
⁶⁸Ga-FAPI as a Diagnostic Tool in Sarcoma: Data from the ⁶⁸Ga-FAPI PET Prospective Observational Trial

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Bone and soft-tissue sarcomas express fibroblast activation protein (FAP) on tumor cells and associated fibroblasts. Therefore, FAP is a promising therapeutic and diagnostic target. Novel radiolabeled FAP inhibitors (e.g., ⁶⁸Ga-FAPI-46) have shown high tumor uptake on PET in sarcoma patients. Here, we report the endpoints of the ⁶⁸Ga-FAPI PET prospective observational trial. **Methods:** Forty-seven patients with bone or soft-tissue sarcomas undergoing clinical ⁶⁸Ga-FAPI PET were eligible for enrollment into the ⁶⁸Ga-FAPI PET observational trial. Of these patients, 43 also underwent ¹⁸F-FDG PET. The primary study endpoint was the association between ⁶⁸Ga-FAPI PET uptake intensity and histopathologic FAP expression analyzed with Spearman *r* correlation. Secondary endpoints were detection rate, positive predictive value (PPV), interreader reproducibility, and change in management. Datasets were interpreted by 2 masked readers. **Results:** The primary endpoint was met, and the association between ⁶⁸Ga-FAPI PET uptake intensity and histopathologic FAP expression was significant (Spearman *r* = 0.43; *P* = 0.03). By histopathologic validation, PPV was 1.00 (95% CI, 0.87–1.00) on a per-patient and 0.97 (95% CI, 0.84–1.00) on a per-region basis. In cases with histopathologic validation, 27 of 28 (96%) confirmed patients and 32 of 34 (94%) confirmed regions were PET-positive, resulting in an SE of 0.96 (95% CI, 0.82–1.00) on a per-patient and 0.94 (95% CI, 0.80–0.99) on a per-region basis. The detection rate on a per-patient basis in ⁶⁸Ga-FAPI and ¹⁸F-FDG PET was 76.6% and 81.4%, respectively. In 8 (18.6%) patients, ⁶⁸Ga-FAPI PET resulted in an upstaging compared with ¹⁸F-FDG PET. ⁶⁸Ga-FAPI PET readers showed substantial to almost perfect agreement for the defined regions (Fleiss κ : primary κ = 0.78, local nodal κ = 0.54, distant nodal κ = 0.91, lung κ = 0.86, bone κ = 0.69, and other κ = 0.65). Clinical management changed in 13 (30%) patients after ⁶⁸Ga-FAPI PET. **Conclusion:** We confirm an association between tumoral ⁶⁸Ga-FAPI PET uptake intensity and histopathologic FAP expression in sarcoma patients. Further, with masked readings and independent histopathologic validation, ⁶⁸Ga-FAPI PET had a high PPV and sensitivity for sarcoma staging.

Key Words: sarcoma; cancer imaging; FAPI; fibroblast activation protein; PET

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Sarcomas are a heterogeneous group of malignant tumors that derive from a mesenchymal origin. Reliable imaging methods are utterly important in the disease management of these patients and focus mainly on CT, MRI, or hybrid imaging, with additional PET using ¹⁸F-FDG. ¹⁸F-FDG PET/CT (referred to as ¹⁸F-FDG PET in this paper) has gained recognition as an efficient imaging modality for sarcomas and has been linked to detection of local recurrence and metastasis, response assessment, and prognosis (1–3). However, downsides of ¹⁸F-FDG include false-positive results due to physiologic uptake or an inflammatory response and false-negative results due to elevated serum blood glucose levels. Therefore, alternative targeted imaging probes are of increasing interest. The fibroblast activation protein (FAP) is highly expressed in carcinoma-associated fibroblasts in the stroma of various tumor entities (4,5) and in activated fibroblasts in stroma tissue to promote wound healing but is absent from normal adult tissues (6–8). Carcinoma-associated fibroblasts influence tumor cells by producing mediators and can promote tumor angiogenesis, migration, and proliferation (9,10). On this basis, a metaanalysis of 15 studies proved that FAP overexpression in solid tumors is associated with a poor outcome and is much more present in tumor tissue than in normal tissue (8). Compared with other tumor entities, sarcomas are unique in terms of FAP expression. Depending on their histogenesis and because of their mesenchymal origin, not just carcinoma-associated fibroblasts but also sarcoma tumor cells themselves often express FAP (11,12). It has been proposed that FAP and dipeptidyl-peptidase 4 are consistently expressed in bone and soft-tissue tumor cells that are histogenetically related to activated fibroblasts or myofibroblasts, irrespective of their malignancy (11). Therefore, FAP is an interesting specific target for diagnostic and therapeutic probes in bone and soft-tissue sarcomas. Only recently have novel radiolabeled FAP inhibitors (FAPIs) been introduced for theranostic approaches, which showed promising diagnostic value for multiple tumor entities, including sarcomas (13,14). These novel radiotracers captivate because of their low background activity, short acquisition delay, and specific imaging target and because they do not require dietary measurements. Additionally, it is possible to link these tracers with strong β -emitting radionuclides (e.g., ¹⁷⁷Lu and ⁹⁰Y) and use them for FAP-targeted radioligand therapies (15–17). Nonetheless, data

on the imaging potential of these radiotracers are scarce, and several clinical trials, such as ours, have been started to evaluate these tracers in tumors, as well as specifically in sarcoma patients (e.g., NCT04457258).

