

Oncologic Staging with ^{68}Ga -FAPI PET/CT Demonstrates a Lower Rate of Nonspecific Lymph Node Findings Than ^{18}F -FDG PET/CT

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Nonspecific lymph node uptake on ^{18}F -FDG PET/CT imaging is a significant pitfall for tumor staging. Fibroblast activation protein α expression on cancer-associated fibroblasts and some tumor cells is less sensitive to acute inflammatory stimuli, and fibroblast activation protein-directed PET may overcome this limitation. **Methods:** Eighteen patients from our prospective observational study underwent ^{18}F -FDG and ^{68}Ga fibroblast activation protein inhibitor (FAPI) PET/CT scans within a median of 2 d (range, 0–22 d). Lymph nodes were assessed on histopathology and compared with SUV measurements. **Results:** On a per-patient basis, lymph nodes were rated malignant in 10 (56%) versus 7 (39%) patients by ^{18}F -FDG PET/CT versus ^{68}Ga -FAPI PET/CT scans, respectively, with a respective accuracy of 55% versus 94% for true lymph node metastases. Five of 6 (83%) false-positive nodes on the ^{18}F -FDG PET/CT scans were rated true negative by the ^{68}Ga -FAPI PET/CT scans. On a per-lesion basis, tumor detection rates were similar (85/89 lesions, 96%). **Conclusion:** ^{68}Ga -FAPI PET/CT imaging demonstrated higher accuracy for true nodal involvement and therefore has the potential to replace ^{18}F -FDG PET/CT imaging for cancer staging.

Key Words: ^{18}F -FDG PET/CT; ^{68}Ga -FAPI PET/CT; lymph node staging; oncologic staging

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For whole-body staging of malignancy, ^{18}F -FDG PET/CT imaging has been used for several decades and is now a standard tool. However, nonspecific lymph node uptake leading to false-positive findings and incorrect treatment decisions is a major limitation of ^{18}F -FDG PET/CT imaging (1,2).

Mechanisms behind the increased ^{18}F -FDG uptake include inflammation and recruitment of a great number of invading and activated immune cells with increased metabolic activity (3). Even though the fibroblast activation protein can be induced by inflammatory stimuli,

such as transforming growth factor β , the increase in expression (per cell) might be comparatively less, and thus, ^{68}Ga -fibroblast activation protein inhibitor (FAPI) PET/CT imaging may overcome the limitations of ^{18}F -FDG PET/CT imaging (4–6).

MATERIALS AND METHODS

We included 18 patients from our database who were enrolled in a prospective observational study (NCT04571086, Institutional Review Board approval 19-8991) between 2020 and 2022 at our institution. Enrollment was offered to all patients who underwent ^{68}Ga -FAPI-46 PET/CT imaging at our department. The Institutional Review Board approved this study, and all subjects signed a written informed consent form. Patients met the following criteria: ^{68}Ga -FAPI and ^{18}F -FDG PET/CT imaging for oncologic staging within 4 wk, histopathologic evaluation of the lymph nodes, and no change in treatment between ^{18}F -FDG and ^{68}Ga -FAPI PET/CT scans (Fig. 1). Clinical indication was oncologic staging or restaging of a tumor entity that was known to demonstrate elevated fibroblast activation protein expression (sarcoma, pancreatic cancer, colon cancer, etc.). One patient with lymph node uptake was reported previously (6).

The median injected activity was 309 MBq (range, 94–440 MBq) for ^{18}F -FDG and 130 MBq (range, 66–194 MBq) for ^{68}Ga -FAPI. The median uptake time was 70 min for ^{18}F -FDG and 16 min for ^{68}Ga -FAPI. We previously compared early versus late uptake scans for ^{68}Ga -FAPI PET/CT and found nearly equal tumor detection (7). Therefore, in our department, the standard protocol is early image acquisition. Descriptive statistics are provided in Figure 2 and Supplemental Figure 2 (supplemental materials are available at <http://jnm.snmjournals.org>). The Mann–Whitney U test was used to compare uptake intensity (SUV) and receiver operating characteristic curves with the Youden index to narrow cutoffs.

