaging, emphasizing the potential of this modality to address the limitations of ^{18}F-FDG in this histological subtype, where lower glycolytic activity often leads to false negatives. The capability of FAPi to identify fibrotic or stromal components of tumors, which are prominent in lobular carcinoma, may account for this improvement. In the study conducted by Kratochwil et al. (14) it was reported that ^{68}Ga-FAPi PET/CT demonstrates high affinity for tumor stromal components, enabling high sensitivity even in tumors with low ^{18}F-FDG avidity. Our study findings are consistent with the literature and can be attributed to the ability of ^{68}Ga-FAPi PET/CT to effectively visualize the microscopic stromal and fibrotic components of tumors.

Of the 21 patients referred to our clinic for restaging due to elevated tumor markers or suspected recurrence on conventional imaging during follow-up, ^{18}F-FDG PET identified recurrence in 8 patients, while ^{68}Ga-FAPi PET/CT detected recurrence in 16 patients (Figure 2). In 5 patients, no lesion was identified with either modality. In our study, ^{18}F-FDG PET/CT failed to detect recurrence in 72.7% of patients who were later identified as having recurrent disease by ^{68}Ga-FAPi PET/CT. Studies in the literature have demonstrated the superiority of ^{68}Ga-FAPi PET/CT

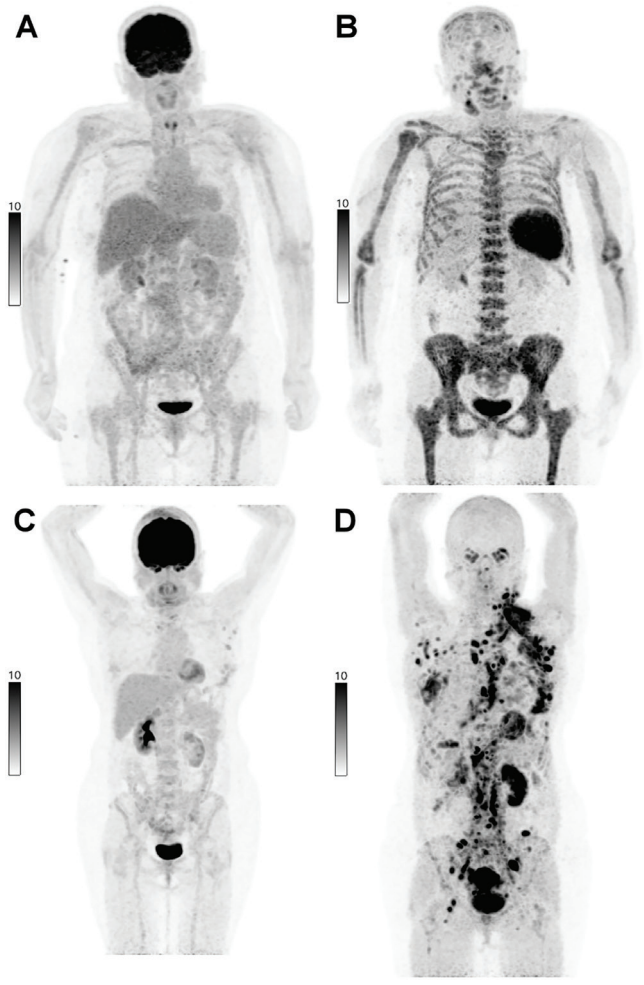

Figure 2. A 67-year-old female patient with invasive lobular breast carcinoma underwent ^{18}F-FDG PET/CT for restaging due to tumor marker progression. The ^{18}F-FDG PET/CT did not reveal any focal lesions to explain the tumor marker progression; it only showed mild, diffuse FDG uptake associated with bone marrow reactivation (A). However, ^{68}Ga-FAPi PET/CT images showed intense and widespread FAP expression suggestive of bone marrow infiltration (B). This finding was later confirmed by histopathological examination. The second patient was a 54-year-old woman with invasive lobular carcinoma of the left breast underwent ^{18}F-FDG PET/CT, which showed a mildly hypermetabolic primary mass and left axillary lymph nodes, and multiple sclerotic bone lesions without significant FDG uptake (C). ^{68}Ga-FAPi PET/CT detected nodular lesions in both breasts; metastatic lymph nodes in the left cervical, bilateral axillary, mediastinal, abdominal, and right femoral regions; suspicious activity along the greater curvature of the stomach; multiple bone metastases (D).

