[^{68}Ga]Ga-DOTA-FAPI-04 PET/CT in The Staging of Gastric Cancer: Improved Diagnostic Efficacy Confirmed By Postoperative Histopathology

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Abstract

Purpose

This study aimed to compare the diagnostic performance of [^{68}Ga]Ga-DOTA-FAPI-04 and [^{18}F]-FDG PET/CT in the primary and metastatic lesions of gastric cancer.

Methods

Fifty-six patients with histologically proven gastric carcinomas were enrolled in this study. Each patient underwent both [^{18}F]-FDG and [^{68}Ga]Ga-FAPI-04 PET/CT within one week. Activity of tracer accumulation in lesions were assessed by maximum standardized uptake value (SUV_{max}) and TBR (lesions SUV_{max}/ ascending aorta SUV_{mean}). Histological work-up including immunohistochemical staining for FAP served as a standard of reference.

Results

[^{68}Ga]Ga-FAPI PET/CT is superior in detecting primary tumors both in patient-based (100% [45/45] vs. 97.8% [44/45]) and lesion-based analyses (97.8% [45/46] vs. 95.7% [44/46]), showing higher SUV_{max} (10.25 vs. 8.13, $P = 0.004$) and TBR (11.63 vs. 5.83, $P < 0.001$), compared with [^{18}F]-FDG PET/CT. The specificity and positive predictive value of [^{68}Ga]Ga-FAPI were significantly higher than that of [^{18}F]-FDG (100.0% vs. 97.7%, $P < 0.001$; 100.0% vs. 57.1%, $P = 0.001$) in determining the lymph node (LN) metastases. [^{68}Ga]Ga-FAPI PET/CT was superior to [^{18}F]-FDG PET/CT in N-staging (47.1% [8/17] vs. 23.5% [4/17]), and in evaluation for LN, peritoneum and bone metastases. [^{68}Ga]Ga-FAPI PET/CT detected positive recurrent lesions in all patients and showed more positive lesions and clearer tumor delineation. Two patients underwent follow-up [^{68}Ga]Ga-FAPI PET/CT scans after chemotherapy, which both showed remission.

Conclusions

[^{68}Ga]Ga-FAPI PET/CT can better detect primary gastric cancer and metastatic lesions in peritoneum, abdominal LNs and bone, showing high usefulness in guiding N staging. Furthermore, [^{68}Ga]Ga-FAPI PET/CT provides more information for patients with recurrence detection and also has great potential in monitoring response to treatment.

Introduction

Gastric cancer is the fifth most diagnosed malignancy and ranks the third most common cause of cancer-related deaths worldwide [1], with over 1 million estimated new cases annually and 784,000 deaths globally in 2018. Although the diagnosis and treatment of gastric cancer have improved, the prognostic outcome associated with this malignancy remains disappointing [2]. Therefore, early diagnosis, accurate staging and quantitative evaluation are of great importance for the treatment management and prognosis of these patients [3].

In clinical routine practice, gastroscopy and imaging examinations are the main approaches for diagnosing gastric cancer. Moreover, imaging modalities, such as computed tomography (CT) and magnetic resonance imaging (MRI), have been used for the primary staging of gastric cancer. However, CT and MRI are inadequate for staging, especially regarding the distant metastasis. [^{18}F]-Fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET/CT) is a potentially valuable imaging modality for providing clinically relevant information on nodal staging and metastatic status of gastric cancer [4]. But [^{18}F]-FDG PET/CT sometimes suffers from low sensitivity in the detection of primary lesions of gastric cancer due to the significant variation of [^{18}F]-FDG uptake in different histologic types of gastric cancer [5]. In addition, the low-to-moderate sensitivity for the detection of lymph node metastases and peritoneal metastases further limits the use of [^{18}F]-FDG for determining the clinical stage of gastric cancer. Hence, there is an urgent need for developing more sensitive PET probes to improve the characterization of gastric cancer and to contribute to individualized patient care.

Fibroblast activation protein (FAP) is highly expressed in cancer-associated fibroblasts (CAFs) of many epithelial carcinomas rather than normal fibroblasts and benign tumor stromal fibroblasts [6, 7]. Therefore, FAP targeted imaging can be considered as a promising approach for the visualization of tumor stroma, which mainly consists of CAFs and contributes up to 90% of the gross tumor mass [6, 7]. The association between FAP overexpression and poor prognosis in cancer patients leads to the hypothesis that FAP activity influences tumor growth, invasion, and metastasis [8–12]. In this regard, FAP-targeted radiopharmaceuticals based on the FAP-specific inhibitor (FAPI) have

recently been developed [9–13]. [^{68}Ga]Ga-FAPI, the most promising PET tracer, has been increasingly investigated in various tumors [13–15]. Previous studies have shown that gastric cancer can take up [^{68}Ga]Ga-FAPI, and more abnormal foci can be detected with [^{68}Ga]Ga-DOTA-FAPI-04 than with [^{18}F]-FDG, especially in the liver regions, peritoneum, mesentery, and omentum [14]. However, to the best of our knowledge, no studies regarding the potential advantage of [^{68}Ga]Ga-FAPI in gastric cancer staging and response to chemotherapy have been reported.

Thus, the aim of this study was to investigate the potential usefulness of [^{68}Ga]Ga-DOTA-FAPI-04 PET/CT for the diagnosis of primary and metastatic lesions in gastric cancer by comparison with [^{18}F]-FDG PET/CT, and to evaluate the diagnostic efficiency and N staging of metastatic lymph nodes based on postoperative pathology, in which FAP expression was confirmed by immunohistochemistry.

Materials And Methods

Patients

This prospective study was approved by the institutional review board of the First Affiliated Hospital, Fujian Medical University and was registered online at NIH ClinicalTrials.gov (NCT04499365). Between August 2020 and August 2021, 56 patients (40 men, 16 women; median age, 63.75 ± 14.91 years) were recruited into this study finally, including 45 patients with primary tumors and 11 patients with recurrent lesions after surgery. The key eligibility criteria were as follows: (i) histologically proven gastric carcinomas by gastroscopy or surgery; (ii) agreeing to perform both [^{18}F]-FDG and [^{68}Ga]Ga-FAPI PET/CT and having signed a written informed consent; (iii) the interval of [^{18}F]-FDG and [^{68}Ga]Ga-FAPI PET/CT scanning was less than 1 week; (iv) no treatment during [^{18}F]-FDG and [^{68}Ga]Ga-FAPI PET/CT scanning interval. Exclusion criteria were as follows: (i) no evaluable lesions after therapy; (ii) pregnant or lactational women.

Radiopharmaceutical Preparation

Good-manufacturing-practice (GMP) grade precursor, DOTA-FAPI-04 was supplied by Jiangsu Huayi Technology Co. (Jiangsu, China). [^{68}Ga]$GaCl_3$ was eluted from a [^{68}Ge]/[^{68}Ga]Ga generator (JSC Isotope, Russia) using 5 mL of 0.1 M hydrochloride acid. Radiolabeling was performed manually in a hot cell as previously reported [16]. [^{18}F]-FDG was purchased from Dongcheng AMS Pharmaceutical (Fujian, China). The radiochemical purity of the final products was both over 95%.