For lymph nodes, SUV_{peak} and target-to-background ratio (TBR) were determined. SUV_{peak} was measured in accordance with PERCIST (1 cm^3 volume of interest). The TBR was calculated in relation to the SUV_{mean} of muscle (pectoralis major) and blood pool (aorta) for ^{18}F -FDG and ^{68}Ga -FAPI (SUV_{max} lymph node/ SUV_{mean} pectoralis or SUV_{mean} aorta). Because of very low physiologic uptake, the liver was unsuitable for calculating the ^{68}Ga -FAPI TBR, and therefore, the liver TBR was not included. Lymph node uptake on PET (positive vs. negative) was determined by PERCIST: SUV_{max} above the PERCIST cutoff (SUV_{mean} of liver [^{18}F -FDG] or muscle [^{68}Ga -FAPI] + $2 \times \text{SD}$)

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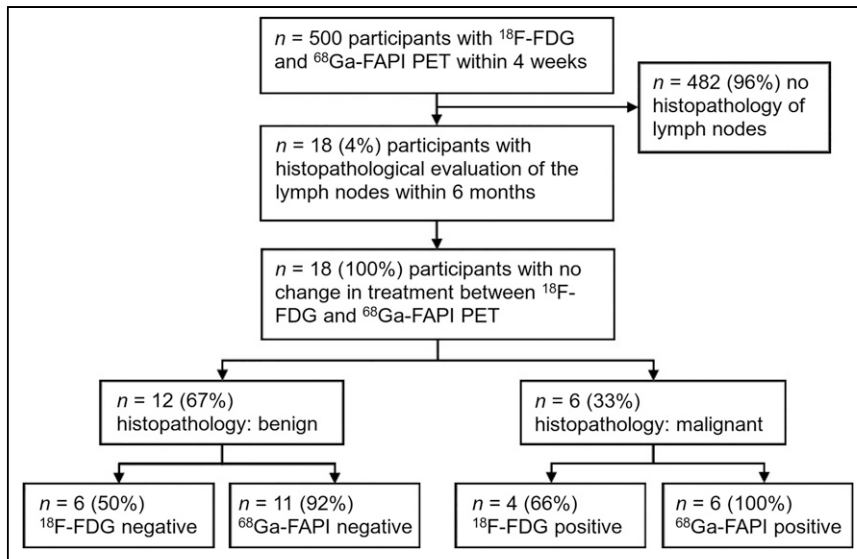


FIGURE 1. Standards for Reporting of Diagnostic Accuracy Studies flow diagram.

was defined as visual positive and SUV_{max} below the PERCIST cutoff as visual negative.

Tumor detection efficacy was determined independently and without access to histopathology data for both modalities by consensus of a nuclear medicine physician and a radiologist, each with at least 5 y of training.

RESULTS

After database screening, we included 18 patients (12 men and 6 women). Figure 1 shows a Standards for Reporting of Diagnostic Accuracy Studies flow diagram for the patients. Patient characteristics are shown in Supplemental Table 1. Two (11%) patients had sarcoma, and 16 (89%) patients had carcinoma of various origins. Eleven (61%) patients had locoregional lesions only, and 7 (39%)

patients showed distant metastases in bone, organs, or distant lymph nodes (Supplemental Table 2).

The mean age of the patients was 56 y (range, 31–73 y). PET scans were performed on 9 (50%) patients for staging and 9 (50%) for restaging of malignancy. The median time between ^{18}F -FDG PET/CT and ^{68}Ga -FAPI PET/CT imaging was 2 d (range, 0–22 d). Biopsy was performed on average 24 d (range, 1–164 d) after the PET scan.

Measured lymph nodes had a median size of 0.7 cm (range, 0.4–1.7 cm) in short-axis diameter and were obtained by open surgery in 12 (67%) patients, by endobronchial ultrasound-guided transbronchial needle aspiration in 3 (17%) patients, by laparoscopy in 2 (11%) patients, and by ultrasound in 1 patient (6%). Four (22%) patients underwent PET scans while being treated with chemotherapy; the remaining patients were not on active therapy during

imaging. Three of these patients had matching ^{18}F -FDG PET/CT and ^{68}Ga -FAPI PET/CT findings. In the remaining patient, the axillary reactive lymph node was positive on ^{18}F -FDG PET/CT and negative on ^{68}Ga -FAPI PET/CT 3 wk after coronavirus disease 19 vaccination on the ipsilateral side (Supplemental Table 3).

