Head-to-head assessment of 68Ga-DOTA-FAPI-04 PET/CT vs 18 F-FDG PET/CT in fibroblastic tumors

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Abstract

Purpose: We aimed to evaluate ^{68}Ga-DOTA-FAPI-04 PET/CT versus ^{18}F-FDG PET/CT in the application of fibroblastic tumors.

Methods: Twenty patients with 6 subtypes of fibroblastic tumors prospectively underwent ^{18}F-FDG and ^{68}Ga-DOTA-FAPI-04 PET/CT examinations to evaluate the lesions. PET/CT findings were confirmed by surgical pathology, puncture biopsy, or imaging follow-up. Two independent sample t tests were used to compare the uptake of ^{18}F-FDG vs. ^{68}Ga-DOTA-FAPI-04 in primary, recurrent and metastatic lesions. One-way ANOVA was used to compare the uptake of ^{18}F-FDG or ^{68}Ga-DOTA-FAPI-04 among primary, recurrent, and metastatic lesions. The uptake of ^{68}Ga-DOTA-FAPI-04 vs. ^{18}F-FDG in different histopathological lesions was compared by two independent sample t tests.

Results: Twenty patients were finally confirmed to have 38 lesions. Although there was no significant difference in the detection of all lesions between ^{68}Ga-DOTA-FAPI-04 and ^{18}F-FDG PET/CT (38 vs. 36, p=0.493), the uptake of ^{68}Ga-DOTA-FAPI-04 in lesions was significantly higher than that of ^{18}F-FDG (p<0.001), including primary (p<0.001), recurrent (p=0.018) and metastatic (p<0.001) lesions. The SUVmax of ^{68}Ga-DOTA-FAPI-04 in primary and recurrent lesions was higher than that in metastasis (p=0.034 and p=0.015, respectively). The SUVmax of ^{68}Ga-DOTA-FAPI-04 in primary and recurrent malignant lesions was significantly higher than that of the intermediate (p<0.001). The SUVmax of ^{18}F-FDG in solitary fibrous tumors (SFTs) was significantly lower than that in non-SFT lesions (p=0.029). The SUVmax of ^{68}Ga-DOTA-FAPI-04 in one case of recurrent SFT with 5 lesions was significantly lower after treatment than before treatment (p =0.016).

Conclusion: ^{68}Ga-DOTA-FAPI-04 outperformed ^{18}F-FDG PET/CT in displaying the primary, recurrent and metastatic lesions of fibroblastic tumors. ^{68}Ga-DOTA-FAPI-04 PET/CT may also show potential value for judging the nature and monitoring the therapeutic response of tumors.

Introduction

Fibroblastic tumors include a variety of tumors based on the World Health Organization (WHO) classification of soft tissue tumors[1, 2], and among them, intermediate and malignant lesions have attracted attention due to their high local invasiveness and recurrence rate, the common tumors being desmoid-type fibromatosis, dermatofibrosarcoma protuberans, inflammatory myofibroblastic tumor, SFT, myxofibrosarcoma, and high-grade fibrosarcoma, which often grow rapidly[3-5]. The most likely explanation is that these tumors often exhibit a multinodular infiltrative growth pattern and tend to infiltrate widely into surrounding tissues[4]. Currently, surgical resection is the first choice for primary tumors, so it is necessary to expand the scope of surgical resection to ensure negative tumor margins, thereby reducing its recurrence rate[3, 6]. Even so, some tumors, such as myxoid fibrosarcoma, have postoperative recurrence rates and metastases of 18.2% and 14.6%, respectively[4]. Therefore, finding the

best method to assess the extent of the primary tumor and detect local recurrence and/or distant metastasis as early and accurately as possible is crucial for patient prognosis.

CT and MRI are routine methods for evaluating primary tumors and monitoring local recurrence. However, considering the metastatic tendency of these tumors, ^{18}F-FDG PET/CT is also currently used as a routine method for evaluating primary, recurrent, metastatic lesions, and previous studies have confirmed its high sensitivity and specificity[7]. In addition to initial staging and restaging, ^{18}F-FDG PET/CT is also valuable in evaluating treatment response and predicting treatment outcomes in soft tissue tumors[8]. However, studies have shown that some SFTs, including malignant tumors, have low ^{18}F-FDG uptake[9, 10], which limits their application in primary tumors and detecting metastases.

The more recently translated PET tracer ^{68}Ga-DOTA-FAPI-04 could specifically target fibroblast activating protein (FAP) in fibroblast-rich tumors[11], while fibroblasts in normal tissues have no or low expression of FAP. Fibroblastic tumors are rich in fibroblasts, thus, ^{68}Ga-DOTA-FAPI-04 may be an ideal imaging agent for these tumors. Recent studies have shown that ^{68}Ga-DOTA-FAPI-04 is superior to ^{18}F-FDG in assessing primary, recurrent and metastatic fibroblastic tumors[12, 13]. In addition to diagnostic imaging, FAPI-conjugated therapeutic nuclides have shown a certain value in the treatment of sarcoma[14], which also provides new ideas for the treatment of recurrent and metastatic lesions of refractory fibroblastic tumors.

In this study, we mainly investigated the potential application value of ^{68}Ga-DOTA-FAPI-04 PET/CT in the evaluation of primary lesions, recurrent lesions, and metastases of fibroblastic tumors compared with ^{18}F-FDG PET/CT.

Materials And Methods

This prospective clinical study (ChiCTR2000038080) was approved by the Ethics Committee of Peking University Cancer Hospital. All enrolled patients signed written informed consent, including 20 patients (8 females and 12 males) who were admitted to Peking University Cancer Hospital from May 2020 to January 2022. ^{68}Ga-FAPI PET/CT in all patients was performed within one week after ^{18}F-FDG PET/CT for the purpose of comparison or further diagnosis. Inclusion criteria: (1) Pathologically confirmed fibroblastic tumors. (2) Patients with high suspicion of tumor recurrence or metastasis after radical surgical resection. (3) Both going ^{18}F-FDG and ^{68}Ga-FAPI PET/CT examination. The exclusion criteria were as follows: (1) A history of two or more malignancies. (2) Without written informed consent for ^{68}Ga-DOTA-FAPI-04 PET/CT. (3) The primary tumor received treatment prior to the examination. The flow chart of patient enrollment is shown in Figure 1.

The preparation and acquisition of ^{18}F-FDG and ^{68}Ga-FAPI

^{18}F was manufactured by an HM-20 medical cyclotron (Sumitomo Corporation, Japan), and its radiochemical purity was greater than 95%. The ^{68}Ge-^{68}Ga generator (1.85 GBq, ITG Co., Ltd, Germany)

was used to elute ^{68}GaCl3 (3 mL, 0.05 M HCl). Then, this reagent was mixed with 20 μg of DOTA-FAPI-04 precursor (HUAYI Technology Co., Ltd., China). After adjusting the pH to 4.0 with sodium acetate, the reaction was conducted at 95°C for 10 minutes. The radiochemical purity of the final product was tested by radioactive HPLC. Prior to intravenous administration, the ^{68}Ga-labelled products were purified with a Sep-Pak Light C18 (Waters, USA) cartridge, diluted with normal saline, and further filtered through a polytetrafluoroethylene filter (0.2 μm).