PET/CT imaging

For [^{18}F]-FDG PET/CT, the patients fasted for more than 6 hours, and were monitored the blood glucose level (<11.0 mmol/L) before the injection of [^{18}F]-FDG (3.7MBq/kg). [^{68}Ga]Ga-FAPI PET/CT scans were obtained after the intravenous injection of 48 ± 12.08 minutes of 111-185 MBq of [^{68}Ga]Ga-FAPI-04. All of the PET/CT images were acquired from the head to upper thighs. The CT scans were performed with tube voltage of 120 kV, effective tube current of 70-120 mA (CareDose 4D [Biograph mCT64, Siemens Healthcare]) and a slice thickness of 3mm. PET scans were immediately performed after the CT scan in 3D acquisition mode (matrix: 200 × 200) with 6-8 bed positions and 2 min/position. PET data were reconstructed iteratively (2 iterations and 21 subsets) with CT data for attenuation correction, and the PET/CT images were then co-registered and displayed using dedicated software (TrueD software, Siemens).

PET/CT imaging analysis

[^{18}F]-FDG and [^{68}Ga]Ga-FAPI PET/CT images were analyzed independently on a Syngo MultiModality Workplace (Siemens, Germany) by two experienced nuclear medicine physician groups (two physicians in each group). Any difference in the determinations between these two physicians was resolved by consensus.

Primary tumors and metastatic lesions were identified as positive if the activity exceeded that of the adjacent background tissues, excluding the possibilities of physiological uptake, trauma, infection, and inflammation. The regions of interest (ROIs) were drawn around the lesions on the transverse slices for semiquantitative analysis. The maximum standard uptake value (SUV_{max}) was automatically calculated, and the target-to-background ratio (TBR) was calculated by dividing the lesion SUV_{max} by the SUV_{mean} of the ascending aorta. Semiquantitative assessment was divided into patient-based and lesion-based investigations. The former included the highest single lesion of the primary tumor or metastases in each organ/region, while the latter referred to the analysis including all lesions (≤5) or the 5 lesions with highest activity (>5) if there were multiple metastases. The visually interpreted PET/CT results were compared with pathological results obtained from gastroscopy or surgery. If tissue diagnosis was not applicable, the follow-up data including the results of laboratory tests and medical imaging could also serve as a reference for tumor diagnosis. Pathological TNM stage was assigned based on the eighth edition of the American Joint Committee on Cancer staging system [17].

Histopathological analysis

Immunohistochemistry (IHC) for FAP (alpha antibody ab207178, Abcam, 1:250) was performed in 17 patients receiving surgery on their paraffin-embedded tissue slides of primary tumor and sectional LN metastases according to standard IHC protocols. Semi-quantitative IHC analyses of FAP expression were performed by an experienced pathologist (scored 0, no staining; scored 1, 1-10% stromal staining; scored 2, 10-50% stromal staining; scored 3, 51-100% stromal staining).

Statistical analysis

Statistical analyses were performed on SPSS software (23.0, IBM Inc.). Continuous variables are expressed as mean ± SD. Categorical variables are expressed as number and percentage. Wilcoxon signed-rank test was used to assess the differences of SUV_{max} and TBR between two groups. The number of positive lesions was compared using the chi-squared test. The McNemar's text and chi-squared test were applied to compare the differences of sensitivity, specificity, accuracy, positive predictive value (PPV) and negative predictive value (PPV) between [^{68}Ga]Ga-FAPI and [^{18}F]-FDG scans. Correlation between the two parameters was determined using Spearman test. A p-value of < 0.05 was defined as statistically significant.

Results

Patients' characteristics

The flow diagram of the study design is presented in Fig. 1. 56 patients with gastric cancer confirmed by surgery or gastroscopy were enrolled in this study. A total of 625 abdominal lymph nodes were resected from 17 patients who underwent surgery, of which 16.6% (104/625) metastatic lesions in 11 patients. Patient characteristics are listed in Table 1.

Table 1
Patients characteristics

Characteristics	N (%)
Patient No.	56
Age, years	
Median(range)	63.75±14.91 (28-85)
Sex	
Male	40 (71.4%)
Female	16 (28.6%)
Patient status	
staging	45
recurrence detection after surgery	11
Histopathology (n = 45)	
Containing SRCC	17 (37.8%)
Without SRCC	28 (62.3%)
T stage (n = 17)	
1	2
2	3
3	9
4	3
N stage (n = 17)	
0	6
2	5
3	6
Clinical stage (n = 17)	
I	5
II	1
III	11
No., number; SRCC: signet-ring cell carcinoma	

Comparison of [^{68} Ga]Ga-FAPI and [^{18} F]-FDG in the detection of primary tumors

Eleven patients with recurrent lesions after surgery were not included in the semiquantitative analysis of primary lesions which had been surgically removed. Remaining 45 patients which had 46 evaluable primary foci were further included for primary lesion assessment. The depth of primary gastric cancer foci was 1.44 ± 0.45 cm (range 0.60-2.91 cm). The number of positive lesions and the semiquantitative parameters of [^{68}Ga]Ga-FAPI and [^{18}F]-FDG PET/CT are displayed in Table 2. For the patient-based analysis, the primary tumors detection rates were 100% (45/45) for [^{68}Ga]Ga-FAPI PET/CT and 97.8% (44/45) for [^{18}F]-FDG PET/CT. The false-negative tumor from [^{18}F]-FDG PET/CT was gastric signet-ring cell carcinoma (Fig. 2). [^{68}Ga]Ga-FAPI PET/CT showed higher uptake (mean SUV_{max}, 10.25 vs. 8.13, P = 0.004) and higher tumor-to-background contrast (mean TBR, 11.63 vs. 5.83, P < 0.001) than [^{18}F]-FDG PET/CT. For the lesion-based analysis, the primary tumor detection rates were 97.8% (45/46) for [^{68}Ga]Ga-FAPI PET/CT and 95.7% (44/46) for [^{18}F]-FDG PET/CT. The pathological finding of the lesion, ignored by the two PETs, was high-grade intraepithelial neoplasia with cancerization, and the lesion was also negative on CT.