Table 1 shows the accuracy of ^{18}F -FDG PET/CT and ^{68}Ga -FAPI PET/CT findings as validated by histopathology. Sensitivity, specificity, positive predictive value, and negative predictive value were higher for ^{68}Ga -FAPI PET/CT than for ^{18}F -FDG PET/CT for lymph node evaluation. Overall accuracy of lymph node assessment was 94% versus 55% for ^{68}Ga -FAPI PET/CT versus ^{18}F -FDG PET/CT.

Figure 2 compares the uptake of ^{68}Ga -FAPI and ^{18}F -FDG in benign and malignant lymph nodes. The Mann–Whitney U test showed that SUV_{peak} and TBRs were significantly higher in malignant than benign lymph nodes on the ^{68}Ga -FAPI PET/CT scan (average SUV_{peak} , 3.5 vs. 1.3, $P = 0.01$; muscle TBR [TBR_{muscle}], 3.5 vs. 1.0, $P < 0.001$; blood TBR, 3.6 vs. 1.2, $P = 0.005$) but not on the ^{18}F -FDG PET/CT scan (average SUV_{peak} , 3.1 vs. 3.5, $P = 0.77$; TBR_{muscle} , 8.7 vs. 8.6, $P = 0.98$; blood TBR, 3.0 vs. 3.3, $P = 0.68$).

Tracer uptake was higher for ^{18}F -FDG than for ^{68}Ga -FAPI in benign lymph nodes of patients 5, 6, 10, 12, 13, and 16 (average SUV_{peak} , 5.6 vs. 1.7) and was higher for ^{68}Ga -FAPI than for ^{18}F -FDG in malignant lymph nodes of patients 8 and 11 (1.6 vs. 0.9) (Supplemental Fig. 1).

Analysis of the receiver operating characteristics showed an overall model quality of less than 0.5 for ^{18}F -FDG PET/CT (SUV_{peak} , TBR_{muscle} , and blood TBR) and thus was too low for a reliable cutoff determination. For ^{68}Ga -FAPI PET/CT imaging, the most appropriate cutoff was 1.7 for SUV_{peak} (sensitivity, 83%; specificity, 75%), 1.5 for TBR_{muscle} (sensitivity, 100%; specificity, 92%), and 1.9 for

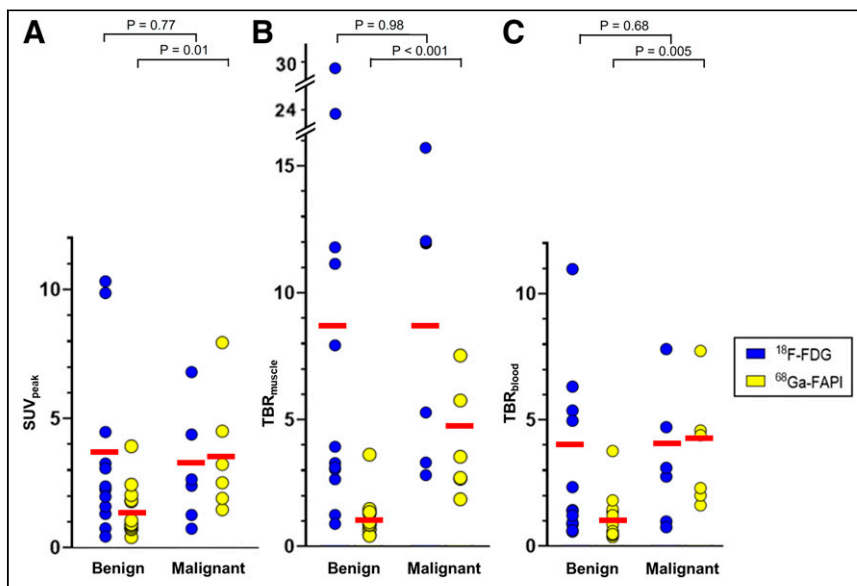


FIGURE 2. SUV_{peak} and TBR of 18 lymph nodes (1 node per patient). (A) SUV_{peak} of lymph nodes. (B) TBR_{muscle} with major pectoral muscle. (C) Blood TBR (TBR_{blood}) with aorta as reference. Statistical significance of difference was assessed by Mann–Whitney U test.

