68Ga-FAPI improves tumor staging in patients with colorectal cancer: comparing to 18F-FDG PET/CT

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Abstract

Purpose

Gallium-68 (^{68}Ga)-labeled fibroblast-activation protein inhibitor (FAPI) is a novel tracer that binds fibroblast-activation protein (FAP), which is overexpressed in colorectal cancers with a prominent stroma including cancer-associated fibroblasts (CAFs). The present study aimed to compare the diagnostic performance of ^{68}Ga -FAPI positron emission tomography (PET)/computed tomography (CT) with that of fluorine-18 (^{18}F)-fluorodeoxyglucose (FDG) PET/CT in primary and metastatic colorectal cancer lesions.

Methods

This prospective study included the image analyses of 37 patients with colorectal cancer who were sequentially evaluated using PET/CT with ^{18}F -FDG and ^{68}Ga -FAPI. Tracer uptakes were compared using Wilcoxon's signed-rank test.

Results

The cohort comprised 37 patients, including 18 treatment-naïve patients and 19 post-treatment patients. In primary colorectal cancer lesions, the average ^{68}Ga -FAPI and ^{18}F -FDG maximum standardized uptake values (SUV_{max}) were 12.5 ± 4.8 and 13.2 ± 5.7 ($P = 0.38$), respectively, in the treatment-naïve group and 6.0 ± 4.3 and 7.9 ± 7.2 , respectively, in the neoadjuvant chemotherapy group ($P = 0.09$); the detection rate was 100% with both tracers (18/18). The SUV_{max} value of ^{68}Ga -FAPI in signet-ring/mucinous carcinomas (12.3 ± 5.2) was higher than that of ^{18}F -FDG (8.3 ± 4.0) ($P = 0.03$). In addition, the average ^{68}Ga -FAPI uptake was lower than that of ^{18}F -FDG in poorly differentiated carcinomas (12.7 ± 3.7 vs. 18.1 ± 4.1 , $P = 0.04$). Compared with ^{18}F -FDG PET/CT, clinical TNM staging based on ^{68}Ga -FAPI PET/CT led to upstaging in 6 patients (16.2%) and downstaging in 3 patients (8.1%). In peritoneal and liver metastases, both the SUV_{max} and the target/background ratio were higher with ^{68}Ga -FAPI compared to ^{18}F -FDG (3.7 vs. 2.6 , $P = 0.02$, and 6.5 vs. 0.89 , $P = 0.01$, respectively).

Conclusion

As a novel PET/CT tracer, ^{68}Ga -FAPI showed its advantage in the detection of lymph nodes, and distant metastases, which improved staging of CRC.

Introduction

Colorectal cancer (CRC) was the fifth most common cause of cancer-related deaths in the United States in 2020 [1]. At diagnosis, 22% of patients with CRC have metastases whereas 50% of patients develop metastases during their lifetime [2, 3]. Optimal imaging for CRC is crucial for accurate initial staging and selection of primary therapy as well as during follow-up examinations for accurate and timely detection of local recurrence and/or metastatic spread.

Noninvasive molecular imaging with novel PET tracers is increasingly being deployed in clinical oncology. Fluorine-18 (^{18}F) fluorodeoxyglucose (FDG) PET/CT, which utilizes altered glucose metabolism in cancer cells, is a valuable imaging modality for the management of CRC [4, 5]. However, ^{18}F -FDG has several limitations such as low specificity, inability to detect small-volume lesions, and lack of isotope uptake in mucinous and signet-ring cell carcinomas [6, 7]. Imaging of the tumor microenvironment beyond the detection of tumor metabolism is a new approach to elucidate *in vivo* tumor biology with potential translational implications in clinical oncology. Fibroblast-activation protein (FAP) is a membrane-anchored peptidase that is highly expressed in cancer-associated fibroblasts (CAFs) in more than 90% of epithelial tumors, including CRC, and contributes to the progression and worse prognosis in a variety of cancers [8–11]. Several recently developed quinolone-based FAP inhibitors (FAPIs) coupled to chelators, including gallium-68 (^{68}Ga)-FAPI, have been demonstrated to provide advantages in staging and restaging compared

with ^{18}F -FDG PET/CT in a spectrum of cancers including peritonitis carcinomatosis [9–11]. Koerber et al. [12] and Pang et al. [13] reported the avidity of ^{68}Ga -FAPi in PET/CT imaging of CRC, supporting the potential utility of FAP-targeted imaging in advanced CRC. Thus, we assessed the avidity of ^{68}Ga -FAPi in CRC to compare the clinical impact of ^{68}Ga -FAPi PET/CT on TNM staging to that of standard-of-care ^{18}F -FDG PET/CT imaging in patients with primary and recurrent/metastatic CRC.