Table 2

Comparison of [^{68}Ga]Ga-FAPI and [^{18}F]-FDG uptake

		Primary tumor	Lymph node	Peritoneal	Bone	Liver	Ovary	Adrenal gland	Erector spinae	Lung
Patient based analysis		**45**	**11**	**13**	**4**	**3**	**2**	**1**	**1**	**1**
Patient No.	**[^{68}Ga]Ga-FAPI PET/CT**	45	5	13	4	3	2	1	1	1
	[^{18}F]-FDG PET/CT	44	5	9	4	3	2	1	1	1
	P **Value**	1.000	NA	0.096	NA	NA	NA	NA	NA	NA
SUVmax	**[^{68}Ga]Ga-FAPI PET/CT**	10.25±3.84	7.36±3.89	8.24±4.46	6.99±3.44	9.01±6.13	4.92±1.35	4.10	6.79	2.74
	[^{18}F]-FDG PET/CT	8.13±4.85	7.64±4.21	5.96±2.14	8.67±5.24	15.19±16.02	4.42±1.00	10.21	9.67	2.85
	Z	-2.843	-0.313	-1.035	-0.289	-0.218	-0.775	NA	NA	NA
	P **Value**	**0.004**	0.754	0.324	0.886	1.000	0.667	NA	NA	NA
TBR	**[^{68}Ga]Ga-FAPI PET/CT**	11.63±5.42	8.83±4.62	9.47±5.85	6.95±4.58	9.27±6.37	5.21±0.18	4.10	6.79	2.45
	[^{18}F]-FDG PET/CT	5.83±3.62	5.21±3.47	4.41±1.86	7.28±4.26	9.88±8.22	3.12±0.18	10.86	10.29	1.64
	Z	-5.375	-1.567	-2.170	0.000	-0.218	-1.549	NA	NA	NA
	P **Value**	**<0.001**	0.117	**0.030**	1.000	1.000	0.333	NA	NA	NA
Lesion based analysis		**46**	**104**	**159**	**64**	**7**	**4**	**1**	**1**	**1**
Lesion No.	**[^{68}Ga]Ga-FAPI PET/CT**	45	20	159	64	7	4	1	1	1
	[^{18}F]-FDG PET/CT	44	16	47	55	5	4	1	1	1
	P **Value**	1.000	0.538	**<0.001**	**0.003**	0.462	NA	NA	NA	NA
SUVmax	**[^{68}Ga]Ga-FAPI PET/CT**	10.25±3.84	6.27±2.13	7.10±3.73	6.44±2.36	7.50±5.25	3.86±1.48	4.1	6.79	2.74
	[^{18}F]-FDG PET/C	8.13±4.85	6.08±3.72	4.48±1.78	7.05±3.83	20.40±13.40	3.43±1.33	10.21	9.67	2.85
	Z	-2.843	-1.178	-3.036	-0.221	-1.543	-0.577	NA	NA	NA
	P **Value**	**0.004**	0.239	**0.002**	0.839	0.149	0.686	NA	NA	NA
TBR	**[^{68}Ga]Ga-FAPI PET/CT**	11.63±5.42	8.03±2.66	8.05±4.79	6.29±3.07	7.40±5.05	4.11±1.28	4.10	6.79	2.45
	[^{18}F]-FDG PET/CT	5.83±3.62	3.73±2.69	3.22±1.38	5.72±3.09	12.41±6.78	2.37±1.22	10.86	10.29	1.64
	Z	**<0.001**	-3.677	-4.654	0.591	-1.543	-1.732	NA	NA	NA

No., number; NA, not applicable

	Primary tumor	Lymph node	Peritoneal	Bone	Liver	Ovary	Adrenal gland	Erector spinae	Lung
P **Value**	**<0.001**	**<0.001**	**<0.001**	0.606	0.149	0.114	NA	NA	NA

No., number; NA, not applicable

SUV_{max}-FAPI and TBR-FAPI both showed positive correlations with primary tumor depth (r = 0.303, P = 0.043 for SUV_{max}-FAPI; r = 0.471, P = 0.001 for TBR-FAPI). However, primary tumor depth had no correlations with SUV_{max}-FDG or TBR-FDG (r = 0.201, P = 0.190 for SUV_{max}-FDG; r = 0.270, P = 0.077 for TBR-FDG). Pathological results showed 17 patients with signet-ring cell carcinoma (SRCC) and the remaining 28 patients without SRCC. In SRCC group, SUV_{max} and TBR of [^{68}Ga]Ga-FAPI were significantly higher than those of [^{18}F]-FDG (mean SUV_{max}, 10.38 vs. 6.17, P = 0.001; mean TBR, 11.52 vs. 4.92, P < 0.001). In non-SRCC group, only the TBR of [^{68}Ga]Ga-FAPI was significantly higher than that of [^{18}F]-FDG (11.69 vs. 6.35, P < 0.001), whereas the difference of SUV_{max} was not significant (10.16 vs. 9.25, P = 0.248).

Seventeen patients had pathological TNM stage, who underwent surgery due to early imaging stages. The TBR-FAPI of T3-4, N1-3 and III-IV groups were significantly higher than that of T1-2, N0 and I-II groups, respectively (Z = -2.319, -2.111 and -2.111, P = 0.019, 0.037 and 0.037, respectively). No significant differences were observed in other semiquantitative parameters, such as SUV-FAPI, SUV_{max}-FDG and TBR-FDG in these groups (Table 3).

Table 3
Comparison of [^{68}Ga]Ga-FAPI and [^{18}F]-FDG primary lesions uptake in different stages

Stages (No.)	[^{68}Ga]Ga-FAPI PET/CT		[^{18}F]-FDG PET/CT	
	SUV_{max}-FAPI	TBR-FAPI	SUV_{max}-FDG	TBR-FDG
T1-2 (5)	7.65±3.84	7.00±3.17	9.25±4.89	5.78±2.94
T3-4 (12)	12.04±4.22	14.16±6.05	6.83±3.69	4.53±1.94
Z	-1.792	-2.319	-1.055	-0.843
P	0.082	**0.019**	0.328	0.442
N0 (6)	8.09±3.59	7.82±3.47	8.69±4.59	5.45±2.76
N1-3 (11)	12.20±4.38	14.37±6.30	6.91±3.85	4.60±2.02
Z	-1.809	-2.111	-1.006	-0.603
P	0.078	**0.037**	0.350	0.591
I-II (6)	8.09±3.59	7.82±3.47	8.69±4.59	5.45±2.76
III-IV (11)	12.20±4.38	14.37±6.30	6.91±3.85	4.60±2.02
Z	-1.809	-2.111	-1.006	-0.603
P	0.078	**0.037**	0.350	0.591

No., number

Comparison of [^{68} Ga]Ga-FAPI and [^{18} F]-FDG in the detection of lymph nodal metastases

The number of LN metastases and the semiquantitative parameters of [^{68}Ga]Ga-FAPI and [^{18}F]-FDG PET/CT are demonstrated in Table 2. 16.6% (104/625) LN metastases in 11 patients was confirmed by the pathological findings obtaining from 17 patients who underwent surgery. For the patient-based analysis, [^{68}Ga]Ga-FAPI and [^{18}F]-FDG PET/CT both correctly identified 45.5% (5/11) of patients of LN metastases. The mean SUV_{max} and TBR of [^{68}Ga]Ga-FAPI were comparable to [^{18}F]-FDG without significant differences (SUV_{max}, 7.36 ± 3.89 vs. 7.64 ± 4.21, P = 0.754; TBR, 8.83 ± 4.62 vs. 5.21 ± 3.47, P = 0.117).