TABLE 1
Accuracy of ^{18}F -FDG PET/CT Vs. ^{68}Ga -FAPI PET/CT for Nodal Staging in 18 Patients

Tracer	Malignant	Benign	Statistics
^{18}F -FDG			
Positive	True positive, $n = 4$	False positive, $n = 6$	Positive predictive value, 56%
Negative	False positive, $n = 2$	True negative, $n = 6$	Negative predictive value, 89%
Statistics	Sensitivity, 66%	Specificity, 50%	Accuracy, 55%
^{68}Ga -FAPI			
Positive	True positive, $n = 6$	False positive, $n = 1$	Positive predictive value, 86%
Negative	False positive, $n = 0$	True negative, $n = 11$	Negative predictive value, 100%
Statistics	Sensitivity, 100%	Specificity, 92%	Accuracy, 94%

Accuracy was tabulated on per-patient basis (1 node per patient).

blood TBR (sensitivity, 83%; specificity, 91%) (Supplemental Fig. 2).

^{18}F -FDG PET/CT and ^{68}Ga -FAPI PET/CT images demonstrating a mismatch of tracer uptake in a benign lymph node are shown in Figure 3, and additional images of matching tracer uptake are shown in Supplemental Figures 3–6.

In our study, the overall tumor detection efficacy on a per-lesion basis was the same for ^{18}F -FDG PET/CT as it was for ^{68}Ga -FAPI PET/CT (96% vs. 96%) (Supplemental Table 4).

DISCUSSION

We demonstrate in patients with various types of cancer that ^{68}Ga -FAPI PET/CT imaging identifies nodal involvement with higher accuracy than ^{18}F -FDG PET/CT imaging because of a lower rate of false-positive and false-negative findings. In addition, in these patients with local or advanced disease, overall tumor detection rates were the same with ^{68}Ga -FAPI PET/CT and ^{18}F -FDG PET/CT imaging.

In line with our findings, several previous studies have reported a high accuracy of ^{68}Ga -FAPI PET/CT imaging for tumor staging. ^{68}Ga -FAPI PET/CT imaging was superior to ^{18}F -FDG PET/CT imaging for the detection of sarcoma, pancreatic and breast cancers, and bone, liver, and peritoneal metastases (8–11).

In our study, ^{68}Ga -FAPI uptake was significantly higher in malignant versus benign lymph nodes, which facilitated correct identification of all malignant lymph nodes. Conversely, almost all benign lymph nodes demonstrated low or absent radiotracer uptake, with false-positive findings in only 1 patient on ^{68}Ga -FAPI PET/CT imaging.

In addition, a lower background uptake for ^{68}Ga -FAPI than for ^{18}F -FDG PET allows for improved delineation of physiologic versus metastatic uptake (10). In contrast, ^{18}F -FDG PET/CT imaging demonstrated uptake above the PERCIST threshold, with false-positive judgment for lymph node assessment in 6 patients. This well-known limitation of ^{18}F -FDG PET/CT imaging is due to the unfavorable properties of its molecular target. ^{18}F -FDG, as a sugar-based tracer, is taken up into cells through glucose transporter 1 in most metabolically active tissues (2,3); ^{68}Ga -FAPI binds to the fibroblast activation protein, which is selectively expressed on activated fibroblasts and some mesenchymal cancer cells (4,5). On ^{18}F -FDG PET/CT imaging, inflammation and associated reactive activation of tissue lead to nonspecific uptake in immune cells, complicating diagnostic interpretation. Publications of vaccine-related ^{18}F -FDG uptake and tracer uptake in inflammatory tissue (arthritis, sarcoidosis) are consistent with the low positive predictive value of ^{18}F -FDG PET/CT scans in our evaluation (6,12,13).

Because of the different molecular mechanism of ^{68}Ga -FAPI PET/CT imaging, it is not as prone to mild immune reactions, which represent most diagnostic pitfalls. However, large or chronic inflammation with associated fibroblast activation might cause an uptake of ^{68}Ga -FAPI as well (14,15). In our study, patient 16 was the only patient with a false-positive uptake of ^{68}Ga -FAPI. Images demonstrated accumulation of both tracers in lymph nodes affected by sarcoidosis, however, with a 7 times higher $\text{TBR}_{\text{muscle}}$ on the ^{18}F -FDG PET/CT scan than on the ^{68}Ga -FAPI PET/CT scan.