Materials And Methods

Patients

This prospective study was approved by the Institutional Review Board of the study institution (no. 2019KT95) and registered in ClinicalTrials.gov (NCT04750772). Written informed consent was obtained from all patients who were recruited for study enrolment in the study institution. The inclusion criteria were as follows: age > 18 years, histologically confirmed CRC, patient referral to the Nuclear Medicine Department for both ^{18}F -FDG and ^{68}Ga -FAPi PET/CT scans for the purpose of staging or restaging aiding to optimize clinical decision making and written informed consent for study participation. Pregnant or lactating female patients and severe liver or kidney dysfunction were excluded from the study. The final study cohort comprised 37 CRC patients. The study flowchart of patient enrolment is presented in **Online Resource 1**.

Synthesis of ^{18}F -FDG and ^{68}Ga -FAPi

^{18}F -FDG was manufactured in accordance with the standard method described by our laboratory using the coincidence ^{18}F -FDG synthesis module. Synthesis and radiolabeling of ^{68}Ga -FAPi-04 were performed as previously described [14]. The radiochemical purity exceeded 95% for both ^{18}F -FDG and ^{68}Ga -FAPi-04. The final products underwent sterility testing before administration via intravenous injection.

PET/CT imaging

All enrolled patients underwent routine ^{18}F -FDG PET/CT and subsequent ^{68}Ga -FAPi PET/CT within one week. All patients fasted for at least six hours before ^{18}F -FDG PET/CT, and a blood glucose level of <10 mmol/L was confirmed before tracer injection. In contrast, patients with a normal diet were intravenously injected 1.85–2.96 MBq/kg ^{68}Ga -FAPi and then underwent imaging using a hybrid PET/CT scanner (Biograph mCT Flow 64; Siemens Medical Solutions USA, Knoxville/ Tennessee) approximately one hour later. Acquisition was commenced in 6–8 bed positions (1 min/bed) that covered the area between the top of the skull and upper thigh. Non-contrast enhanced CT was performed using 100-mA modulation at 120 kV with a slice thickness of 3 mm for attenuation correction and anatomical localization. All data were transferred to the Syngo MultiModality Workplace (version VE40F; Siemens Healthcare) and reconstructed to create display images of coronal, axial, and sagittal planes.

Image analysis

All images were blinded reviewed by two groups of physicians with 10-year experience in nuclear medicine and radiology. All changes and different opinions were interpreted in consensus.

Visual assessment was used, and the positive uptake was defined as focal tracer uptake higher than the background. Circular volumes of interest inside tumor lesions and healthy tissues were used to quantify radiotracer biodistribution. Tracer uptake was quantified using maximum standardized uptake value (SUV_{max}). Primary lesions, lymph nodes, and distant metastases were respectively analyzed. The lymph nodes were classified into three groups according to the location: cervical-supraclavicular, thoracic, and abdominal/pelvic.

Tumour-node-metastasis (TNM) classification was used based on the NCCN guidelines [15, 16]. In all patients, change in TNM stage, localization of metastases, and oncologic or radiooncologic management were recorded. The histopathologic or conventional imaging were used as the references.

Statistical analysis

All statistical analyses were performed using SPSS 23.0 (IBM, Armonk, NY, USA). The uptakes of positive lesions in ¹⁸F-FDG and ⁶⁸Ga-FAPI PET/CT were compared using Wilcoxon's signed-rank test. A two-tailed *P* value of <0.05 was considered to indicate statistically significant differences.

Results

Patient characteristics

The clinical characteristics of 37 patients enrolled in the study are summarized in Table 1. Briefly, the median cohort age was 64 (range, 33–87) years, and 23 patients (62.2%) were male. The primary tumor was localized in colon in 13 patients (35.1%). The most common histologic grade was moderate differentiation in 62.2% of the patients, and 4 (10.8%) and 4 patients (10.8%) had mucinous/signet-ring cell carcinoma and adenocarcinoma with a mucinous component, respectively. Finally, 18 (48.7%) patients underwent PET/CT imaging for initial assessment and staging whereas the remaining 19 patients (51.3%) underwent PET/CT for restaging or therapeutic evaluation.