For the lesion-based analysis, [^{68}Ga]Ga-FAPI PET/CT revealed 19.2% (20/104) of LN metastases with a mean SUV_{max} and TBR of 6.27 ± 2.13 (range, 0.99-11.30) and 8.03 ± 2.66 (range, 1.16-13.23). [^{18}F]-FDG PET/CT was inferior to [^{68}Ga]Ga-FAPI PET/CT in detecting LN metastases with 15.4% (16/104) and the mean SUV_{max} and TBR were 6.08 ± 3.72 (range, 1.75-13.00) and 3.73 ± 2.69 (range, 0.89-9.49). The difference of mean SUV_{max} between [^{68}Ga]Ga-FAPI and [^{18}F]-FDG was not significant (6.27 vs. 6.08, $P = 0.239$); however, the mean TBR displayed significant difference between the two PETs (8.03 vs. 2.66, $P < 0.001$). Table 4 exhibits results of N-Staging according to [^{18}F]-FDG and [^{68}Ga]Ga-FAPI PET/CT in 17 patients who underwent the surgery. Of these 625 resected lymph nodes, there were 16 true-positive, 12 false-positive, 509 true-negative and 88 false-negative findings on [^{18}F]-FDG PET/CT and 20 true-positive, non-false-positive, 521 true-negative and 84 false-negative findings on [^{68}Ga]Ga-FAPI PET/CT. The sensitivity, specificity, accuracy, PPV and NPV of [^{68}Ga]Ga-FAPI were all higher than those of [^{18}F]-FDG (19.2% vs. 15.4%, $P = 0.463$; 100.0% vs. 97.7%, $P < 0.001$; 86.6% vs. 84.0%, $P = 0.202$; 100.0% vs. 57.1%, $P = 0.001$; 86.1% vs. 85.3%, $P = 0.672$), but only the difference in specificity and PPV was significant.

Table 4
Results of N-Staging according to [^{18}F]-FDG and [^{68}Ga]Ga-FAPI PET/CT

No.	LN (Mets/total)	[^{18}F]-FDG							[^{68}Ga]Ga-FAPI					
		N-P	TP	FP	TN	FN	N-FAPI	Effect	TP	FP	TN	FN	N-FDG	Effect
1	0/32	0	0	2	30	0	1	↑	0	0	32	0	0	→
2	8/34	3a	0	0	26	8	0	↓	0	0	26	8	0	↓
3	0/37	0	0	1	36	0	1	↑	0	0	37	0	0	→
4	6/49	2	2	0	43	4	1	↓	4	0	43	2	2	→
5	4/37	2	0	4	29	4	2	⇄	0	0	33	4	0	↓
6	0/30	0	0	0	30	0	0	→	0	0	30	0	0	→
7	0/48	0	0	0	48	0	0	→	0	0	48	0	0	→
8	8/45	3a	1	0	37	7	1	↓	1	0	37	7	1	↓
9	10/23	3a	0	0	13	10	0	↓	0	0	13	10	0	↓
10	12/49	3a	7	2	35	5	3a	→	7	0	37	5	3a	→
11	16/45	3b	1	0	29	15	1	↓	1	0	29	15	0	↓
12	2/22	2	0	0	20	2	0	↓	0	0	20	2	0	↓
13	28/60	3b	5	0	32	23	2	↓	7	0	32	21	3a	↓
14	0/10	0	0	0	10	0	0	→	0	0	10	0	0	→
15	6/59	2	0	1	52	6	1	↓	0	0	53	6	0	↓
16	0/22	0	0	2	20	0	1	↑	0	0	22	0	0	→
17	4/23	2	0	0	19	4	0	↓	0	0	19	4	0	↓
	104/625		**16**	**12**	**509**	**88**			**20**	**0**	**521**	**84**		

No., number; LN, lymph node(s); Mets, metastases; Total, total number of resected lymph nodes;

N-P, N-staging according to postoperative pathological results; N-FAPI, N-staging according to [^{68}Ga]Ga-FAPI PET/CT; N-FDG, N-staging according to [^{18}F]-FDG PET/CT;

→, unchanged; ↑, upgraded; ↓, degraded;

⇄, unchanged, but due to false positive lymph node;

TP, true positive; FP, false positive; TN, true negative; FN, false negative

In contrast to pathological staging, [^{68}Ga]Ga-FAPI accurately predicted N stages of 47.1% (8/17) of patients and degraded N stages of 52.9% (9/17) of patients. [^{18}F]-FDG accurately predicted N stages of 29.4% (5/17) of patients, degraded N stages of 52.9% (9/17) of patients and upgraded N stages of 17.7% (3/17) of patients. Noteworthily, of these five patients with correct N stages, patient# 5 was accurately staged N2 due to 4 false positive lymph nodes. Therefore, [^{68}Ga]Ga-FAPI PET/CT was superior to [^{18}F]-FDG PET/CT in N-staging of gastric cancer patients (47.1% [8/17] vs. 23.5% [4/17]), but no significant difference was observed (P = 0.282).

Comparison of [^{68} Ga]Ga-FAPI and [^{18} F]-FDG in the detection of other metastases

The number and semiquantitative parameters of positive metastasis are shown in Table 2. For the patient-based analysis, the TBR of [^{68}Ga]Ga-FAPI was significantly higher than that of [^{18}F]-FDG in the peritoneal metastases (mean TBR, 9.47 vs. 4.41, P = 0.030). For the lesion-based analysis, [^{68}Ga]Ga-FAPI PET/CT detected more metastatic lesions in peritoneal and bone (159 vs. 47, P < 0.001; 64 vs. 55, P = 0.003). However, only the SUV_{max} and TBR of peritoneal metastases derived from [^{68}Ga]Ga-FAPI significantly higher than those derived from [^{18}F]-FDG (7.10 vs. 4.48, P = 0.002; 8.05 vs. 3.22, P < 0.001).

Comparison of [^{68} Ga]Ga-FAPI and [^{18} F]-FDG in the detection of recurrence

Regarding the 11 patients with recurrence after surgery, [^{68}Ga]Ga-FAPI PET/CT detected positive lesions in all patients, while [^{18}F]-FDG PET/CT detected positive lesions in only 9 patients. Moreover, [^{68}Ga]Ga-FAPI PET/CT showed more positive lesions and clearer tumor delineation (Fig. 3).

Monitoring Response To Chemotherapy

Two patients underwent a follow-up [^{68}Ga]Ga-FAPI PET/CT after chemotherapy. The primary gastric lesion and peritoneal metastases had nearly relieved after 4 cycles chemotherapy in one patient (Fig. 4), and follow-up [^{68}Ga]Ga-FAPI PET/CT showed no abnormal radioactive uptake in these lesions. The other patient was partially relieved after 4 cycles of chemotherapy. [^{68}Ga]Ga-FAPI uptake was significantly reduced in the primary gastric lesion, and the number of peritoneal metastases was also decreased which were not shown in [^{18}F]-FDG PET/CT before chemotherapy. These results further confirmed the true positive results of the initial [^{68}Ga]Ga-FAPI PET/CT scan.

Immunohistochemistry Analysis

76.5% (13/17) of gastric tumor showed markedly positive FAP immunostaining (scored 3); meanwhile, 5.9% (1/17) and 17.6% (3/17) showed moderately (scored 2) and slightly (scored 1) FAP immunostaining. Furthermore, the SUV_{max} and TBR of [^{68}Ga]Ga-FAPI were positively correlated with FAP expression (r = 0.503, P = 0.040; r = 0.539, P = 0.026, respectively). The FAP expression showed no correlation with the tumor depth and the number of LN metastases (r = 0.336, P = 0.187; r = 0.336, P = 0.609). FAP was overexpressed on the cell surface of CAFs in all tumor specimens (Fig. 5), and the expression of FAP could also be observed in tumor cells cytoplasm in one patient.