The aim of this prospective observational study was to investigate the association between histopathologic FAP expression and ^{68}Ga -FAPI PET uptake intensity in bone and soft-tissue sarcoma. We further aimed to analyze ^{68}Ga -FAPI PET sensitivity, specificity, PPV, and impact on management.

MATERIALS AND METHODS

Study Design and Patients

The flow of patients is illustrated in Figure 1. This was a subgroup analysis of the ongoing ^{68}Ga -FAPI PET observational trial. Until November 2020, adult patients with sarcomas who underwent clinical ^{68}Ga -FAPI PET were offered the opportunity to consent to an observational trial conducted at University Hospital Essen (NCT04571086). Before enrollment, patients gave written consent to undergo ^{68}Ga -FAPI PET for a clinical indication. They were enrolled irrespective of prior conventional imaging or treatment. The inclusion criteria were scheduling of ^{68}Ga -FAPI PET for staging or restaging of sarcoma as part of clinical routine and an age of at least 18 y. Clinical indications for ^{68}Ga -FAPI PET were staging of high-risk patients, evaluation of the localization of tumor lesions before biopsy or surgery, equivocal imaging results, or evaluation of therapeutic options (Table 1). The exclusion criteria were an inability to consent to the study or to tolerate a PET scan; women who were pregnant, lactating, or breast feeding were also excluded. The primary endpoint was an association between ^{68}Ga -FAPI PET uptake intensity and histopathologic FAP expression. The primary endpoint was met if PET uptake and tissue FAP expression showed a significant correlation by Spearman correlation testing (ordinal data).

Secondary endpoints were the detection rate and positive predictive value (PPV) of ^{68}Ga -FAPI PET on a per-patient and per-region-basis for tumor location, confirmed by histopathology or biopsy; the sensitivity and specificity of ^{68}Ga -FAPI PET on a per-patient and per-region-basis for detection of tumor location confirmed by histopathology or biopsy;

the impact on management; interreader reproducibility; and a change in staging or prognostic groups.

The time line of investigations is illustrated in the Supplemental Figure 1 (supplemental materials are available at <http://jnm.snmjournals.org>). The study was initiated, planned, conducted, analyzed, and published by the investigators. No financial support was received from commercial entities. All reported investigations were conducted in accordance with the Declaration of Helsinki and with the national regulations. This observational trial was registered on clinicaltrials.gov (NCT04571086) and approved by the local Ethics Committee (permits 19-8991-BO and 20-9485-BO). Patients gave written informed consent for inclusion in the observational trial.

Imaging

Clinical PET scans were performed in the craniocaudal direction on a Biograph mMR, Biograph mCT, or Biograph mCT Vision (Siemens Healthineers). All ^{68}Ga -FAPI-46 PET scans were performed as PET/CT, whereas ^{18}F -FDG PET scans were performed either as PET/MRI or PET/CT, depending on the clinical indication. Such scans are referred to in this paper as ^{68}Ga -FAPI PET and ^{18}F -FDG PET, respectively. The mean injected activity of ^{68}Ga -FAPI was 144 ± 36 MBq, and that of ^{18}F -FDG was 214 ± 102 MBq. ^{68}Ga -FAPI PET images were acquired approximately 10 min (mean, 13.6 ± 8.5 min) after injection, and ^{18}F -FDG PET images were acquired at approximately 60 min (mean, 69.2 ± 16.5 min) after injection. For PET/CT, a diagnostic CT scan was obtained with a standard protocol (80–100 mA, 120 kV) before the PET scan. Intravenous iodinated contrast medium was administered to 45 (96%) patients. For each scan, the number of lesions per region and per patient and the size of the lesion with the highest uptake per region were recorded. Any focal uptake higher than the surrounding background and not associated with physiologic uptake was considered suggestive of malignancy. The SUV_{max} of tumor lesions was measured with a region-growing algorithm with a threshold of 40% of the maximal uptake (Syngo.via software; Siemens Healthcare) for the lesion with the highest uptake at the respective cancer site (primary; local nodal; distant nodal; lung; bone metastasis; and other organ, skin, or soft-tissue metastasis). PET/CT and MR images were read independently by 2 experienced, masked nuclear medicine physicians or radiologists each for the respective modalities. The readers were aware of the primary tumor site. Divergent findings were discussed and reported in a separate consensus session between readers.

Lesion Validation

All patients were followed up for histopathologic analysis and, if possible, respective FAP immunohistochemistry. Lesions were included if ^{68}Ga -FAPI PET findings could be directly validated with histopathologically proven lesions. Validation was performed by the unmasked local investigators after they had reviewed the images and reports, following the prespecified criteria of the study protocol. In patients with histopathologic results, positive ^{68}Ga -FAPI PET findings were validated as true- or false-positive. Regions negative on ^{68}Ga -FAPI PET but with a subsequently confirmed tumor lesion by histopathologic analysis were considered false-negative results.