Table 1
Patients' characteristics

Characteristic	Value
No. of patients (n)	37
Age, median (range)	64 (33–87)
Sex (male:female)	23:14
Colon cancer	13 (35.1%)
Rectal cancer	24 (64.9%)
Treatment status	
Treatment-naive	18
Neoadjuvant treatment	12
Chemotherapy/radiotherapy after surgery	7
Pathology	
Adenocarcinoma (poorly differentiated)	5
Adenocarcinoma (moderately differentiated)	23
Adenocarcinoma (well-differentiated)	1
Mucinous/signet-ring cell carcinoma	4
Adenocarcinoma with mucinous component	4
Purpose of PET/CT	
Staging	18
Restaging/therapeutic evaluation	19

Safety

All patients tolerated ⁶⁸Ga-FAPI PET-CT without any complications. No signs of drug-related side effects were reported during the entire observation period of >5 hours.

Distribution

The SUV_{max} was determined for normal tissues/organs and primary tumors, after ^{68}Ga -FAPI and ^{18}F -FDG PET/CT which were sequentially performed in all enrolled patients. The ^{68}Ga -FAPI activity was significantly lower than that of ^{18}F -FDG in several normal organs ($P < 0.001$ for several), especially brain (SUV_{max} , 0.3 ± 0.2 vs. 9.6 ± 2.2 , $P < 0.001$) and liver (SUV_{max} , 1.4 ± 0.4 vs. 3.1 ± 0.5 , $P < 0.001$), leading to significantly high tumor-to-background ratios of >2 at both sites ($P < 0.001$). The ^{68}Ga -FAPI uptake was slightly higher than that of ^{18}F -FDG in salivary and thyroid glands and the pancreas ($P < 0.001$ for all). The detailed distribution of ^{18}F -FDG and ^{68}Ga -FAPI uptakes is presented in Fig. 1.

Primary tumors

The histopathological data of the primary tumor were available for all treatment-naïve patients ($n = 18$) and those who received neoadjuvant chemotherapy ($n = 12$). One of these 30 patients had two primary lesions. Therefore, a total of 31 primary lesions were measured. The sensitivity was 100% (31 of 31) with both ^{68}Ga -FAPI and ^{18}F -FDG PET/CT. The average SUV_{max} and median SUV_{max} (range) of primary lesions with ^{68}Ga -FAPI and ^{18}F -FDG PET/CT were 10.0 ± 5.6 and 11.1 ± 6.7 , 9.7 (2.0–25.5) and 10.4 (2.4–25.7), respectively ($P = 0.11$). The average SUV_{max} values of ^{68}Ga -FAPI and ^{18}F -FDG PET were 12.5 ± 4.8 vs. 13.2 ± 5.7 , respectively, in the treatment-naïve group and 6.0 ± 4.3 vs. 7.9 ± 7.2 , respectively, in the neoadjuvant chemotherapy group ($P = 0.384$ and $P = 0.09$).

The analysis of treatment-naïve primary tumors revealed that the avidity of ^{68}Ga -FAPI (12.3 ± 5.2) was significantly higher than that of ^{18}F -FDG (8.3 ± 4.0) in signet-ring/mucinous carcinomas ($P = 0.03$) (Fig. 2). In addition, the uptake of ^{68}Ga -FAPI was significantly lower than that of ^{18}F -FDG in poorly differentiated carcinomas (average SUV_{max} , 12.7 ± 3.7 vs. 18.1 ± 4.1 ; $P = 0.04$). There was no significant difference in the SUV_{max} of primary lesions between ^{68}Ga -FAPI and ^{18}F -FDG PET/CT among the well-differentiated and moderately differentiated carcinomas ($P = 0.08$). Interestingly, in the neoadjuvant chemotherapy group, there was no significant difference in the SUV_{max} of primary lesions between ^{68}Ga -FAPI and ^{18}F -FDG PET/CT among all carcinoma types ($P = 0.09$).

Changes in TNM staging

Compared to staging based on ^{18}F -FDG PET/CT, ^{68}Ga -FAPI-PET/CT resulted in additional findings in 21 of the 37 patients, which led to changes in staging in a total of 9 patients. Specifically, 6 of the 18 treatment-naïve patients (31.6%) were upstaged and 1 of the 18 treatment-naïve patients (5.6%) were downstaged (Table 2).