PET/CT Imaging

The Biograph mCT Flow 64 PET/CT scanner (Siemens Healthcare) was used for image acquisition. All patients fasted for more than 6 hours before examination, and ^{18}F-FDG was administered intravenously (3.0-3.7 MBq/kg), ensuring that the patient's blood glucose was less than 10 mmol/L. None of the patients required fasting prior to ^{68}Ga-DOTA-FAPI-04 PET/CT. ^{68}Ga-DOTA-FAPI-04 was intravenously injected at a dose of 3.0-3.5 (MBq/kg). Then, the images were collected at approximately 60±10 min. The patients remained in a quiet environment for approximately 60 min before the examination. None of the patients reported any adverse reactions after drug injection. Low-dose plain scanning CT (120 kV, 146 mAs, slice thickness: 3-5 mm) was performed for attenuation correction and anatomical localization, with a matrix of 512×512. A total of 6-8 beds of PET scans were acquired (1.5 min/bed) with a matrix of 200 × 200. Transverse, sagittal and coronal PET and PET/CT fusion images were obtained by data reconstruction using an ordered subset expected maximum algorithm.

Imaging analysis

The imaging data were read independently by two accredited physicians with more than 10 years of experience in the nuclear medicine department. Disagreements were settled by collective discussion for consensus. All the image data were processed in the Siemens workstation (Syngo.via VB20, MM Oncology), and the lesion boundary was manually delineated as the volume of interest (VOI). The volume maximum standardized uptake value (SUVmax) of all the lesions was automatically measured. Needle biopsy or surgical pathology results were used as the gold standard for all primary tumors and two recurrent lesions. The remaining recurrent and metastatic lesions were confirmed by follow-up CT or MRI.

Statistical analysis

Statistical analysis was performed by SPSS (version 21.0, IBM, USA). Data subjected to normal distribution are expressed as the mean ± standard deviation (M±SD), and normality was verified by the Kolmogorov–Smirnov test. Categorical variables were analysed through the chi-squared test, and Fisher’s exact test was performed when the absolute frequency in crosstab was £ 5. The SUVmax of ^{18}F-FDG and ^{68}Ga-DOTA-FAPI-04 in lesions were compared by two independent sample T tests. One-way ANOVA was used to compare the uptake of ^{18}F-FDG and ^{68}Ga-DOTA-FAPI-04 among the primary, recurrent and metastatic lesions. Two-tailed $p<0.05$ was considered to be statistically significant.

Results

Patient characteristics

All patient characteristics are shown in Table 1. This research included 20 patients, with a median age of 43 years, ranging from 22 years to 78 years, including 12 males and 8 females. The primary lesions were evaluated in 16 patients, and the secondary lesions were evaluated in 4 patients, including 2 patients with postoperative recurrence, 1 patient with recurrence with metastasis, and 1 patient with multiple lung metastases after surgery. A total of 38 lesions were found in 20 patients, including 18 primary lesions, 8 recurrent lesions, and 12 metastatic lesions. The long diameter of all lesions ranged from 0.94-29.1 cm, including 1.5-29.1 cm for primary lesions, 2.66-13.5 cm for recurrent lesions, and 0.94-2.7 cm for metastatic lesions. Twelve patients with primary disease underwent surgical resection, 1 patient with recurrent disease underwent surgical resection accompanied by postoperative radiotherapy, and the remaining patients underwent nonsurgical treatment.

The ^{68}Ga-DOTA-FAPI-04 vs. ^{18}F-FDG PET/CT for detecting the lesions

The detection rate of ^{18}F-FDG PET/CT for all lesions was 94.7% (36/38) and that of ^{68}Ga-DOTA-FAPI-04 PET/CT for all lesions was 100% (38/38). There was no significant difference in the detection rates between them (p=0.493). The detection rates of ^{68}Ga-DOTA-FAPI-04 and ^{18}F-FDG PET/CT for primary lesions were both 100% (18/18). The detection rates of ^{68}Ga-DOTA-FAPI-04 and ^{18}F-FDG PET/CT for recurrent lesions were also both 100% (8/8). The detection rate of ^{68}Ga-DOTA-FAPI-04 PET/CT for metastatic lesions was 100% (12/12) and 83.33% (10/12) for ^{18}F-FDG PET/CT. There was no significant difference in the detection rate of metastatic lesions between the two imaging methods (p=0.478). ^{18}F-FDG and ^{68}Ga-DOTA-FAPI-04 PET/CT for the detection of lesions are shown in Table 2.

^{68}Ga-DOTA-FAPI-04 vs. ^{18}F-FDG PET/CT based on all lesion subtypes

The SUVmax of ^{68}Ga-DOTA-FAPI-04 in all lesions was significantly higher than that of ^{18}F-FDG, 13.44±10.42 vs. 3.05±1.39 (p<0.001) (Table 3). The SUVmax of ^{68}Ga-DOTA-FAPI-04 in primary lesions was significantly higher than that of ^{18}F-FDG, 15.27±8.77 vs. 3.32±1.51 (p<0.001) (Figure 2a, 3, Table 3). The SUVmax of ^{68}Ga-DOTA-FAPI-04 in recurrent lesions was significantly higher than that of ^{18}F-FDG, 18.59±16.32 vs. 3.09±0.96 (p=0.018) (Figure 2a, 4, Table 3). The SUVmax of ^{68}Ga-DOTA-FAPI-04 in metastases was significantly higher than that in ^{18}F-FDG, 7.29±3.26 vs. 2.61±1.42 (p<0.001) (Figure 2a, 5, Table 3).

The uptake of ^{68}Ga-DOTA-FAPI-04 or ^{18}F-FDG among primary, recurrent and metastatic lesions

The SUVmax of ^{68}Ga-DOTA-FAPI-04 in primary lesions was higher than that in metastasis, 15.27±8.77 vs. 7.29±3.26, (p=0.034) (Figure 2b), and the SUVmax of ^{68}Ga-DOTA-FAPI-04 in recurrent lesions was also higher than that in metastasis, 18.59±16.32 vs. 7.29±3.26, (p=0.015) (Figure 2b). However, the SUVmax

of ^{68}Ga-DOTA-FAPI-04 in recurrent lesions was not significantly different from that in primary lesions, 18.59±16.32 vs. 15.27±8.77, (p=0.423) (Figure 2b). There was no significant difference in the uptake of ^{18}F-FDG between primary, recurrent and metastatic tumors, SUVmax (primary 3.32±1.51 vs. recurrent 3.09±0.96, p=0.693), (primary 3.32±1.51 vs. metastatic 2.61±1.42, p=0.176), (recurrent 3.09±0.96 vs. metastatic 2.61±1.42, p=0.153) (Figure 2b).

The uptake of ^{68}Ga-DOTA-FAPI-04 or ^{18}F-FDG in different histopathological lesions, the intermediate vs. the malignant and the SFT vs. the non-SFT.

Among the primary and recurrent lesions, there were 22 intermediate lesions and 4 malignant lesions. The uptake of ^{68}Ga-DOTA-FAPI-04 in malignant lesions was significantly higher than that in intermediate lesions, SUVmax (35.78±15.44 vs. 12.72±5.86, p<0.001) (Figure 6a). There was no significant difference in ^{18}F-FDG uptake between malignant and intermediate lesions, SUVmax (3.73±0.92 vs. 3.16±1.41, p=0.456) (Figure 6a).