Immunohistochemistry

Biopsy and surgical specimen were stained with standard hematoxylin and eosin and

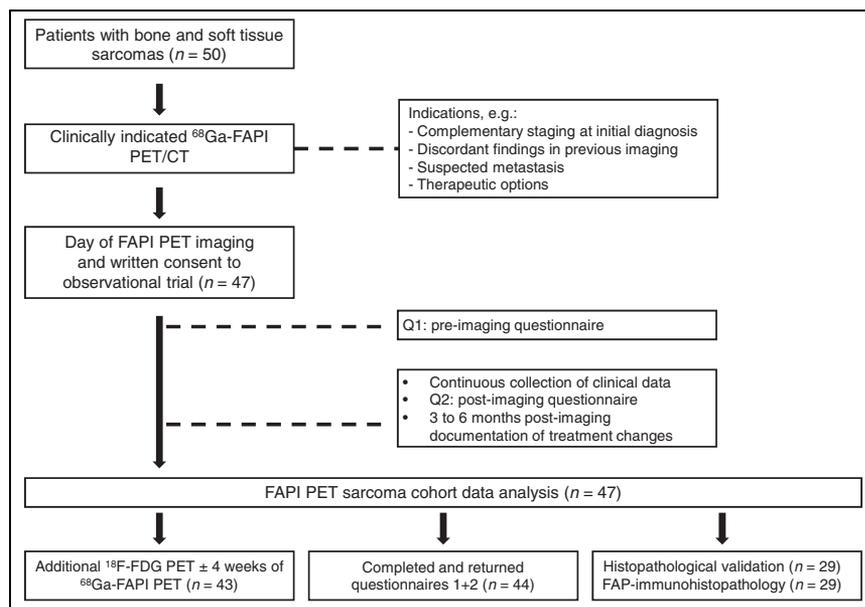


FIGURE 1. Enrollment flowchart.

TABLE 1
Patient Characteristics

Characteristic	Data
Age (y)	
Mean	48.1 (SD, 17.3)
Median	54.0 (range, 18.0, 89.0)
Sex	
Female	23 (48.9%)
Male	24 (51.1%)
Sarcoma type	
Bone sarcoma	20 (42.6%)
Osteosarcoma	8 (17.0%)
Ewing sarcoma	2 (4.3%)
Others	10 (21.3%)
Soft-tissue sarcoma	27 (57.4%)
Not otherwise specified/ undifferentiated pleomorphic sarcoma	6 (12.8%)
Leiomyosarcoma	4 (8.5%)
Others	17 (36.2%)
Grading	
High grade	35 (74.5%)
Low grade	5 (10.6%)
Not applicable	7 (14.9%)
Staging	
Localized	16 (34.0%)
Synchrone metastasized	9 (19.1%)
Metachrone metastasized	22 (46.8%)
Prior therapies	
Chemotherapy	13 (27.7%)
Chemotherapy and radiotherapy	15 (31.9%)
Radiotherapy	2 (4.3%)
None	17 (36.2%)
Indication for PET	
Staging	17 (36.2%)
Restaging	20 (42.6%)
Localization before local therapy	10 (21.3%)
Intended treatment before PET	
Chemotherapy	26 (55.3%)
Resection	12 (25.5%)
Radiation	5 (10.6%)
Resection/radiation	2 (4.3%)
Watch and wait	2 (4.3%)

Data are number followed by percentage in parentheses, except for age. Total $n = 47$.

FAP immunohistochemistry. For immunohistochemical staining, the tissue slides were incubated with the anti-FAP antibody after antigen retrieval, followed by secondary antibody incubation.

FAP expression was evaluated by 1 experienced pathologist under light microscopy with $\times 40$ power in accordance with a system by

Henry et al. (18). The entire tumor tissue sample on the slide was assessed, excluding the invasive front or areas of active tumor growth. Semiquantitative analysis of FAP expression was rated following a previously described scoring system (18–20): 0 was defined as the complete absence of, or weak, FAP immunostaining in less than 1% of the sample; 1+, as focal positivity in 1%–10%; 2+, as positive FAP immunostaining in 11%–50%; and 3+, as FAP immunostaining in more than 50%. Tumor cells and stromal cells were assessed for semiquantitative analysis. The pathologist was not aware of the PET findings.

Survey Design

Referring physicians were asked to complete and return 2 questionnaires. The first assessed the existing treatment plan for the patient without the information from ^{68}Ga -FAP PET. The second inquired about intended management after receipt of the written clinical report and the ^{68}Ga -FAP PET images. After return of the second questionnaire, all other pending imaging findings were disclosed. Implementation of the intended management was verified by patient file review or information provided by the referring physician.

Statistical Analysis

The primary endpoint was the association between ^{68}Ga -FAP PET uptake intensity and histopathologic FAP expression. Validation was via immunohistochemical FAP staining or molecular analyses of pathologic specimens. PET uptake and tissue FAP expression were compared by Pearson correlation testing for continuous data and Spearman correlation testing for ordinal data. In addition, uptake and expression data were compared descriptively for each score, uptake, and expression range. The PPV and SE of ^{68}Ga -FAP PET on a per-patient and per-region basis for detection of tumor location confirmed by histopathology or biopsy were calculated and are reported, along with the corresponding 2-sided 95% CIs. The CIs were constructed using the Wilson score method. Additionally, 1-way ANOVA was used for analysis of histopathologic FAP expression and uptake values. Uptake measurements of tumor lesions, nontumor lesions, and background were tested for statistically significant differences using nonparametric paired t tests (Wilcoxon signed-rank test). All statistical analyses were performed using R statistics (version 3.4.1; www.r-project.org) or Prism (version 8.4.2; GraphPad Software).