Table 2
Comparison of FDG PET-based and FAPI PET-based TNM staging of 37 CRC Patients

#	Treatment status	TNM stage (FDG PET based)	TNM stage (FAPI PET based)	Additional finding in FAPI-PET	Change in staging
1	Post-operation	M1a	M1a	None	None
2	Treatment-naïve	T4aN2bM0 (ⅢB)	T4aN2bM1a (Ⅳa)	Peritoneal metastasis	Upstage
3	Post-operation	M1c	M1c	None	None
4	Treatment-naïve	T4aN2bM1c (Ⅳc)	T4aN2bM1c (Ⅳc)	2 LNs	None
5	Treatment-naïve	T1/2N0M1 (Ⅱa)	T1/2N0M0 (Ⅰ)	No rectal metastasis	Downstage
6	Treatment-naïve	T4aN2aM1c (Ⅳ)	T4aN2aM1c (Ⅳ)	2 LNs	None
7	Neoadjuvant treatment	yT3N0M1a (Ⅱa)	yT3N0M1a (Ⅱa)	None	None
8	Neoadjuvant treatment	yT0N0M0	yT0N0M0	None	None
9	Neoadjuvant treatment	yT0N0M0	yT0N0M0	None	None
10	Neoadjuvant treatment	yT0N1aM0	yT0N0M0	None	None
11	Neoadjuvant treatment	yT0N0M1a (Ⅱa)	yT0N0M0	No small intestinal metastasis	Downstage
12	Neoadjuvant treatment	yT0N0M0	yT0N0M0	None	None
13	Neoadjuvant treatment	yT4aN0M0 (Ⅲb)	yT4aN0M0 (Ⅲb)	None	None
14	Neoadjuvant treatment	yT0N0M0 (0)	yT0N0M0 (0)	None	None
15	Treatment-naïve	T3N1bM1a (Ⅲa)	T3N1bM1a (Ⅲa)	1 LN	None
16	Treatment-naïve	T4bN2bM0 (Ⅳc)	T4bN2bM0 (Ⅳc)	5 LNs	None
17	Treatment-naïve	T4aN1bM0 (Ⅲb)	T4aN1bM0 (Ⅲb)	1 LN	None
18	Treatment-naïve	T3N0M0 (Ⅱa)	T3N0M0 (Ⅱa)	None	None
19	Neoadjuvant treatment	yT0N0M0 (0)	yT0N0M0 (0)	None	None
20	Treatment-naïve	T3N2aM1a (Ⅲa)	T3N2aM1a (Ⅲa)	1 LN	None
21	Treatment-naïve	T4aN1bM0 (Ⅲb)	T4aN1bM0 (Ⅲb)	1 LN	None
22	Treatment-naïve	T3N1bM0 (Ⅲb)	T3N1bM1c (Ⅳc)	1 LN+ Peritoneal metastasis	Upstage
LN, lymph node; <i>FDG</i> , fluorodeoxyglucose; <i>FAPI</i> , fibroblast-activation protein inhibitor; SUV_{max} , maximum standardized uptake value					

#	Treatment status	TNM stage (FDG PET based)	TNM stage (FAPI PET based)	Additional finding in FAPI-PET	Change in staging
23	Treatment-naive	T3N1bM0 (Ⅷb)	T3N1bM0 (Ⅷb)	1 LN	None
24	Post-operation	M1	M0	No metastatic recurrence in anastomotic stoma	Downstage
25	Neoadjuvant treatment	yT3N0M1a (Ⅷa)	yT3N0M1a (Ⅷa)	None	None
26	Treatment-naive	T3N1bM0 (Ⅷ)	T3N1bM0 (Ⅷ)	1 LN	None
27	Treatment-naive	T3N0M0 (Ⅷ)	T3N1aM0 (Ⅷb)	1 LN	Upstage
28	Treatment-naive	T3N1cM0 (Ⅷ)	T3N1cM1a (Ⅷa)	1 LN + Left acetabulum metastasis	Upstage
29	Post-operation	M1c	M1c	None	None
30	Neoadjuvant treatment	yT3N1aM0 (Ⅷb)	yT3N1bM0 (Ⅷb)	1 LN	None
31	Post-operation	M1a	M1a	None	None
32	Neoadjuvant treatment	yT3N2aM0	yT3N2aM0	None	None
33	Treatment-naive	T4bN2bM0 (Ⅷ)	T4bN2bM0 (Ⅷ)	2 LNs	None
34	Post-operation	M1a	M1a	None	None
35	Treatment-naive	T4aN1aM0 (Ⅷb)	T4aN2bM0 (Ⅷc)	7 LNs	Upstage
36	Treatment-naive	T4aN2aM0 (Ⅷ)	T4aN2aM1a (Ⅷa)	2 LNs + Liver metastasis	Upstage
37	Post-operation	M1c	M1c	No right axillary and internal mammary LNs metastases	None
LN, lymph node; <i>FDG</i> , fluorodeoxyglucose; <i>FAPI</i> , fibroblast-activation protein inhibitor; SUV_{max} , maximum standardized uptake value					