There were 23 SFT lesions and 15 non-SFT lesions. The uptake of ^{18}F-FDG in SFT lesions was significantly higher than that in non-SFT lesions, SUVmax (3.65±1.97 vs. 2.66±0.60, p=0.029) (Figure 6b). The uptake of ^{68}Ga-DOTA-FAPI-04 in SFT lesions was higher than that in non-SFT lesions, SUVmax (14.67±12.19 vs. 11.55±6.55), but the difference was not statistically significant (p=0.374) (Figure 6b).

^{68}Ga-DOTA-FAPI-04 PET/CT for the therapeutic evaluation of SFT

One recurrent SFT patient with a total of 5 lesions underwent more than 30 rounds of radiotherapy, and there was a significant difference in ^{68}Ga-DOTA-FAPI-04 uptake of the recurrent lesions before and after treatment (Figure 7-8, Table 4). The interval between the two ^{68}Ga-DOTA-FAPI-04 PET/CT examinations was approximately 5 months. There were no significant differences in the long diameter, short diameter or density of all recurrent lesions before and after treatment (Figure 8, Table 4). The tumor was assessed as stable disease (SD) based on size-based RECIST but as partial metabolic response (PMR) by PERCIST criteria[15]. The patient is in good condition thus far during follow-up. The patient's progression-free survival (PFS) was 37 months, and the overall survival (OS) was 47 months.

Discussion

This study prospectively compared ^{68}Ga-DOTA-FAPI-04 and ^{18}F-FDG PET/CT for the evaluation of primary, recurrent, metastatic fibroblastic lesions, indicating the high practical value of ^{68}Ga-DOTA-FAPI-04 PET/CT in fibroblastic tumors.

Assessment of the extent of primary tumor involvement is essential to reduce postoperative recurrence rates. Previous studies have found that the metabolism of fibroblastic tumors in ^{18}F-FDG PET/CT is very different, ranging from mild to obvious radioactive uptake, and the application of ^{18}F-FDG PET/CT in these tumors is always controversial[16-19]. In this study, ^{68}Ga-DOTA-FAPI-04 PET/CT SUVmax (6.10-

27.20) was found to be significantly superior to ^{18}F-FDG PET/CT SUVmax (2.00-6.90) in evaluating fibroblastic primary tumors, which is more conducive to outlining the boundary between the tumor and the surrounding normal tissue, thus obtaining the negative surgical margin as much as possible. Previous studies have also demonstrated that ^{68}Ga-DOTA-FAPI-04 PET/CT is equivalent or superior to ^{18}F-FDG PET/CT in assessing primary tumors in a variety of epithelioid tumors, including lung cancer, digestive system tumors, and nasopharyngeal carcinoma[20-23]. Recent studies have demonstrated the perfect diagnostic performance of ^{68}Ga-DOTA-FAPI-04 PET/CT for mesenchymal origin-containing fibroblastic tumors, with a sensitivity and positive predictive value of 96% and 100%, respectively, and the strong correlation between FAPI immunohistochemical expression and SUVmax was confirmed at the pathological level[24].

Considering the high tendency of recurrence and metastasis of fibroblastic tumors, it is extremely important to find appropriate means to monitor the occurrence. This research confirmed the extreme phrenetic uptake of ^{68}Ga-DOTA-FAPI-04 in the recurrence and metastases of the lesions. The suitability of ^{18}F-FDG PET/CT is inferior due to the low uptake of the agent in recurrent and metastatic lesions. A recent evaluation of ^{18}F-FDG matched ^{68}Ga-DOTA-FAPI-04 PET/CT in recurrent soft tissue sarcoma found that ^{68}Ga-DOTA-FAPI-04 was superior to ^{18}F-FDG in terms of sensitivity (97.52% vs 65.96%), specificity (60.71% vs 21.43%), PPV (96.15% vs 89.42%), NPV (70.88% vs 5.88%) and accuracy (94.19% vs 61.94%) in diagnosing recurrent disease (P <0.001), accompanied by significantly higher SUVmax (12.64 ± 15.67 vs. 7.76 ± 4.45, p<0.001)[13], which is consistent with our research. This study also found that the uptake of ^{68}Ga-DOTA-FAPI-04 in primary and recurrent tumors was higher than that in metastatic tumors (p<0.05). Therefore, on the one hand, it is speculated that it may be related to the generally smaller metastatic lesions, on the other hand, it may also be related to the changes in the tumor microenvironment in the transplanted organ. Previous studies have also shown that the expression of FAP in tumors is regulated by a variety of cytokines[25, 26]. The uptake of ^{18}F-FDG was low in primary, recurrent and metastatic lesions, without a significant difference.

Various studies have also shown that ^{68}Ga-DOTA-FAPI-04 PET/CT leads to tumor upstaging or downstaging of various neoplasms, especially from locoregional to metastatic lesions, leading to changes in the patient's treatment plan[27-29]. In this study, ^{68}Ga-DOTA-FAPI-04 PET/CT found more metastases in one patient with malignant SFT, but compared with ^{18}F-FDG PET/CT, ^{68}Ga-DOTA-FAPI-04 PET/CT did not change the staging, restaging and treatment decisions of all patients, which may be related to the inert metastatic tendency and lower sample size of the tumors. The study also found that for primary and recurrent lesions, the uptake of ^{68}Ga-DOTA-FAPI-04 in malignant lesions was significantly higher than that in intermediate lesions. Therefore, it was speculated that fibroblasts in malignant lesions were more active and expressed more FAP, which is particularly important for screening out malignant lesions and formulating treatment plans in advance. Conversely, ^{18}F-FDG cannot be used in the identification of malignant lesions. In this study, when comparing the difference in imaging agent uptake between intermediate and malignant lesions, the malignant lesions were not included in metastasis

because the nature of tumors would be affected by surrounding tissues and their microenvironment, and the activity of tumors itself would change[30]. Interestingly, the uptake of ^{18}F-FDG in the SFT group was lower than that in the non-SFT group, but there was no significant difference in the uptake of ^{68}Ga-DOTA-FAPI-04 between the two groups, which remains to be further studied to determine whether it can reflect the higher invasiveness of non-SFT.

With the diversification of cancer treatment, an increasing number of solid tumors are being evaluated beyond RECIST criteria because of obvious lag based on tumor size and volume[31]. New structured qualitative treatment response criteria based on ^{18}F-FDG PET/CT have been proposed and have achieved substantial implications for response assessment in a variety of tumors[8, 32]. However, for tumors with low ^{18}F-FDG uptake at baseline, such as SFT, this approach is ineffective. It is encouraging that ^{68}Ga-DOTA-FAPI-04 PET/CT may early monitor the treatment effect of recurrent SFT through the dynamic change of SUVmax. The uptake of ^{68}Ga-DOTA-FAPI-04 in the tumor was significantly reduced after multiple radiotherapy compared to baseline in this study, SUVmax (4.42±1.11 vs. 9.34±3.46, p=0.016), but the long, short diameter and density of the tumor did not change significantly. Although this objective change has not been verified from pathology, it has given better inspiration for prospective follow-up research by expanding the sample. In addition, fibroblast activated protein (FAP) is currently a promising target for the treatment of many malignancies, including pancreatic, breast, rectal and ovarian cancers. FAP can be labelled with radionuclides for therapeutic diagnostic applications, and frequently used radiopharmaceuticals include ^{90}Y-FAPI-46[33], [^{177}Lu]FAPI-46[34], and [^{225}Ac]FAPI-46[35].
Patients tolerated treatment well with few side effects (pancytopenia, leukopenia, and pain)[36]. Based on the high uptake of FAPIs by primary, recurrent and metastatic fibroblastic tumors, therapeutic FAPI probes could be an ideal treatment for recurrent and metastatic lesions, which needs to be further confirmed in prospective trials.