RESULTS

Patient Characteristics

By November 2020, 47 patients with sarcomas had been enrolled at the University Hospital Essen. Four patients were imaged with ^{68}Ga -FAP-04 (8.5%), and 43 patients were imaged with ^{68}Ga -FAP-46 (91.5%). All patients imaged with ^{68}Ga -FAP-46 underwent ^{18}F -FDG PET/CT ($n = 35$; 81.4%) or PET/MRI ($n = 8$; 18.6%) within a month before or after the ^{68}Ga -FAP PET (mean, 3.7 ± 6.5 d; range, -30 to $+7$ d). In all patients, no therapeutic changes occurred during the interval between the ^{68}Ga -FAP and ^{18}F -FDG PET scans. Table 1 details the patients' clinical characteristics. Information on the included tumor entities can be found in Supplemental Table 1. No adverse events were reported.

Association Between ^{68}Ga -FAP PET Uptake Intensity and FAP Expression

The ^{68}Ga -FAP uptake values and histopathologic FAP scores ($n = 29$) are compared in Figure 2 and Supplemental Table 2. Histopathology samples were from needle biopsies ($n = 4$), open biopsies ($n = 5$), or surgical excisions or resections ($n = 20$). ANOVA of SUV_{max} and histopathologic FAP score showed significant differences ($P = 0.037$). Comparison of SUV_{max} with the established

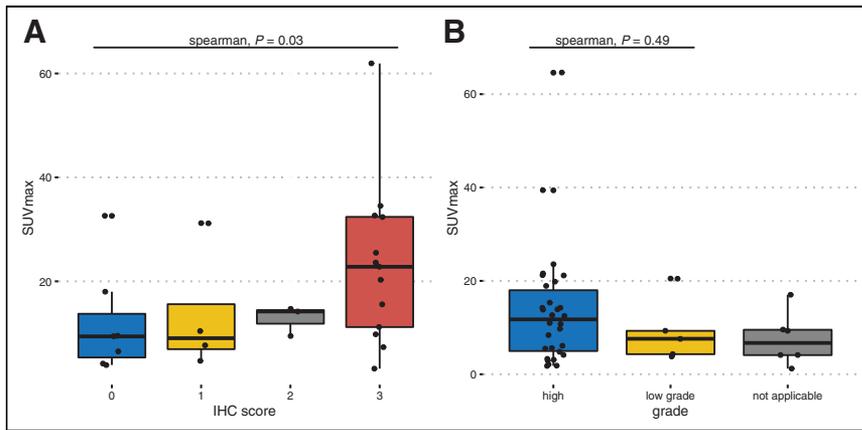


FIGURE 2. Primary endpoint: association between ^{68}Ga -FAPI PET uptake intensity and FAP immunohistochemistry (IHC) score. (A) ^{68}Ga -FAPI SUV_{max} by immunohistochemistry score, with positive correlation ($r = 0.43$, $P < 0.05$). (B) ^{68}Ga -FAPI SUV_{max} for patients separated into high-grade and low-grade groups and patients with tumor entities for which grading does not apply. Uptake does not significantly differ between groups ($P = 0.49$).

immunohistochemical scoring system showed a moderate linear relationship (SUV_{max} , Spearman $r = 0.43$; $P < 0.05$) (Fig. 2A). Uptake was higher in lesions with a FAP score of 3 than in lesions with no FAP expression (mean, 23.1 ± 15.4 for FAP score of 3 vs. 12.0 ± 10.2 for a FAP score of 0). Furthermore, stratification into low- and high-grade sarcomas showed similar uptake between groups on ^{68}Ga -FAPI PET (Fig. 2B) (Spearman $r = -0.24$; $P = 0.49$), with no statistically significant difference or correlation. Additional information about uptake values and tracer-to-background ratios is shown in Supplemental Tables 3 and 4 and Supplemental Figure 2.

Detection Rate and Accuracy

In total, 29 patients (61.7%) and 37 regions could be validated by histopathology. The PPV and sensitivity on a per-patient and per-region basis are shown in Table 2, and Supplemental Table 5 shows a contingency table for PPV, negative predictive value, SE, and SD. In PET-positive patients with histopathologic validation ($n = 27$), PPV was 1.00 on a per-patient basis and 0.97 on a per-region basis (secondary endpoint; 95% CI, 0.87–1.00 and 0.84–1.00, respectively).

PET and 90 (53.6%) on ^{18}F -FDG PET. An example patient is shown in Figure 3.

Reproducibility

On a region basis, both masked readers showed substantial to almost perfect agreement for both ^{68}Ga -FAPI PET and ^{18}F -FDG PET. The Fleiss κ -values are listed in Table 4. The raw reading-data are available as Supplemental Spreadsheets 1–4. Especially for disease in the nodal and lung regions, the readers showed higher agreement on ^{68}Ga -FAPI PET than on ^{18}F -FDG PET (local nodal $\kappa = 0.54$ vs. 0.27; distant nodal $\kappa = 0.91$ vs. 0.37; lung $\kappa = 0.86$ vs. 0.76). Interreader agreement on no disease versus local disease versus metastatic disease was similar for ^{68}Ga -FAPI and ^{18}F -FDG ($\kappa = 0.71$ vs. 0.72).