Discussion

FAP-targeted imaging is a new approach to visualize the tumor stroma, and [^{68}Ga]Ga-FAPI PET/CT has shown excellent performance in the diagnosis of a variety of tumors [15, 18–20]. Our study demonstrated that [^{68}Ga]Ga-FAPI PET/CT was superior to [^{18}F]-FDG in detecting primary lesions and metastases in gastric cancer patients for staging and recurrence detection. With low abdominal background activity, [^{68}Ga]Ga-FAPI holds potential advantages in showing primary gastric foci and metastases of abdominal lymph nodes, peritoneum, abdominal parenchymal organs, resulting in a higher tumor-to-background contrast than [^{18}F]-FDG simultaneously.

In 45 patients with 46 evaluable primary gastric cancer, [^{68}Ga]Ga-FAPI PET/CT (97.8%, 45/46) was more sensitive than [^{18}F]-FDG PET/CT (95.7%, 44/46) in detecting primary foci, which was consistent with previous studies [21–24]. The pathology of the false negative lesion on both [^{68}Ga]Ga-FAPI and [^{18}F]-FDG was high-grade intraepithelial neoplasia with cancerization, and the lesion was also ignored by the CT, possibly because the tumor size was too small to be detected. The pathology of another lesion with [^{68}Ga]Ga-FAPI-positive and [^{18}F]-FDG-negative was SRCC (Fig. 2), which CT showed diffuse thickening gastric wall. Previous studies had shown that [^{18}F]-FDG PET/CT had lower sensitivity and tracer uptake in SRCC and mucinous carcinoma than in conventional adenocarcinoma [25–27], which was resulted from the relatively low expression level of glucose transporter 1 (GLUT-1) [28]. Therefore, a subgroup analysis was performed in our study. We found that in 17 patients with SRCC, the tracer uptake of [^{68}Ga]Ga-FAPI (SUV_{max}, 10.38 ± 3.12; TBR, 11.52 ± 4.63) was significantly higher than

that of [^{18}F]-FDG (SUV_{max}, 6.17 ± 3.94; TBR, 4.92 ± 3.41). In addition, analysis of all primary gastric tumors also showed that [^{68}Ga]Ga-FAPI PET/CT had significantly higher tracer uptake and tumor-to-background contrast than those of [^{18}F]-FDG PET/CT. Therefore, [^{68}Ga]Ga-FAPI presented as a promising alternative to [^{18}F]-FDG.

The invasion depth in primary gastric cancer is an important factor on determining the prognosis. However, previous studies pointed out that the SUV_{max} of [^{18}F]-FDG was not correlated with the degree of penetration [29]. Our study indicated that SUV_{max}-FAPI and TBR-FAPI both showed positive correlations with primary tumor depth and the TBR-FAPI of T3-4 and III-IV groups were significantly higher than that of T1-2 and I-II groups, which was consistent with the study reported by Jiang et al [21]. As such, our study showed that [^{68}Ga]Ga-FAPI PET/CT could better evaluate the invasion extent of gastric cancer. Additionally, we also found that TBR-FAPI at N0 stage was significantly higher than that at N1-3, suggesting that TBR of [^{68}Ga]Ga-FAPI may indicate the possibility of lymph node metastases.

LN staging is crucial in the treatment and prognosis of gastric cancer patients [30, 31]. However, the usefulness of [^{18}F]-FDG PET/CT in LN metastases of gastric cancer remained controversial [32, 33]. On LN analysis, our study only included 17 patients receiving surgery, who had postoperative pathologic findings with lymph nodes as a reference. We found that the uptake of [^{68}Ga]Ga-FAPI in metastatic LNs was higher than that of [^{18}F]-FDG, which was in coincident with the research by Chen et al [22]. The sensitivity in the diagnosis of metastatic LNs for [^{68}Ga]Ga-FAPI and [^{18}F]-FDG were 19.2% (20/104) and 15.4% (16/104) in our study, respectively, which were distinctly lower than previous studies [21, 22], which can be explained by the fact that the included patients in our current study were at a relatively early stage. Other parameters regarding diagnostic performance in LNs metastases were in line with previous studies [21, 22]. Specifically, the sensitivity, specificity, accuracy, PPV and NPV of [^{68}Ga]Ga-FAPI were all higher than that of [^{18}F]-FDG in our study. Furthermore, [^{68}Ga]Ga-FAPI predicted N staging more accurately than [^{18}F]-FDG, which will be helpful for clinicians to determine an individualized treatment.

Additionally, we found that [^{68}Ga]Ga-FAPI PET/CT outperformed [^{18}F]-FDG PET/CT in visualizing peritoneal and bone metastases, and the tracer uptake was more obvious in peritoneal metastasis, which was similar to the results of other studies [22, 23, 34]. This ascribed to the indeed lower abdominal background with almost no physiological activity in the gastrointestinal wall and other abdominal viscera in [^{68}Ga]Ga-FAPI PET/CT, which was completely obvious limitations in [^{18}F]-FDG [35]. Peritoneal metastasis is usually diffuse in gastric cancer patients. Therefore, the strengths of [^{68}Ga]Ga-FAPI in detecting peritoneal metastases could more accurately reveal the extent of invasion, which was conducive to assess response to treatment. In this study, a follow-up [^{68}Ga]Ga-FAPI PET/CT of two patients with peritoneal carcinomatosis after chemotherapy was conducted. The one patient whose lesions were [^{68}Ga]Ga-FAPI-positive and [^{18}F]-FDG-positive reached complete remission (Fig. 3). The other one whose lesions were [^{68}Ga]Ga-FAPI-positive and [^{18}F]-FDG-negative had partial remission and [^{68}Ga]Ga-FAPI PET/CT showed the peritoneal metastasis decreased after chemotherapy, which further confirmed the true-positive peritoneal metastasis in pretherapy [^{68}Ga]Ga-FAPI imaging. Regardless, our results suggested that [^{68}Ga]Ga-FAPI had great potentiality in monitoring post-treatment response. It should also be noted that few metastases in other organs were found in our study; thus, the superiority of [^{68}Ga]Ga-FAPI imaging could not be further analyzed in these lesions, which will be investigated in our further studies with increased sample size.

The IHC revealed that FAP was overexpressed on the surface of CAFs cells in all tumor specimens. Notably, we found the SUV_{max} was positively correlated with FAP expression. FAP has been demonstrated to have some pro-tumorigenic activities [36–38], indicating that SUV_{max} of [^{68}Ga]Ga-FAPI PET/CT may serve as a quantitative marker to predict the prognosis. Studies in various tumours reported that overexpression of FAP was associated with increased LN metastases and poor overall survival [39]. Our study showed that high FAP expression was not correlated with the increased LN metastases, possibly due to the limited sample size. Owing to the unavailability of long-term follow-up, no conclusion on overall survival could be drawn, which will be investigated in our further research.

Several limitations of this study also need to be mentioned. First, although 56 patients with gastric cancer enrolled in this study was the largest number among the resemble published studies, but sample sizes still need to be increased to strengthen our interpretation and our conclusion. Second, there were too few other parenchymal metastases such as ovaries, adrenal glands, lung, and erector spinae in this cohort to conclude on the detection of those lesions. Third, most patients (39/56) in this cohort did not undergo surgery or biopsy for metastatic lesions to confirm the positive lesions, but the follow-up and other imaging data (such as MRI, CT) were available as a reference. Lastly, the small sample size (17/56) included in the analysis of lymph nodes, which had postoperative pathologic findings as a reference.