The limitations of this study are the small number of patients and the limited inclusion of fibroblastic tumors. Due to the low incidence and the wide variety of fibrous tumors, further research including different subtypes is required in multiple centers. The second minor defect is that this study did not correlate the SUVmax of ^{68}Ga-DOTA-FAPI-04 with the immunohistochemistry of pathology FAPI, but the correlation has been reported in previous studies[37].

Conclusions

^{68}Ga-DOTA-FAPI-04 PET/CT is a promising imaging agent for the application of fibroblastic tumors. This study confirms that ^{68}Ga-DOTA-FAPI-04 PET/CT outperformed ^{18}F-FDG PET/CT in displaying the primary, recurrent and metastatic lesions of fibroblastic tumors. ^{68}Ga-DOTA-FAPI-04 PET/CT may also show potential value for judging the nature and monitoring the therapeutic response of tumors.

Declarations

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Conflicts of interest: None declared to all authors.

Availability of data and material: The patient data generated during the current study are not publicly available due to patient privacy considerations. All other data are available from the correspondingauthor on reasonable request

Ethics approval: This study was approved by the Ethics Committee of Peking University Cancer Hospital (2019KT95), and registered in the Chinese Clinical Trial Registry (ChiCTR2000038080).

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Tables

Table 1: Summary of Patient Characteristics

Characteristics	value
No. of patients	20
Primary	16
Recurrence/metastatic	4
Pattern of patients	
Single	15
Multiple	5
Gender	
Male	12
Female	8
Median age (Range)	43(22-78)
Treatment	
Surgically removed	13
Combined radiotherapy after surgery	1
Arterial embolization and targeted therapy	1
Chemotherapy without surgery	2
Radiotherapy for recurrent lesions	1
Targeted therapy and immunotherapy	2
Histopathology	
Solitary fibrous tumor	13
Desmoid tumor	2
Dermatofibrosarcoma protuberans	1
Malignant solitary fibrous tumor	2
Myxofibrosarcoma	1
High-grade fibrosarcoma	1
No. of lesions	38
Primary	18
Recurrent	8
Metastatic	12

Long diameter of lesions (Range) (cm)	
All	0.94-29.1
Primary	1.5-29.1
Recurrent	2.66-13.5
Metastatic	0.94-2.7
Involved sites	
Pleura	13
Chest wall	5
Lung	7
Abdominal pelvic	12
Bone	1

Table 2 The ^{18}F-FDG and ^{68}Ga-DOTA-FAPI-04 PET/CT for detecting lesions

	Total numbers	^{18}F-FDG	^{68}Ga-FAPI	*p*
All lesions	38	36(94.7%)	38(100%)	0.493
Primary lesions	18	18(100%)	18(100%)	/
Recurrence	8	8(100%)	8(100%)	/
Metastases	12	10(83.33%)	12(100%)	0.478

Table 3 SUVmax of ^{18}F-FDG vs. ^{68}Ga-DOTA-FAPI-04 on all and subtypes of lesions

	^{18}F-FDG	^{68}Ga-FAPI	*p*
All lesions	3.05±1.39 (1.00-6.90)	13.44±10.42 (3.10±54.50)	<0.001*
Primary lesions	3.32±1.51 (2.00-6.90)	15.27±8.77 (6.10-27.20)	<0.001*
Recurrence	3.09±0.96 (2.10-5.10)	18.59±16.32 (5.30-54.50)	0.018*
Metastases	2.61±1.42 (1.00-6.60)	7.29±3.26 (3.10-16.10)	<0.001*

*p<0.05

Table 4 Imaging characteristics of ^{68}Ga-FAPI in one patient with SFT before and after treatment

	Before treatment	After treatment	*p*
Long diameter (cm)	8.26±3.05 (5.59-13.50)	10.22±3.53 (7.54-16.12)	0.374
Short diameter (cm)	4.36±1.08 (3.52-6.24)	5.27±2.10 (2.91-8.22)	0.415
Density (HU)	27.60±1.52 (26-29)	25.80±4.32 (22-31)	0.405
SUVmax	9.34±3.46 (5.30-13.70)	4.42±1.11 (3.20-6.20)	0.016*