Change in Management

Completed and returned pre- and postimaging questionnaires were available for 44 patients (93.6%), and the implemented management was assessed. As depicted in Figure 4A, for 28 (64%) patients no change in management was documented. Major changes (e.g., change in therapeutic regimen) were documented for 7 (16%)

TABLE 2

^{68}Ga -FAPI PET Accuracy: PPV and Sensitivity of ^{68}Ga -FAPI PET Confirmed by Histopathologic Validation on Per-Patient and Per-Region Basis

Validation group	Total regions or patients (n)	No. confirmed	No. ruled out	PPV or sensitivity
PPV				
Histopathologic validation				
PET-positive (per patient)	27	27 (100%)	0 (0%)	1.00 (95% CI, 0.87 to 1.00)
PET-positive (per region)	33	32 (97%)	1 (3%)	0.97 (95% CI, 0.84 to 1.00)
Sensitivity				
Histopathologic findings				
Confirmed (per patient)	28	27 (96%)*	1 (4%) [†]	0.96 (95% CI, 0.82 to 1.00)
Confirmed (per region)	34	32 (94%)*	2 (6%) [†]	0.94 (95% CI, 0.80 to 0.99)

*PET-positive.

[†]PET-negative.

TABLE 3
Detection Efficacy

Site	PET-positive results	
	⁶⁸ Ga-FAPI (n = 43)	¹⁸ F-FDG (n = 43)
Per-patient basis	42 (97.7%)	41 (95.3%)
Per-region basis		
Primary	33 (76.7%)	35 (81.4%)
Local nodal	5 (11.6%)	7 (16.3%)
Distant nodal	5 (11.6%)	8 (18.6%)
Lung	15 (34.9%)	14 (32.6%)
Bone	12 (27.9%)	9 (20.9%)
Other	23 (53.5%)	16 (37.2%)

Data are number followed by percentage in parentheses.

patients; minor changes (e.g., modification of intended therapy) occurred in 6 (14%) patients. For 3 (6%) of the patients, whether the intended treatment was implemented was not reported. The types of major changes are highlighted in Figure 4B and Supplemental Table 7. The most frequent major change was a treatment shift toward systemic therapy in 3 (43%) patients, best supportive care in 2 (29%), active surveillance in 1 (14%), and local therapy in 1 (14%). Minor changes were equally distributed between modified local therapy (50%) and modified systemic therapy (50%).

Change in Staging

The changes in staging between ¹⁸F-FDG PET and ⁶⁸Ga-FAPI PET are given in Table 5. Five patients were excluded from the analysis because of incomparable ¹⁸F-FDG PET datasets (n = 43). In most patients, the staging did not differ between ⁶⁸Ga-FAPI and ¹⁸F-FDG PET. Of note, 8 (18.6%) patients were upstaged by ⁶⁸Ga-FAPI PET: 6 were upstaged from locoregional disease on ¹⁸F-FDG

PET to metastatic disease on ⁶⁸Ga-FAPI PET, and 2 patients had no signs of disease on ¹⁸F-FDG PET but were staged as metastatic or locoregional on ⁶⁸Ga-FAPI PET. As shown in Supplemental Table 7, in only 2 upstaged patients did this result in a major change in management. Downstaging by ⁶⁸Ga-FAPI PET occurred in 3 (7%) patients.

DISCUSSION

For clinical translation of ⁶⁸Ga-FAPI PET, the association between ⁶⁸Ga-FAPI uptake and histopathologic target expression needs to be established. Previously published data indicate high uptake of ⁶⁸Ga-FAPI tracers in sarcoma (13,21). We therefore aimed to assess the association between ⁶⁸Ga-FAPI PET uptake and FAP expression in sarcoma patients, validated by FAP immunohistochemistry. The primary endpoint was met, and we showed an association between ⁶⁸Ga-FAPI PET uptake intensity and histopathologic FAP expression. Further, we established a good diagnostic performance for ⁶⁸Ga-FAPI PET, compared with ¹⁸F-FDG PET, in this cohort of sarcoma patients and showed a high sensitivity of 96% and a PPV of 1.00 for FAP-positive lesions.

To our knowledge, these are the first prospective data on ⁶⁸Ga-FAPI PET in a cohort of sarcoma patients. Our study had several strengths when compared with several prior retrospective and prospective trials evaluating ⁶⁸Ga-FAPI PET. The study was strengthened by prospective follow-up, lesion validation, and correlation with histopathologic FAP expression; by a head-to-head comparison with ¹⁸F-FDG PET; by use of masked readings; and by use of pre- and postimaging questionnaires to measure management changes.

Specific binding of FAPI-04 to FAP was demonstrated previously in vitro (15,22,23). In addition, several clinical studies reported histopathologic FAP expression in tumor lesions in smaller cohorts (24,25). Nonetheless, they neither compared FAP expression level with uptake values nor showed a detailed analysis of FAP immunohistochemistry and PET lesions. We demonstrated a relationship between FAP immunohistochemistry and SUV_{max}. However, one must remember that FAP immunohistochemistry expression levels are heterogeneous in tumor tissue. The spatial intratumoral heterogeneity was addressed by assessment of the entire tumor area on the slide, but we did not stain different tumor sites or metastases, and considering the small number of biopsies, a sampling bias cannot not be excluded. Notably, 7 patients had positive ⁶⁸Ga-FAPI PET results whereas FAP immunohistochemistry was negative. In this study, these lesions were reported as false-positive, but possible explanations for this discrepancy are sampling errors or unspecific tracer binding in areas of inflammation or necrosis (26–28).