In all patients who were upstaged based on ^{68}Ga -FAPI-PET/CT findings (6/37, 16.2%), the changes were based on the detection of new or additional distant metastases in one or more organ systems. All additional findings were confirmed by biopsy (9/21, 42.9%) or other conventional imaging (12/21, 57.1%). Moreover, in 11 patients, new lymph node metastases were detected but did not change the stage (Table 2). The median ^{68}Ga -FAPI uptake was higher than that of ^{18}F -FDG in both abdominal and pelvic lymph nodes (6.6 vs. 3.5, $P < 0.001$, and 3.95 vs. 1.85, $P < 0.001$, respectively) (Fig. 3). However, the median ^{68}Ga -FAPI uptake was lower than that of ^{18}F -FDG in thoracic lymph nodes (2.0 vs. 3.2, $P = 0.014$) (Table 3).

Table 3
Comparison of ^{18}F -FDG and ^{68}Ga -FAPI uptake in colorectal tumor sites

	No. of patients	Lesion size (cm)		^{18}F -FDG PET/CT		No. of positive lesions	^{68}Ga -FAPI PET/CT		No of positive lesions	P value
		Median	Range	Median SUV_{max}	SUV_{max} range		Median SUV_{max}	SUV_{max} range		$\text{SUV}_{\text{max}}^{\text{FDG}}$ vs. $\text{SUV}_{\text{max}}^{\text{FAPI}}$
Primary tumor	18	1.3	0.3-2.7	13.1	4.6-25.7	19	12.7	4.6-25.5	19	0.384
Involved lymph nodes										
Cervical-supraclavicular	1	NA	0.5-0.7	NA	2.1-3.7	2	NA	1.1-1.8	1	NA
Thoracic*	10	1.0	0.7-1.4	3.2	2.4-7.9	17	2.0	1.3-12.9	13	0.014
Abdominal [§]	5	0.9	0.4-2.8	3.5	2.3-9.1	20	6.6	1.8-20.5	34	< 0.001
Pelvic	13	0.7	0.3-2.9	2.85	2.0-6.6	56	3.95	1.1-17.6	84	< 0.001
Involved bone and viscera										
Liver	5	1.0	0.7-5.2	2.95	2.5-7.8	5	2.6	1.7-5.0	8	0.068
Lung	4	0.8	0.4-1.5	1.5	0.5-9.2	15	1.5	0.4-4.2	12	0.414
Bone	2	NA	1.4-3.1	NA	5.3-8.8	2	NA	7.3-9.5	2	NA
Peritoneum	10	0.9	0.3-9.0	2.6	1.1-10.5	17	3.7	2.4-12.6	23	0.016
* Lymph nodes in thoracic regions includes mediastinal or/and hilar, axillary and internal mammary lymph nodes										
[§] Lymph nodes in abdominal regions includes paraaortic, retroperitoneal, and celiac lymph nodes										
^{18}F , fluorine 18; ^{68}Ga , gallium 68; <i>FDG</i> , fluorodeoxyglucose; <i>FAPI</i> , fibroblast-activation protein inhibitor; SUV_{max} , maximum standardized uptake value; <i>NA</i> , not applicable										

Imaging with ^{68}Ga -FAPI-PET/CT led to upstaging to stage IV based on the detection of peritoneal and bone metastases in two and one patient with newly diagnosed CRC, respectively (Table 2). In all 10 patients, the ^{68}Ga -FAPI SUV_{max} was higher than that of ^{18}F -FDG in peritoneal metastases (3.7 vs. 2.6, $P = 0.01$) (Table 3). Compared with the ^{18}F -FDG PET/CT images, the peritoneal metastases were clearly visible in the ^{68}Ga -FAPI PET/CT images (Fig. 4 and 5). There was no significant difference in the ^{68}Ga -FAPI and ^{18}F -FDG SUV_{max} values in positive lung lesions ($P = 0.414$) (Table 3).