*p<0.05

Figures

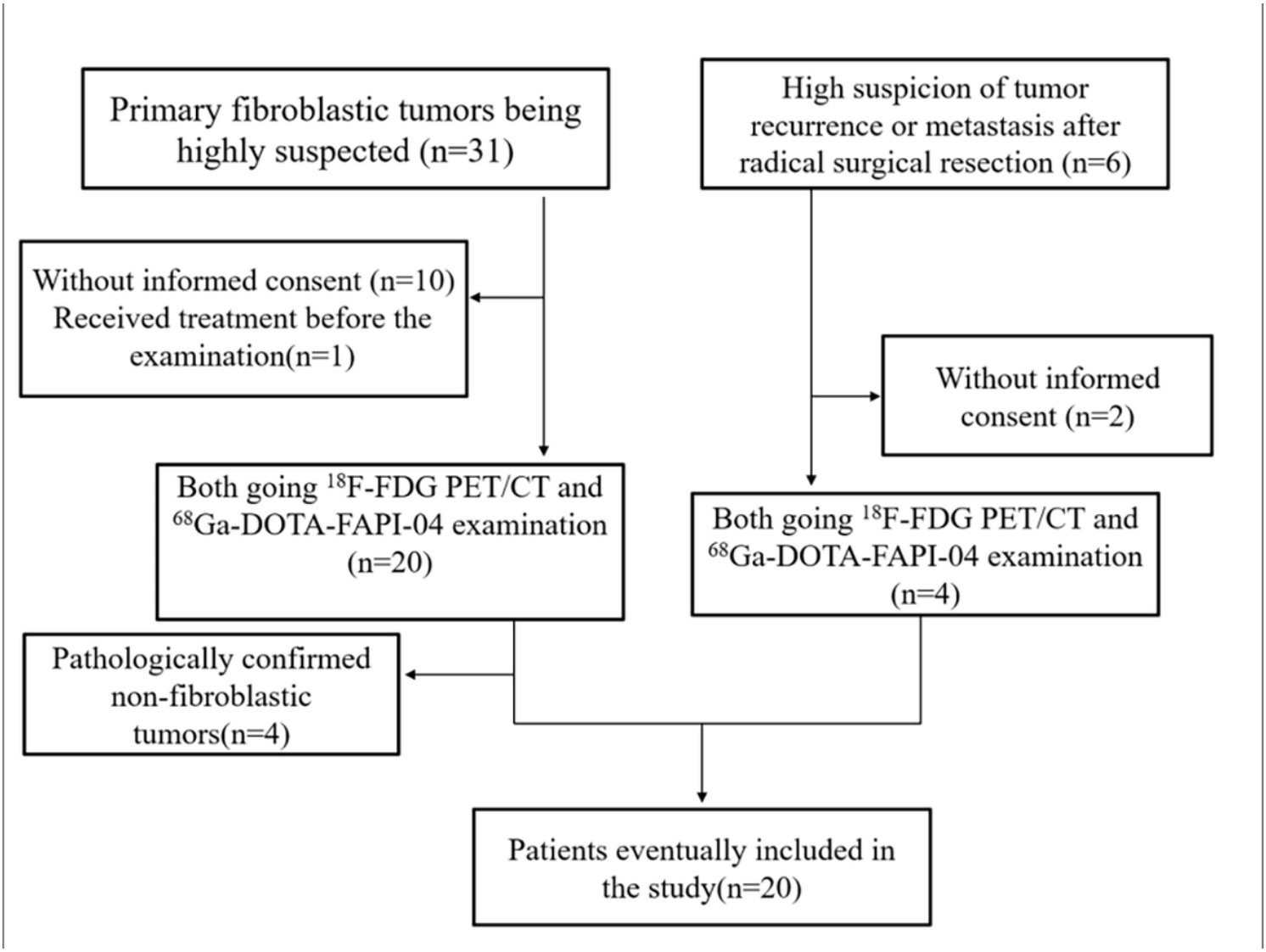

Figure 1

Flow chart of patient enrollment.

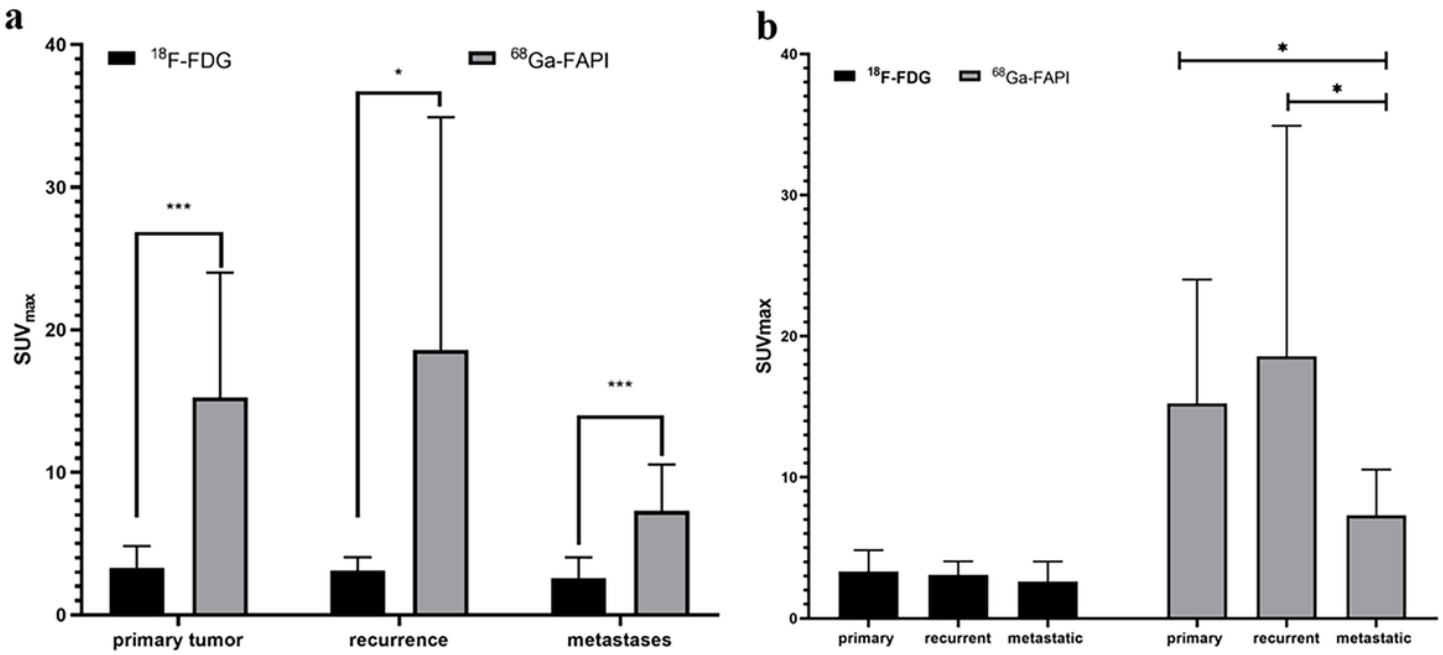

Figure 2

Comparing the uptake of ^{18}F-FDG and ^{68}Ga-DOTA-FAPI-04 in primary, recurrent and metastatic lesions (a). The differences in the uptake of ^{18}F-FDG or ^{68}Ga-DOTA-FAPI-04 among primary, recurrent and metastatic lesions (b). (*p<0.05, ***p<0.001).