In the assessment of diagnostic accuracy, ⁶⁸Ga-FAPI PET demonstrated high PPV and sensitivity. When compared with ¹⁸F-FDG PET, ⁶⁸Ga-FAPI PET had a slightly lower detection efficacy for local nodal findings, although tumor-to-background uptake was higher and the

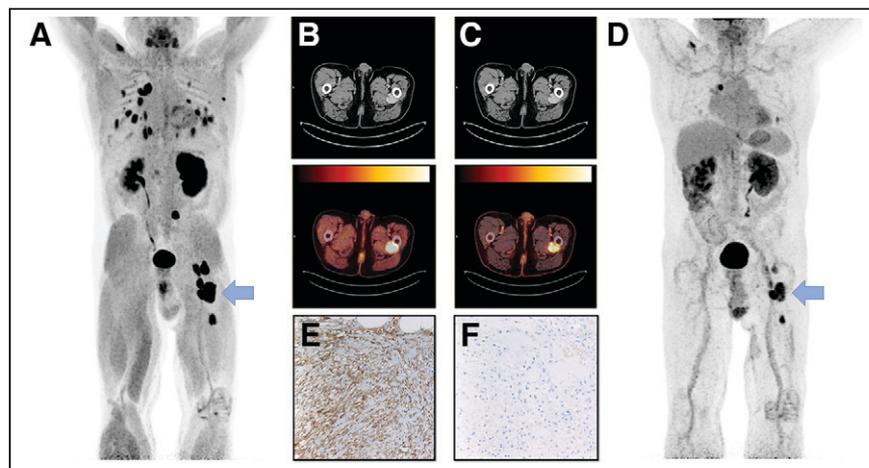


FIGURE 3. Case presentation: 69-y-old patient with metastatic low-grade myofibroblastic sarcoma. (A–D) Images of primary tumor of dorsal left thigh show higher uptake with ⁶⁸Ga-FAPI (SUV_{max}, 34.5; A and B) than with ¹⁸F-FDG (SUV_{max}, 20.6; C and D). Shown are maximum-intensity-projection PET images (A and D), axial CT images (B and C, top), and axial PET images (B and C, bottom). (E and F) Primary lesion (arrow) demonstrated high FAP expression on immunohistochemistry (E), compared with negative immunohistochemistry seen in different patient (F).

TABLE 4

Reproducibility: Interreader Agreement (Fleiss κ) on Per-Region Basis for ^{18}F -FDG PET and ^{68}Ga -FAPI PET

Region	Fleiss κ	
	^{18}F -FDG (n = 43)	^{68}Ga -FAPI (n = 47)
Primary	0.77	0.78
Local nodal	0.27	0.54
Distant nodal	0.37	0.91
Lung	0.78	0.86
Bone	0.66	0.69
Other	0.67	0.65
No disease vs. local disease vs. metastatic disease	0.718	0.706

interpretations were more reproducible. Compared with ^{18}F -FDG PET, ^{68}Ga -FAPI PET resulted in upstaging or downstaging in 8 patients, especially from locoregional to metastatic disease, which agrees with reported upstaging from other studies with various cancers (including 3 sarcoma patients) and pancreatic cancer (29,30). ^{68}Ga -FAPI PET resulted in changes in the treatment plan for 13 patients. Of these 13, 7 had major changes after ^{68}Ga -FAPI PET; nonetheless, these changes were triggered by upstaging in only 2 of these patients. All in all, the impact of ^{68}Ga -FAPI PET on management was low, when compared with findings for PSMA PET or somatostatin receptor PET in other tumor types (31,32). Reasons for a lower rate include the advanced tumor stage and pretreatment of the enrolled patients, as well as a high number of high-grade soft-tissue and bone sarcomas. In high-grade sarcoma, staging often does not change the initial planned therapy concept of induction chemotherapy and local treatment.

Aside from the diagnostic potential of FAPI radiotracers in sarcoma patients, the high uptake in tumor lesions enables FAP-targeted radioligand therapy similar to PSMA or somatostatin receptor-targeted therapies. Recently, 3 cases undergoing FAP-targeted radioligand therapy were reported; one of these cases was in a patient with sarcoma, who was treated with ^{153}Sm -labeled FAP-targeted FAPI-46 radioligand therapy (15–17).

This study had some limitations. Bone and soft-tissue sarcomas are a group of rare and heterogeneous tumors, as is reflected by

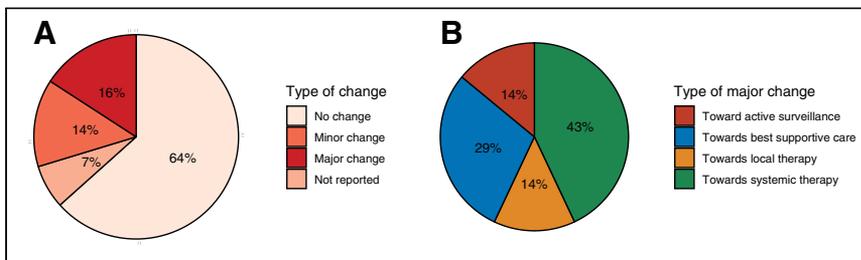


FIGURE 4. Change in management. (A) pie chart of implemented management change after FAPI-PET for 44 patients. Types of changes were categorized as no change, minor change (e.g. modification of systemic or local treatment), major change (e.g. treatment shift towards local or systemic therapy) and no report of implementation of intended treatment. (B) shows the types of major change after FAPI-PET in 7 patients. Major shift towards systemic therapy were noted most often.