^{68}Ga-FAPi PET/CT: Gallium-68 fibroblast activation protein inhibitor positron emission tomography/computed tomography, ^{18}F-FDG: ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography

over ^{18}F-FDG PET/CT in detecting primary and metastatic lesions. Kömek et al. (15) showed that ^{68}Ga-FAPi-04 PET/CT detected more lesions compared to ^{18}F-FDG PET/CT and exhibited higher tumor-to-background ratios. Similarly, a study highlighted the superiority of ^{68}Ga-FAPi PET/CT over ^{18}F-FDG PET/CT, particularly in invasive lobular carcinoma (5). Additionally, the study conducted by Chen et al. (16) evaluated the potential use of ^{68}Ga-FAPi PET/CT in the detection, staging, and restaging of various cancer types and compared it with ^{18}F-FDG PET/CT. The results demonstrated that ^{68}Ga-FAPi PET/CT offers higher sensitivity and specificity in various cancer types, particularly in breast cancer. While these studies emphasize the role of ^{68}Ga-FAPi PET/CT in the assessment of primary breast masses, axillary lymph nodes, and distant metastases, none have specifically focused on its utility in detecting breast cancer recurrence. Our study differs from prior investigations by not only validating the diagnostic superiority of ^{68}Ga-FAPi PET/CT in primary staging and metastasis detection, but also by revealing its extended capacity for restaging and recurrence identification.

Study Limitations

The main limitation of the present study is the relatively small sample size, particularly within each histopathological subgroup. Therefore, subgroup-based comparisons should be interpreted with caution, and the present findings should be considered preliminary and hypothesis-generating. Since the study specifically focused on breast cancer patients with low or limited ^{18}F-FDG uptake, patient recruitment was inherently restricted. Larger multicenter prospective studies with standardized imaging protocols, pathological confirmation when feasible, and long-term clinical follow-up are required to validate these findings. This study demonstrates the diagnostic superiority of ^{68}Ga-FAPi PET/CT over ^{18}F-FDG PET/CT, especially in invasive lobular carcinoma and challenging histological subtypes. However, the absence of long-term clinical outcome data in the study can be considered a limitation. Another limitation of the present study is the use of two FAP-targeting ligands, ^{68}Ga-DOTA-FAPi-46 and ^{68}Ga-DOTA-FAP-2286. Although both target the fibroblast activation protein, potential differences in pharmacokinetics, biodistribution, background activity, and lesion uptake may influence SUV-based measurements. Because the study was not designed as a head-to-head comparison and no patient underwent imaging with both tracers, the possible impact of ligand-related differences could not be formally assessed. Prospective studies using a single ligand or employing direct intraindividual comparison protocols are warranted. Another limitation is that histopathological confirmation was not available for every ^{68}Ga-FAPi-positive metastatic lesion. Therefore, final lesion classification was based on a composite reference standard including histopathology when available, correlation with diagnostic contrast-enhanced CT and/or MRI, follow-up imaging for at least 6 months, clinical course, and multidisciplinary tumor board consensus. Future multicenter prospective studies with larger populations and subgroup analyses are needed to confirm its efficacy. Additionally, long-term survival and cost-effectiveness data will support its potential role in breast cancer management and inform personalized treatment strategies.

Conclusion

^{68}Ga-FAPi PET/CT was more effective than conventional ^{18}F-FDG PET/CT in detecting and staging breast cancer in our cohort, especially invasive lobular carcinoma. The study findings support the use of ^{68}Ga-FAPi PET/CT as a complementary imaging tool not for all breast cancers, but particularly for low-^{18}F-FDG-avidity histological subtypes, in whom ^{18}F-FDG PET/CT has limited sensitivity for detecting extra-axillary and distant metastases. Larger multicenter studies with pathological confirmation of metastatic sites are warranted to validate these results and further define the clinical utility of FAPi imaging in this subset of patients.

Ethics

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

Informed Consent: This is a single-center prospective study.

Footnotes

Authorship Contributions

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

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