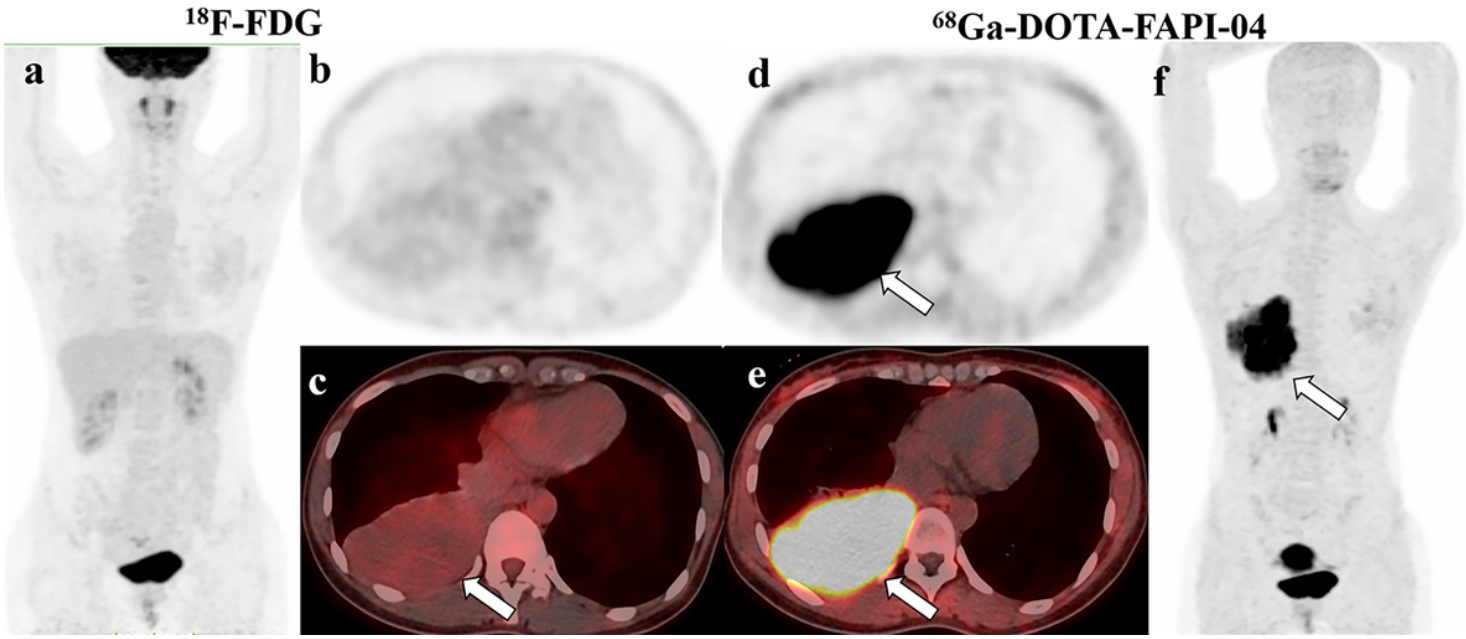

Figure 3

A 41-year-old female was found to have a large mass in the right thoracic cavity by chest CT, and PET/CT was performed for further examination. ^{18}F-FDG MIP imaging showed no abnormal radioactive

concentration (a), and axial imaging showed mild radioactive concentration of the right thoracic tumor (b, c, arrow), SUVmax2.1. ^{68}Ga-DOTA-FAPI-04 MIP (f, arrow) and axial imaging (d, e, arrows) showed abnormal radioactive uptake of the right thoracic mass, SUVmax 19.9. The patient underwent mass resection, and the postoperative pathology was SFT.

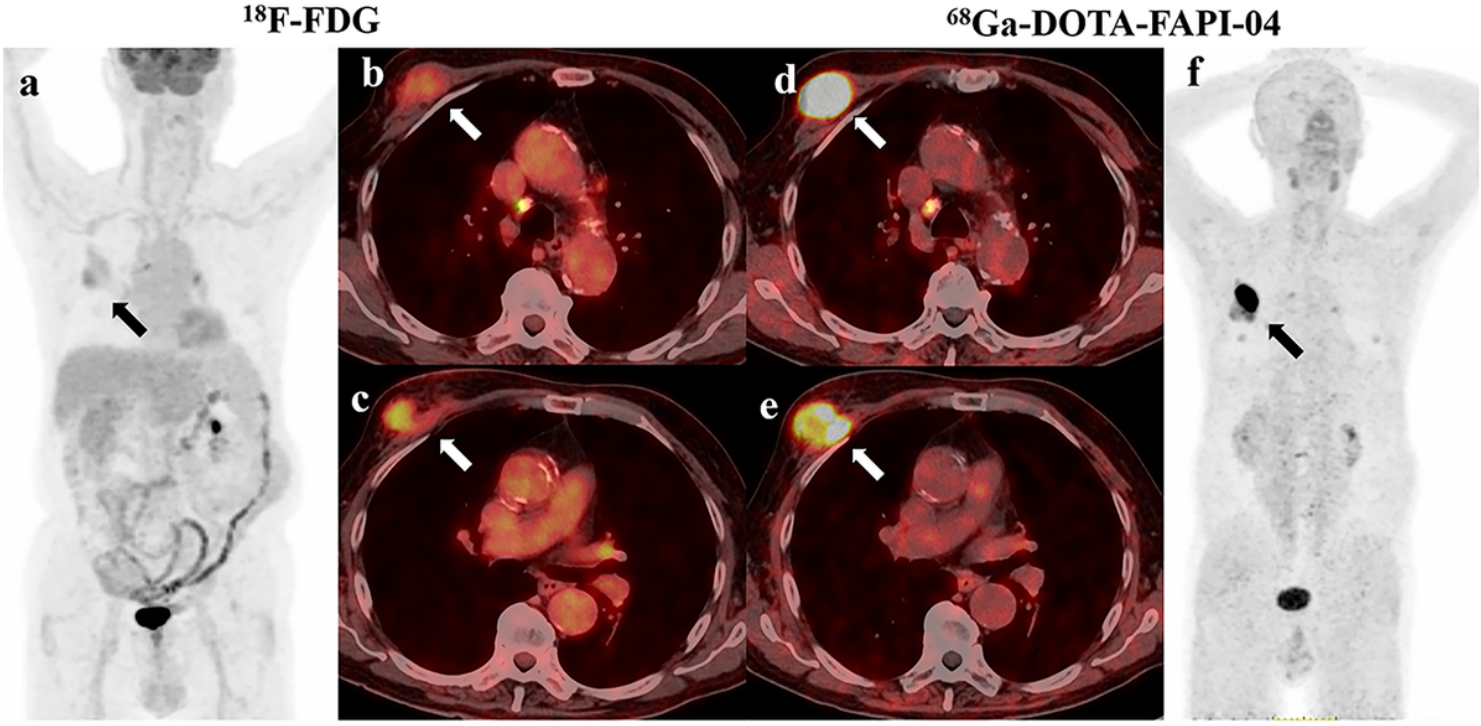

Figure 4

A 78-year-old man with myxofibrosarcoma underwent surgical resection for more than 1 year. PET/CT was performed to evaluate recurrence. ^{18}F-FDG PET/CT MIP (a, arrow) and axial fusion images showed two recurrent lesions with radioactive uptake (b, c, arrows), SUVmax 3.3, 5.1. ^{68}Ga-DOTA-FAPI-04 PET/CT MIP (f, arrow) and axial fusion images (d, e, arrows) showed obvious radioactive uptake in recurrent lesions, SUVmax 28.6, 18.9. The involvement of lesions in ^{68}Ga-DOTA-FAPI-04 PET/CT was larger than that in ^{18}F-FDG PET/CT. The patient underwent extended resection of the recurrent tumor, and radiotherapy was performed after surgery.