Conclusion

Compared with [^{18}F]-FDG PET/CT, [^{68}Ga]Ga-FAPI PET/CT has superiority in detecting primary gastric cancer and metastatic lesions in peritoneum, abdominal lymph nodes and bone, and it has certain effect on guiding N staging. Furthermore, [^{68}Ga]Ga-FAPI PET/CT provides

more information for patients with recurrence detection and has great potential in monitoring response to treatment.

Declarations

Funding information

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Compliance with ethical standards

Conflict of Interest

The authors declare that they have no conflict of interest.

Ethics approval

All procedures involving human participants were carried out in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This article does not contain any experiments with animals.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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Figures

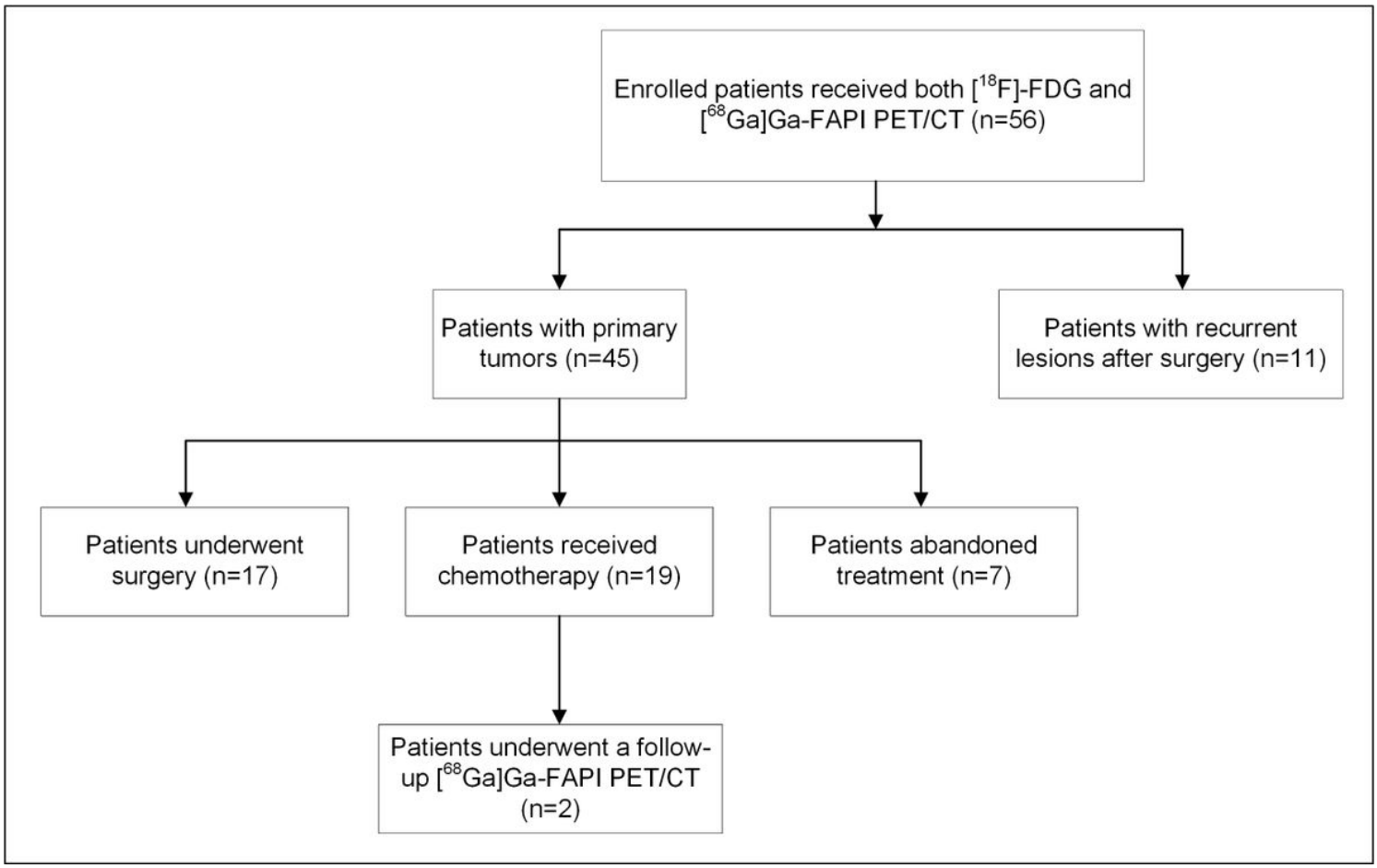

Figure 1

Flow diagram shows the composition of enrolled patients.