TABLE 5

Change in Stage by Addition of ^{68}Ga -FAPI PET

^{18}F -FDG	^{68}Ga -FAPI		
	Locoregional (n = 13)	Metastatic (n = 29)	No disease (n = 1)
Locoregional	10 (76.9%)	6 (20.7%)	1 (100%)
Metastatic	2 (15.4%)	22 (75.9%)	0 (0%)
No disease	1 (7.7%)	1 (3.4%)	0 (0%)

the variety of tumor entities included in this analysis. Because of the small sample size, we could not perform subgroup analyses, despite the possibility of differences in FAP expression or ^{68}Ga -FAPI uptake in certain sarcoma entities. Despite similar diagnostic performance, ^{68}Ga -FAPI PET—in contrast to ^{18}F -FDG PET—was unable to distinguish sarcoma grades (3,33).

CONCLUSION

We established in this prospective clinical study on sarcoma patients an association between target expression and ^{68}Ga -FAPI PET SUV. We further found ^{68}Ga -FAPI PET to have high accuracy and, when compared with ^{18}F -FDG PET, a similarly high detection rate and reproducibility. ^{68}Ga -FAPI PET is a valuable diagnostic tool in patients with sarcoma. The prognostic and therapeutic potential of ^{68}Ga -FAPI imaging should be explored in future studies to improve disease management.

DISCLOSURE

Lukas Kessler is a consultant for BTG and AAA and received fees from Sanofi outside the submitted work. Justin Ferdinandus received a Junior Clinician Scientist Stipend from the University Duisburg-Essen. Wolfgang Fendler is a consultant for Endocyte and BTG and received fees from RadioMedix, Bayer, and Parexel outside the submitted work. Rainer Hamacher is supported by the Clinician Scientist Program of the University Medicine Essen Clinician Scientist Academy (UMEA) sponsored by the faculty of medicine and Deutsche Forschungsgemeinschaft (DFG). Rainer Hamacher has received travel grants from Lilly, Novartis, and PharmaMar, as well as fees from Lilly outside the submitted work. Martin Schuler reports personal fees from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Janssen, MorphoSys, Novartis, Takeda, Roche, Amgen, and MSD outside the submitted work. Lars Podleska reports personal fees from Belpharma SA, Luxembourg, outside the submitted work. Sebastian Bauer reports grants from Incyte; grants and personal fees from Blueprint Medicines and Novartis; personal fees from Deciphera, Lilly, Daichii-Sankyo, Plexxikon, Exelixis, and Bayer, other from Pfizer, during the conduct of the study; as well as personal fees from Pharmamar, Lilly, Roche, and GSK outside the submitted work. No other potential conflict of interest relevant to this article was reported.

KEY POINTS

QUESTION: Is there an association between ^{68}Ga -FAPi uptake intensity and FAP expression in bone and soft-tissue sarcomas, and how well does ^{68}Ga -FAPi PET perform diagnostically in sarcoma patients?

PERTINENT FINDINGS: We observed an association between ^{68}Ga -FAPi uptake intensity and immunohistochemical FAP expression in sarcomas and showed ^{68}Ga -FAPi PET to have high accuracy in sarcoma patients.

IMPLICATIONS FOR PATIENT CARE: ^{68}Ga -FAPi PET has diagnostic utility in patients with sarcoma, with future implications for FAP-targeted therapies.