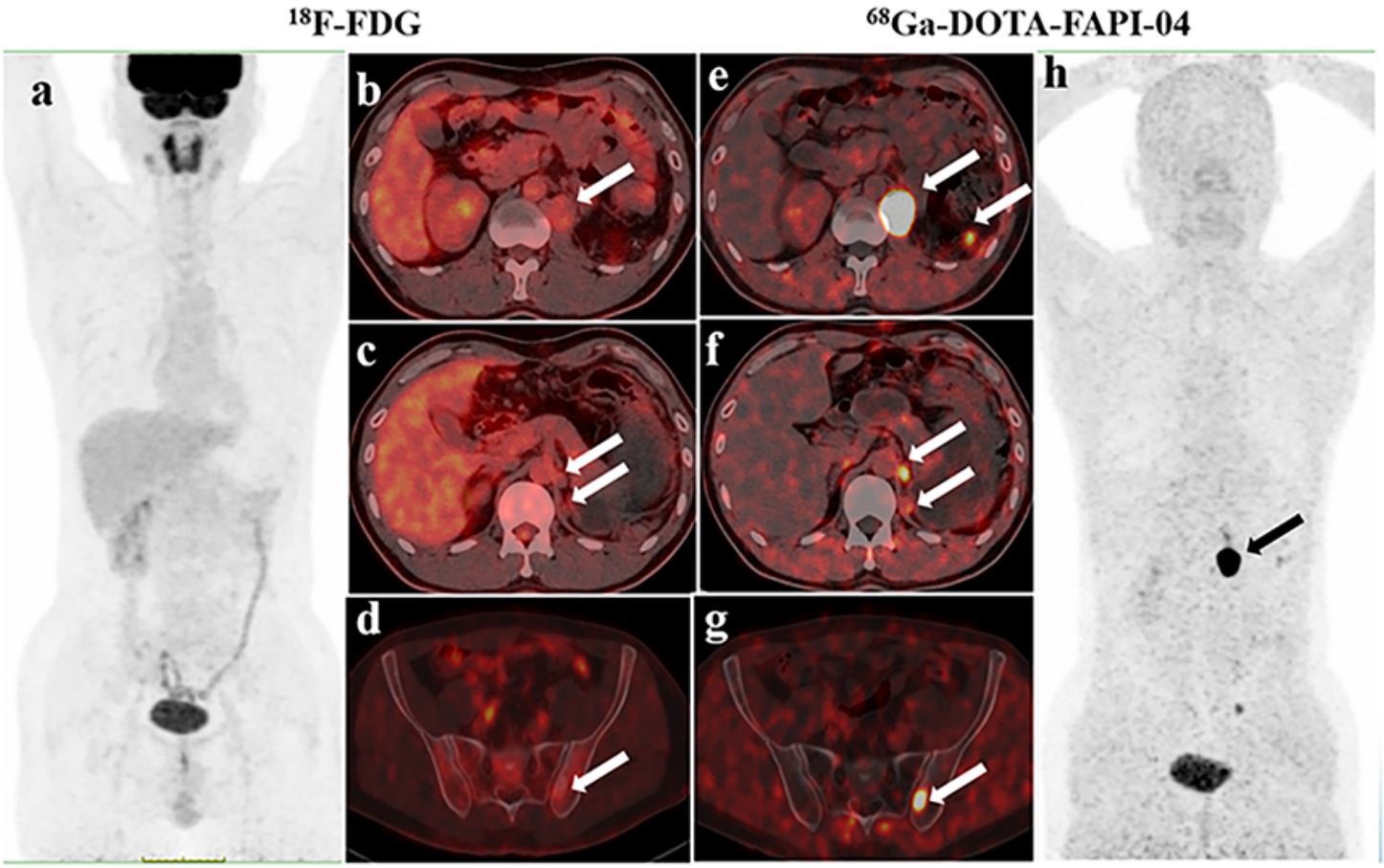

Figure 5

A 35-year-old male underwent left kidney, spleen, and part of the psoas muscle resection for malignant SFT. PET/CT was performed to assess recurrence and metastases. ^{18}F-FDG PET/CT MIP image (a) showed no abnormal ^{18}F-FDG uptake. Fusion images showed recurrent nodules in the psoas muscle, SUVmax 3.1 (b, arrow). Two metastatic nodules of the diaphragm had no abnormal radioactivity, SUVmax2.4, 2.6 (c, arrows), and the local density of the left iliac bone was slightly increased, SUVmax2.3 (d, arrow). ^{68}Ga-DOTA-FAPI-04 PET/CT MIP (h, arrow) and axial fusion images showed significantly increased uptake of ^{68}Ga-DOTA-FAPI-04 in the psoas major, SUVmax54.5 (e, arrow). Except for two intraperitoneal uptake nodules, SUVmax 3.1, 6.5 (f, arrows), the peritoneal ^{68}Ga-DOTA-FAPI-04 concentration was also seen, SUVmax 5.7 (e, arrow), accompanied by increased ^{68}Ga-DOTA-FAPI-04 uptake in the left iliac bone, SUVmax 8.7 (g, arrow).

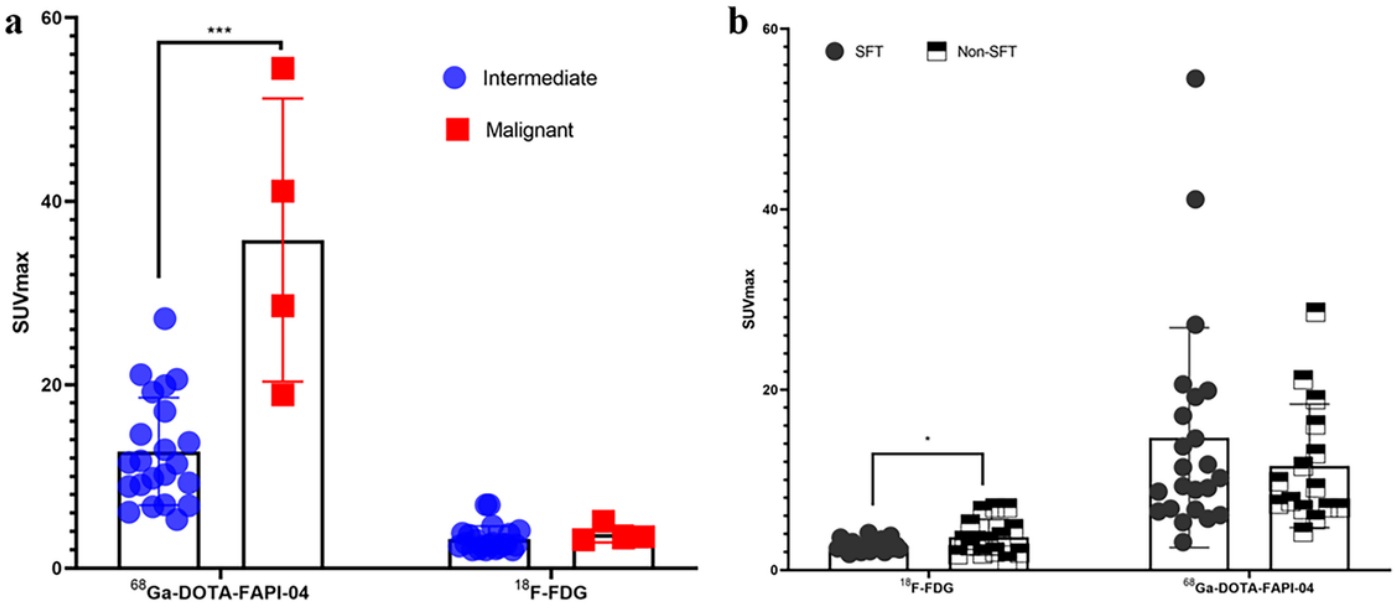

Figure 6

Uptake of ^{18}F-FDG and ^{68}Ga-DOTA-FAPI-04 in intermediate vs malignant lesions as well as SFT vs non-SFT lesions. (*p<0.05, ***p<0.001)