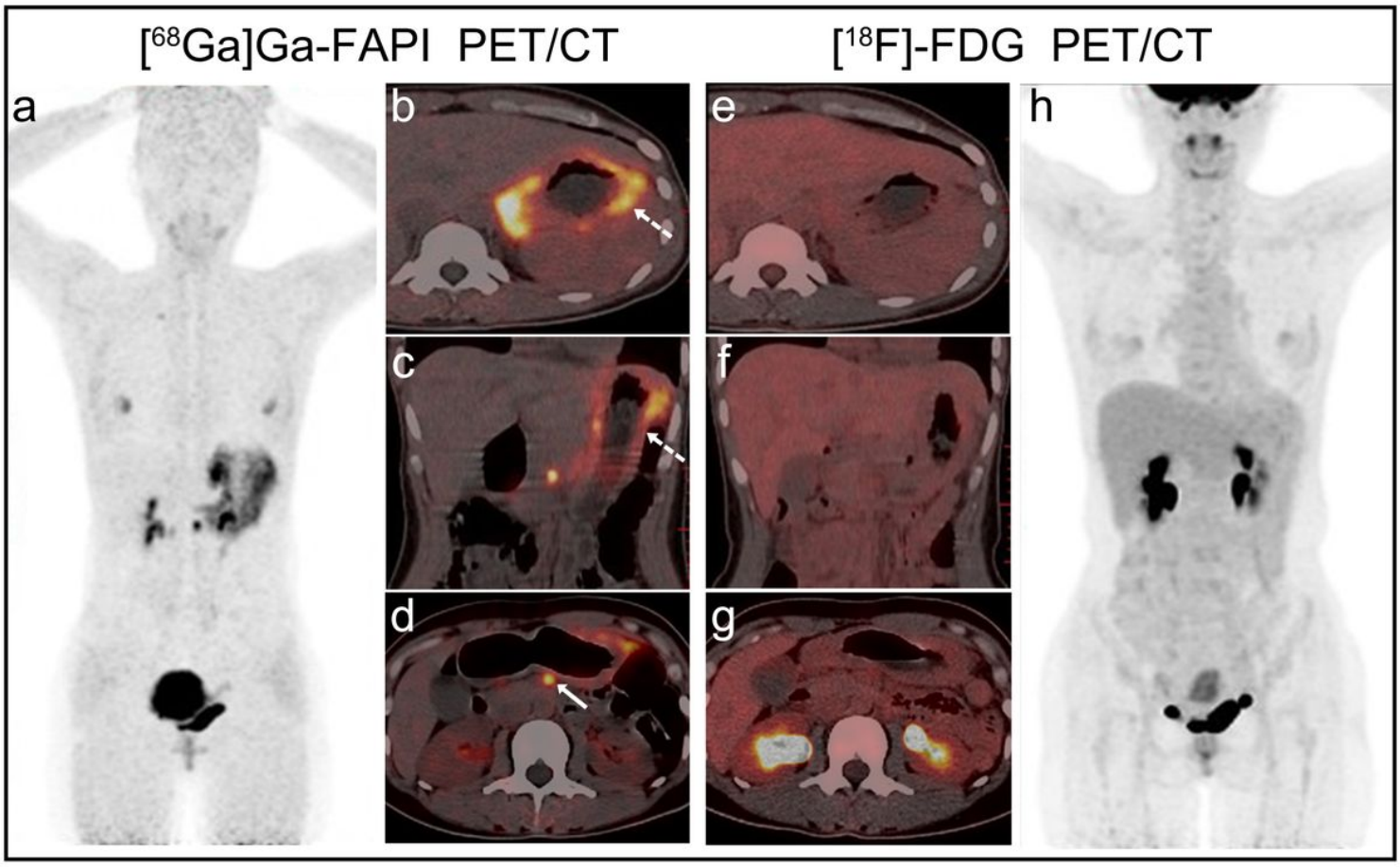

Figure 2

A 40-year-old woman with newly diagnosed signed-ring cell carcinoma underwent [18F]-FDG and [68Ga]Ga-FAPI PET/CT for initial staging before treatment. [68Ga]Ga-FAPI PET/CT (a-d) showed intense tracer uptake in gastric cancer (SUVmax = 11.06, dotted arrows) and perigastric lymph nodes (SUVmax = 8.2, solid arrow). Inversely, [18F]-FDG PET/CT (e-h) showed there was no clear [18F]-FDG uptake in the primary gastric tumor and perigastric lymph nodes.

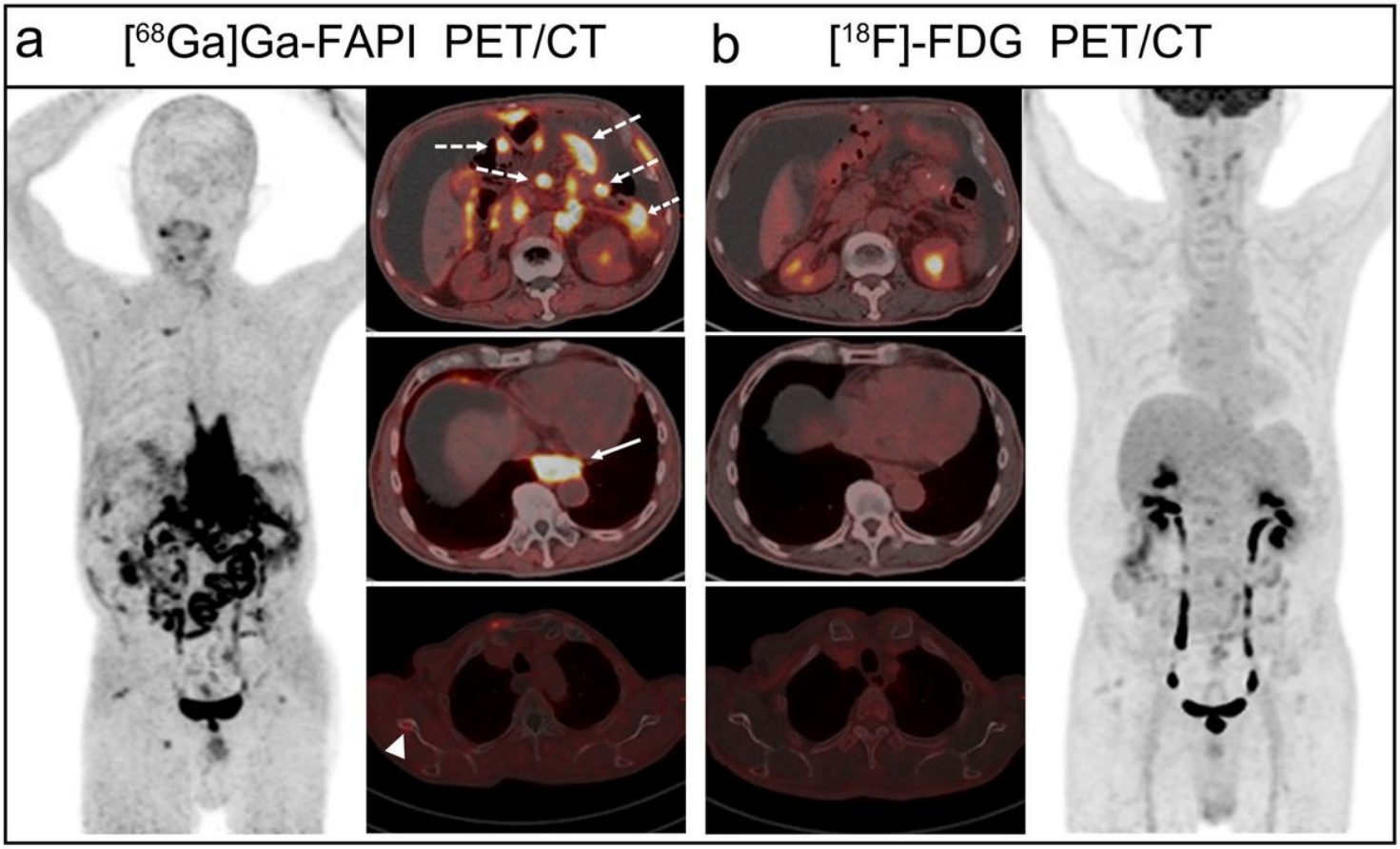

Figure 3

An 83-year-old man, confirmed a poorly cohesive gastric carcinoma by surgery, underwent PET/CT scan to detect recurrence. [68Ga]Ga-FAPI PET/CT showed higher tracer uptake and larger lesion extent than [18F]-FDG PET/CT (upper row, dotted arrow) for peritoneal carcinomatosis. Furthermore, [68Ga]Ga-FAPI PET/CT showed intense activity in anastomotic stoma (middle row, solid arrow) and right scapula (lower arrow, arrowhead), which revealed negative in [18F]-FDG PET/CT.