Although the ^{68}Ga -FAPI and ^{18}F -FDG SUV_{max} values did not significantly differ in positive liver lesions (median, 2.6 vs. 2.95, $P = 0.07$), the number of positive liver lesions detected by ^{68}Ga -FAPI PET/CT was higher than that detected with ^{18}F -FDG PET/CT because of the lower background SUV_{max} of ^{68}Ga -FAPI. Eight positive liver lesions detected by ^{68}Ga -FAPI PET/CT were confirmed as metastases by operation/biopsy and other imagines; only five of these positive liver lesions were detected by ^{18}F -FDG PET/CT (62.5%, 5/8). The tumor/liver ratio of ^{68}Ga -FAPI was significantly higher than that of ^{18}F -FDG ($P = 0.01$), and the liver metastases

were clearly visible in ^{68}Ga -FAPI PET/CT images and finally demonstrated by MRI scan (Fig. 6). The detailed comparison of liver metastases detected with ^{68}Ga -FAPI and ^{18}F -FDG PET/CT are presented in Table 4.

Table 4
Comparison of ^{18}F -FDG and ^{68}Ga -FAPI uptake in liver metastases

	^{18}F -FDG PET/CT	^{68}Ga -FAPI PET/CT	<i>P</i> value (SUV _{max} of ^{18}F -FDG vs. SUV _{max} of ^{68}Ga -FAPI)
SUV _{max} of liver lesion	2.95 (2.5–7.8)	2.6 (1.7–5.0)	0.068
Background SUV _{max} of liver	3.3 (3.0–3.9)	0.5 (0.4–0.7)	0.01
TBR	0.89 (0.6–2.4)	6.5 (4.2–7.1)	0.012
<i>TBR</i> , tumor/background ratio; <i>^{18}F</i> , fluorine 18; <i>^{68}Ga</i> , gallium 68; <i>FDG</i> , fluorodeoxyglucose; <i>FAPI</i> , fibroblast-activation protein inhibitor; <i>SUV_{max}</i> , maximum standardized uptake value			

Discussion

In the present prospective study, we aimed to investigate the avidity of ^{68}Ga -FAPI-04 in CRC and to explore the potential utility of ^{68}Ga -FAPI PET/CT as the sole imaging modality in primary and recurrent CRC. Our analyses indicated that ^{68}Ga -FAPI PET/CT improved tumor staging in CRC patients because of favorable tumor/background activity and low tracer uptake in the gastrointestinal tract. Moreover, we found signet-ring/mucinous carcinomas accumulated more ^{68}Ga -FAPI than ^{18}F -FDG, while FAPI-avidity was lower than FDG-avidity in poorly differentiated carcinomas.

As key constituents of the tumor stroma, CAFs can support an immunosuppressive microenvironment, tumor cell growth, progression, and metastatic potential. Expressed by CAFs, FAP is an attractive diagnostic and therapeutic target [8, 10, 17, 18]. ^{68}Ga -FAPI PET/CT imaging is characterized by high tumor/background activity and is more sensitive than ^{18}F -FDG PET/CT in identifying primary gastrointestinal carcinoma lesions [12, 19].

The origin, number, and distribution of FAP-expressing CAFs as well as the number of FAP molecules per cell may differ among tumors. Mona et al. [20] reported the presence of a strong association between tumor ^{68}Ga -FAPI uptake intensity and histopathological FAP expression in colon cancer. We expected variations in intratumoral tracer distribution in treatment-naïve patients with specific histopathologic types of CRC. In this study, we firstly demonstrated more FAP expression in signet-ring/mucinous carcinomas, which normal exhibited low ^{18}F -FDG uptake [6, 7, 21, 22]. The finding revealed ^{68}Ga -FAPI PET/CT would have the lower false negative rate in detecting primary and metastatic CRC lesions, comparing to ^{18}F -FDG PET/CT. Interestingly, we also found that poorly differentiated carcinomas exhibited significantly lower ^{68}Ga -FAPI uptake compared with ^{18}F -FDG even though this subtype were both ^{68}Ga -FAPI- and ^{18}F -FDG-avidity.