REFERENCES

- Annovazzi A, Rea S, Zoccali C, et al. Diagnostic and clinical impact of ^{18}F -FDG PET/CT in staging and restaging soft-tissue sarcomas of the extremities and trunk: mono-institutional retrospective study of a sarcoma referral center. *J Clin Med*. 2020;9:2549.
- Grimer R, Judson I, Peake D, Seddon B. Guidelines for the management of soft tissue sarcomas. *Sarcoma*. 2010;2010:50618.
- Ioannidis JPA, Lau J. ^{18}F -FDG PET for the diagnosis and grading of soft-tissue sarcoma: a meta-analysis. *J Nucl Med*. 2003;44:717–724.
- Jacob M, Chang L, Pure E. Fibroblast activation protein in remodeling tissues. *Curr Mol Med*. 2012;12:1220–1243.
- Kelly T, Huang Y, Simms AE, Mazur A. Fibroblast activation protein- α : a key modulator of the microenvironment in multiple pathologies. In: *International Review of Cell and Molecular Biology*. Elsevier; 2012:83–116.
- Rettig WJ, Garin-Chesa P, Beresford HR, Oettgen HF, Melamed MR, Old LJ. Cell-surface glycoproteins of human sarcomas: differential expression in normal and malignant tissues and cultured cells. *Proc Natl Acad Sci USA*. 1988;85:3110–3114.
- Niedermeyer J, Garin-Chesa P, Kriz M, et al. Expression of the fibroblast activation protein during mouse embryo development. *Int J Dev Biol*. 2001;45:445–447.
- Liu F, Qi L, Liu B, et al. Fibroblast activation protein overexpression and clinical implications in solid tumors: a meta-analysis. *PLoS One*. 2015;10:e0116683.
- Koczorowska MM, Tholen S, Bucher F, et al. Fibroblast activation protein- α , a stromal cell surface protease, shapes key features of cancer associated fibroblasts through proteome and degradome alterations. *Mol Oncol*. 2016;10:40–58.
- Kalluri R. The biology and function of fibroblasts in cancer. *Nat Rev Cancer*. 2016;16:582–598.
- Dohi O, Ohtani H, Hatori M, et al. Histogenesis-specific expression of fibroblast activation protein and dipeptidylpeptidase-IV in human bone and soft tissue tumours. *Histopathology*. 2009;55:432–440.
- Scanlan MJ, Raj BKM, Calvo B, et al. Molecular cloning of fibroblast activation protein α , a member of the serine protease family selectively expressed in stromal fibroblasts of epithelial cancers. *Proc Natl Acad Sci USA*. 1994;91:5657–5661.
- Kratochwil C, Flechsig P, Lindner T, et al. ^{68}Ga -FAPi PET/CT: tracer uptake in 28 different kinds of cancer. *J Nucl Med*. 2019; 60:801–805.
- Giesel FL, Kratochwil C, Lindner T, et al. ^{68}Ga -FAPi PET/CT: biodistribution and preliminary dosimetry estimate of 2 DOTA-containing FAP-targeting agents in patients with various cancers. *J Nucl Med*. 2019;60:386–392.
- Lindner T, Loktev A, Altmann A, et al. Development of quinoline-based theranostic ligands for the targeting of fibroblast activation protein. *J Nucl Med*. 2018;59: 1415–1422.
- Ballal S, Yadav MP, Kramer V, et al. A theranostic approach of [^{68}Ga]Ga-DOTA-SA.FAPi PET/CT-guided [^{177}Lu]Lu-DOTA-SA.FAPi radionuclide therapy in an end-stage breast cancer patient: new frontier in targeted radionuclide therapy. *Eur J Nucl Med Mol Imaging*. 2021;48:942–944.
- Kratochwil C, Giesel FL, Rathke H, et al. [^{153}Sm]samarium-labeled FAPi-46 radioligand therapy in a patient with lung metastases of a sarcoma. *Eur J Nucl Med Mol Imaging*. 2021;48:3011–3013.
- Henry LR, Lee HO, Lee JS, et al. Clinical implications of fibroblast activation protein in patients with colon cancer. *Clin Cancer Res*. 2007;13:1736–1741.
- Iwasa S, Jin X, Okada K, Mitsumata M, Ooi A. Increased expression of seprase, a membrane-type serine protease, is associated with lymph node metastasis in human colorectal cancer. *Cancer Lett*. 2003;199:91–98.
- Ariga N, Sato E, Ohuchi N, Nagura H, Ohtani H. Stromal expression of fibroblast activation protein/seprase, a cell membrane serine proteinase and gelatinase, is associated with longer survival in patients with invasive ductal carcinoma of breast. *Int J Cancer*. 2001;95:67–72.
- Giesel FL, Kratochwil C, Lindner T, et al. ^{68}Ga -FAPi PET/CT: biodistribution and preliminary dosimetry estimate of 2 DOTA-containing FAP-targeting agents in patients with various cancers. *J Nucl Med*. 2019;60:386–392.
- Loktev A, Lindner T, Mier W, et al. A tumor-imaging method targeting cancer-associated fibroblasts. *J Nucl Med*. 2018;59:1423–1429.
- Loktev A, Lindner T, Burger E-M, et al. Development of fibroblast activation protein-targeted radiotracers with improved tumor retention. *J Nucl Med*. 2019;60: 1421–1429.
- Röhrich M, Loktev A, Wefers AK, et al. IDH-wildtype glioblastomas and grade III/IV IDH-mutant gliomas show elevated tracer uptake in fibroblast activation protein-specific PET/CT. *Eur J Nucl Med Mol Imaging*. 2019;46:2569–2580.
- Shi X, Xing H, Yang X, et al. Comparison of PET imaging of activated fibroblasts and ^{18}F -FDG for diagnosis of primary hepatic tumours: a prospective pilot study. *Eur J Nucl Med Mol Imaging*. 2021;48:1593–1603.
- Chen H, Zhao L, Ruan D, et al. Usefulness of [^{68}Ga]Ga-DOTA-FAPi-04 PET/CT in patients presenting with inconclusive [^{18}F]FDG PET/CT findings. *Eur J Nucl Med Mol Imaging*. 2021;48:73–86.
- Luo Y, Pan Q, Zhang W, Li F. Intense FAPi uptake in inflammation may mask the tumor activity of pancreatic cancer in ^{68}Ga -FAPi PET/CT. *Clin Nucl Med*. 2020; 45:310–311.
- Schmidkonz C, Rauber S, Atzinger A, et al. Disentangling inflammatory from fibrotic disease activity by fibroblast activation protein imaging. *Ann Rheum Dis*. 2020;79:1485–1491.
- Chen H, Pang Y, Wu J, et al. Comparison of [^{68}Ga]Ga-DOTA-FAPi-04 and [^{18}F]FDG PET/CT for the diagnosis of primary and metastatic lesions in patients with various types of cancer. *Eur J Nucl Med Mol Imaging*. 2020;47:1820–1832.
- Röhrich M, Naumann P, Giesel FL, et al. Impact of ^{68}Ga -FAPi PET/CT imaging on the therapeutic management of primary and recurrent pancreatic ductal adenocarcinomas. *J Nucl Med*. 2021;62:779–786.
- Calais J, Czernin J, Eiber M, et al. Most of the intended management changes after ^{68}Ga -DOTATATE PET/CT are implemented. *J Nucl Med*. 2017;58:1793–1796.
- Fendler WP, Ferdinandus J, Czernin J, et al. Impact of ^{68}Ga -PSMA-11 PET on the management of recurrent prostate cancer in a prospective single-arm clinical trial. *J Nucl Med*. 2020;61:1793–1799.
- Eary JF, Conrad EU, Bruckner JD, et al. Quantitative [^{18}F]fluorodeoxyglucose positron emission tomography in pretreatment and grading of sarcoma. *Clin Cancer Res*. 1998;4:1215–1220.