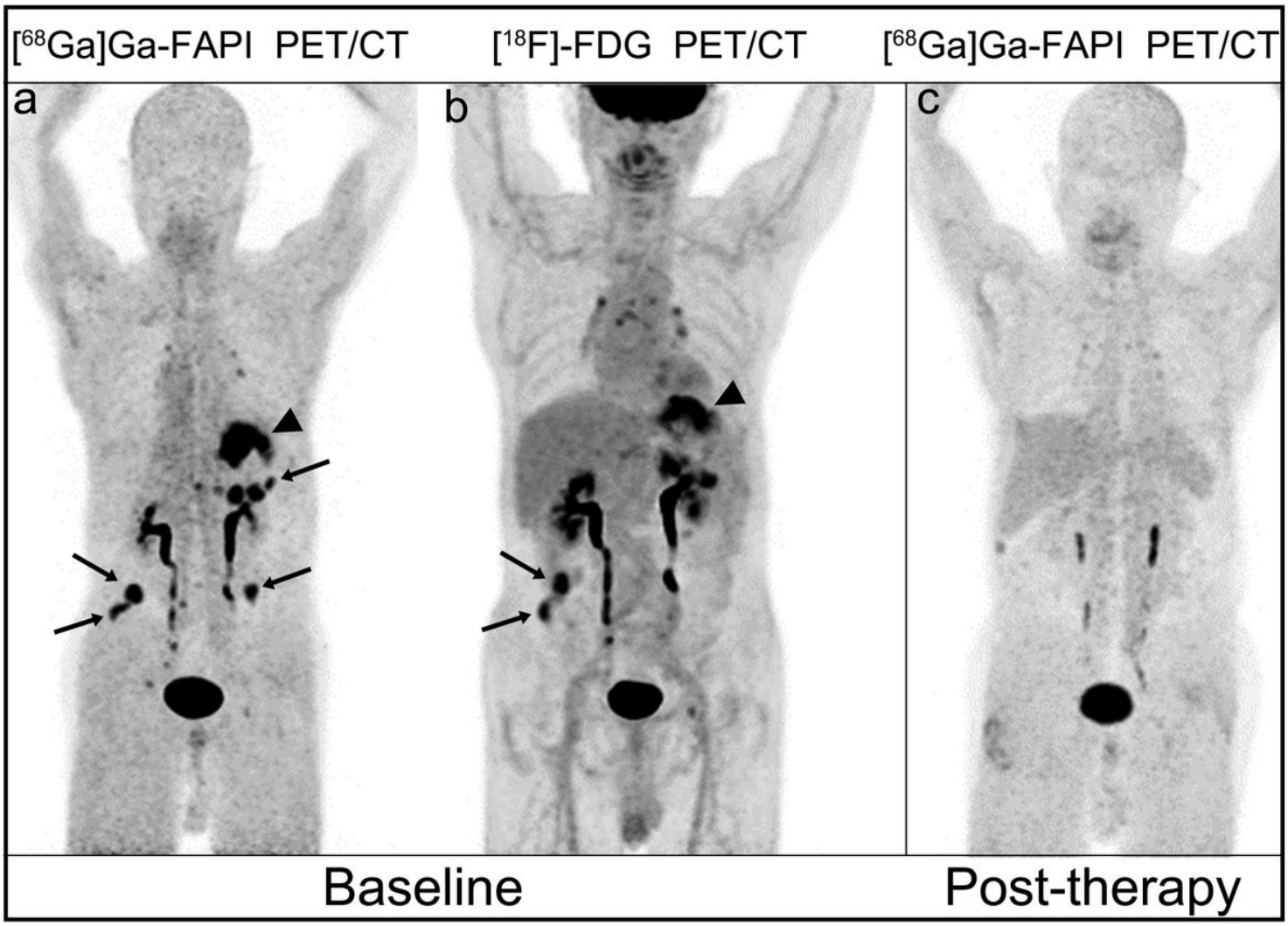

Figure 4

A 83-year-old man with gastric adenocarcinoma underwent PET/CT scans for initial staging. [68Ga]Ga-FAPI PET/CT showed higher tracer uptake than [18F]-FDG PET/CT in the primary tumor (a, arrowhead, SUVmax = 11.73; b, arrowhead, SUVmax = 9.49) and more peritoneal carcinomatosis (a, b, solid arrow). He was treated with neoadjuvant chemotherapy and had a follow-up [68Ga]Ga-FAPI PET/CT (c), which showed negative [68Ga]Ga-FAPI uptake in these lesions.

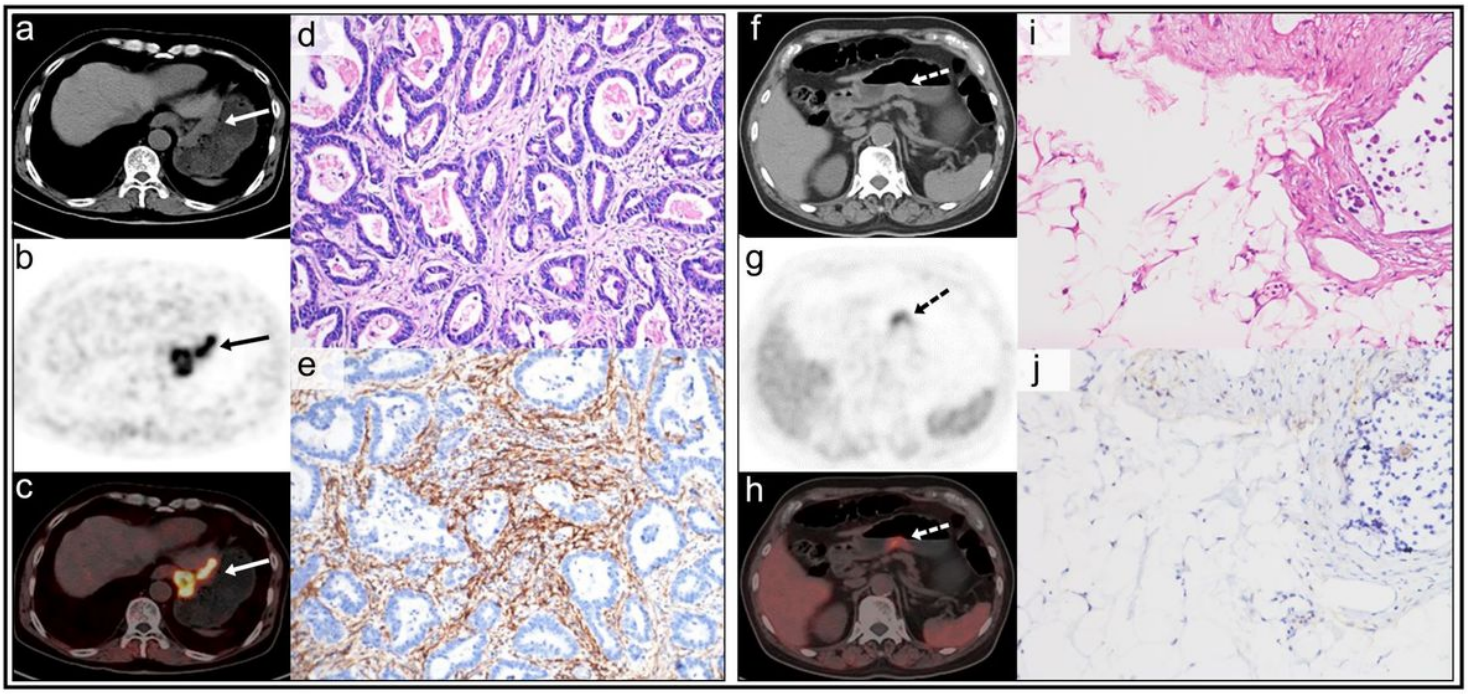

Figure 5

A 64-year-old man with a moderately differentiated gastric adenocarcinoma was confirmed by postoperative pathology. [68Ga]Ga-FAPI PET/CT showed high tracer uptake (SUVmax = 11.25) in the primary tumour (a-c, solid arrow). The histological work-up (d, e) including immunohistochemistry for FAP confirmed FAP overexpressed in primary tumour and scored 3. The other patient presented with mucinous adenocarcinoma, which showed mild-moderate uptake (SUVmax = 4.65) in [68Ga]Ga-FAPI PET/CT (f-h, dotted arrow). The pathological results (i, j) showed slight FAP expression in stromal cells and scored 1.