Although the SUV for the ^{68}Ga -FAPI PET/CT imaging showed an overlap for benign and malignant nodes as well (16), the overlap was much less with ^{18}F -FDG PET/CT imaging. Specifically, absolute SUV proved to be less accurate than $\text{TBR}_{\text{muscle}}$.

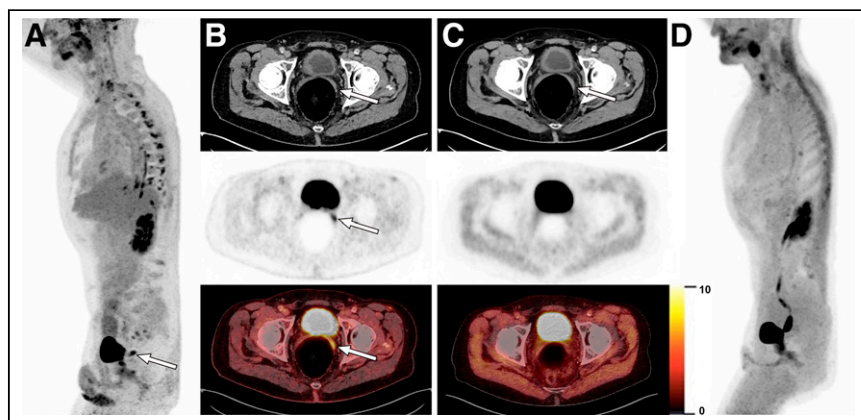


FIGURE 3. Patient 10, 72-y-old man with urothelial carcinoma of bladder being evaluated for restaging after chemotherapy, showing mismatch of tracer-avid lymph node in ^{18}F -FDG PET/CT and non-tracer-avid lymph node in ^{68}Ga -FAPI PET/CT. Histopathology result was benign. ^{18}F -FDG PET/CT images (A and B) and ^{68}Ga -FAPI PET/CT images (C and D), maximum-intensity projections (A and D), axial CT (B and C, top), PET (B and C, middle), and fused PET/CT (B and C, bottom) are shown.

Nodal staging is a critical element for initial treatment as it affects tumor stage directly and, consequently, therapy. Reactive tracer accumulation is particularly common in exposed locations such as axillary, mediastinal, or inguinal lymph nodes. Reactive uptake in the ipsi- and contralateral axillary lymph nodes interferes with staging of lung or breast cancer and significantly influences therapy decisions, as does reactive uptake in the inguinal region in prostate or lower-extremity cancers (2,6,11).

Although suggestive lymph nodes can be biopsied for validation, this invasive procedure comes with additional costs and potential complications such as bleeding or nerve damage (15). To avoid complications, further studies with larger cohorts are needed to compare the accuracy of both tracers, which will help to reduce additional histopathologic workup and incorrect management decisions.

Our study has limitations: we present a small cohort of patients who were highly selected for suggestive lymph nodes with a histopathology workup. Although histopathology is the gold standard, sampling errors during biopsy cannot be ruled out. Furthermore, the use of PERCIST in general and the use of muscle as a reference region have not yet been validated for ^{68}Ga -FAPI PET/CT imaging.

CONCLUSION

False-positive lymph node staging due to inflammation is a well-known limitation of ^{18}F -FDG PET/CT imaging. Here, we demonstrate in patients with various types of cancer that a ^{68}Ga -FAPI PET/CT scan identifies nodal involvement with higher accuracy because of a lower rate of false-positive findings than for ^{18}F -FDG PET/CT. In the future, ^{68}Ga -FAPI PET/CT staging may help to avoid additional workup or unnecessary treatment.

DISCLOSURE

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KEY POINTS

QUESTION: Can ^{68}Ga -FAPI PET/CT scanning prevent pitfalls of inflammatory uptake in lymph nodes?

PERTINENT FINDINGS: We compared PET/CT uptake and lymph node biopsy results for ^{18}F -FDG and ^{68}Ga -FAPI using a head-to-head study. Accuracy for nodal assessment was higher for ^{68}Ga -FAPI PET/CT (94%) than for ^{18}F -FDG PET/CT (55%) because of a lower rate of false-positive and false-negative findings. Both imaging modalities revealed an equal tumor detection rate.

IMPLICATIONS FOR PATIENT CARE: ^{68}Ga -FAPI was superior to ^{18}F -FDG at assessing dignity of lymph nodes by PET/CT.

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