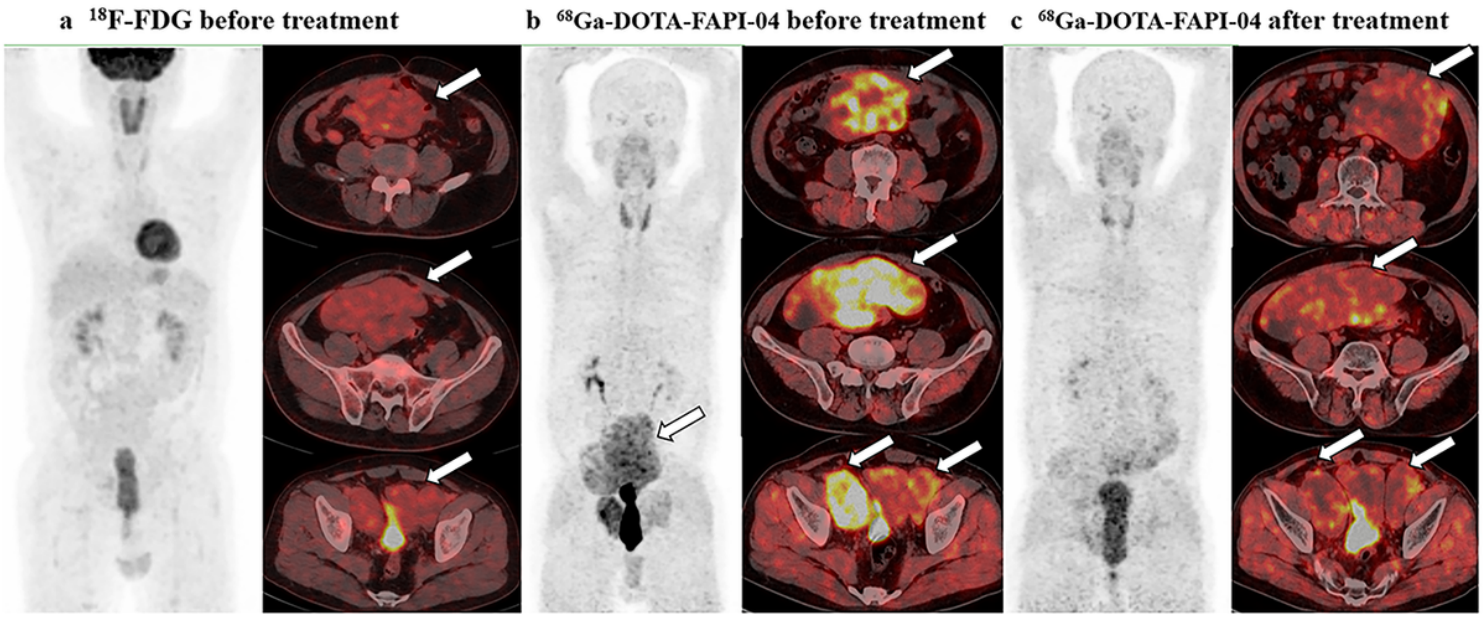

Figure 7

A 61-year-old man underwent resection of SFT of the prostate 3 years ago. PET/CT was performed for further evaluation of recurrence. ^{18}F-FDG PET/CT (a, before treatment) showed multiple abdominal and pelvic masses, SUVmax 2.1-3.6. ^{68}Ga-DOTA-FAPI-04 PET/CT (b, before treatment) showed multiple masses with increased ^{68}Ga-DOTA-FAPI-04 uptake in the lower abdomen, SUVmax 5.3-13.7. After more than 30 rounds of radiotherapy, the patient underwent re-examination with ^{68}Ga-DOTA-FAPI-04 PET/CT (c,

after treatment), which showed that the tumor size did not change significantly, but the ^{68}Ga-DOTA-FAPI-04 uptake was lower than before, with an SUVmax of 3.2-6.2.

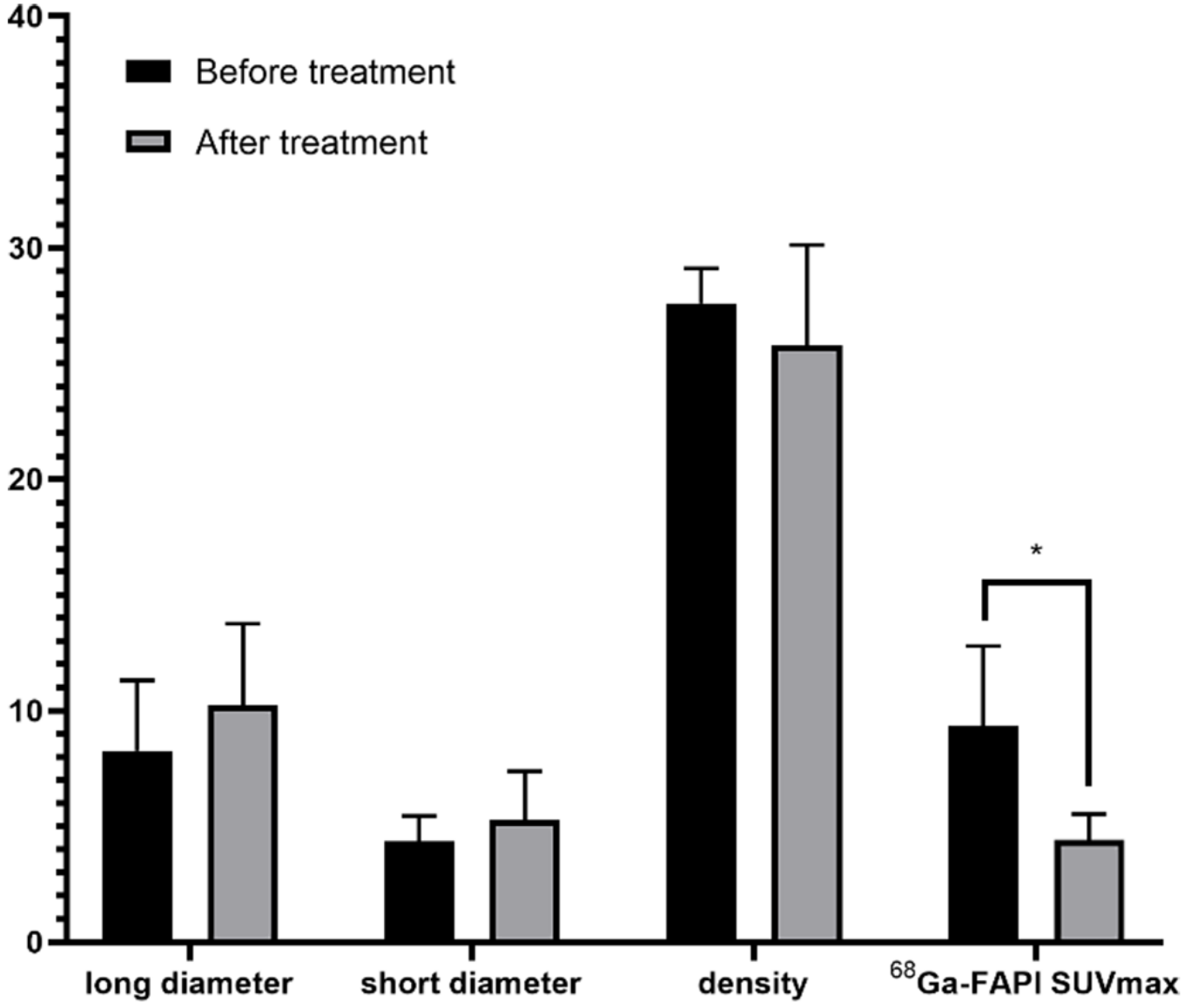

Figure 8

Changes in the long diameter, short diameter, density and ^{68}Ga-DOTA-FAPI-04 uptake of recurrent SFT before and after treatment. (*p<0.05)