TNM classification provides the traditional and current guidelines to classify the extent of cancer spread. The degree of tumor progression and invasion at the time of surgical resection, as well as patient outcome, are estimated on the basis of this staging system for CRC. Our study demonstrated that ^{68}Ga -FAPI-PET/CT was able to detect both primary tumors and metastases arising from CRC. The sensitivity was 100% with both ^{68}Ga -FAPI and ^{18}F -FDG PET/CT and no significance was found in SUV values in ^{68}Ga -FAPI and ^{18}F -FDG PET/CT imagines. Furthermore, we found that FAPI and FDG uptakes in treatment-naïve lesions had no significant difference from those in posttreatment lesions. Thus, ^{68}Ga -FAPI-PET/CT had a similar detecting efficiency to ^{18}F -FDG PET/CT in T stage.

The superiority of ^{18}F -FDG PET/CT in CRC is evident in the detection of lymph nodes and distant metastases and the detection of additional metastases can significantly change treatment plans [23–25]. However, several studies showed that the detection of

metastatic regional nodes was low/moderate using ^{18}F -FDG PET/CT, demonstrating the limitations of this method [26, 27]. Several studies suggest that CRC commonly harbor cancer-associated fibroblasts expressing fibroblast activation protein. Thus, this study had explored the reliability of ^{68}Ga -FAPI-PET/CT in detection of metastatic CRC lesions. Our result revealed that ^{68}Ga -FAPI PET/CT identified additional findings in 30 metastatic and 2 inflammatory lymph nodes from 17 patients with CRC, and improved N stage in CRC patients. In addition, the ^{68}Ga -FAPI uptake was higher than the ^{18}F -FDG uptake in abdominal and pelvic involved lymph nodes, whereas thoracic FDG-avid inflammatory/age-related lymph nodes showed FAPI-negative.

According to M stage, early detection of isolated metastasis to the liver or other sites often improves survival following radical resection [28]. Because of the moderate FDG-uptake in liver, ^{18}F -FDG PET/CT was not the first choice for identifying the liver metastasis. Our data showed hepatic background was significantly lower when using ^{68}Ga -FAPI compared to ^{18}F -FDG, in according to the previous study. Thus, FAPI-imaging might be advantageous for patients with suspected liver metastases leading to a potential high detection rate. In the present study, the smallest diameter of the detected lesions was approximately 0.7 cm. Peritoneum is another common site of CRC metastasis [29] and the degree of peritoneal metastasis also determines the choice of treatment [24, 30, 31]. The detection rate of peritoneal metastasis using ^{18}F -FDG PET/CT is not high, primarily due to intestinal inflammatory uptake, small lesions, and other factors including rare pathological types. ^{68}Ga -FAPI is an active fibroblast-targeted imaging agent, and the development of peritoneal metastases is primarily due to active fibroblasts [29], supported by the significantly higher ^{68}Ga -FAPI uptake in peritoneal metastatic lesions compared with ^{18}F -FDG observed in the present study.

In the present study, we also found that the ^{68}Ga -FAPI uptake was significantly higher than that of ^{18}F -FDG in uterus, which might be caused by the presence of active fibroblasts in the uterus [32]. This finding suggests that the SUV_{max} value of lesions (primary or/and metastases) located in the pelvic area might be affected by a high ^{68}Ga -FAPI uptake, a potential shortcoming of ^{68}Ga -FAPI PET/CT imaging.

This study also has several limitations which should be acknowledged. The cohort size was small, and the number of patients with bone metastases was low. Future studies with larger cohorts are warranted to provide a more comprehensive analyses on the utility of ^{68}Ga -FAPI PET/CT in CRC.

Conclusion

^{68}Ga -FAPI PET/CT has several clear advantages over ^{18}F -FDG PET/CT, including the detection of lymph nodes and distant metastases, which improves the staging of patients with CRC. Additionally, patients might feel more comfortable during the ^{68}Ga -FAPI PET/CT scan because of no fasting.

Declarations

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Data availability The data used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval The study was approved by the Institutional Review Board of Beijing Cancer Hospital (no. 2019KT95) and registered in ClinicalTrials.gov (NCT04750772).

Consent to participate Patients provided written informed consent.

Consent to publish Patients signed informed consent regarding publishing their data and photographs.

Conflicts of interest The authors declare no potential conflicts of interest.

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Figures

Figure 1

PET-based biodistribution analysis of 37 patients evaluated with ^{68}Ga -FAPI PET/CT and ^{18}F -FDG PET/CT one hour after the injection of the tracer

Figure 2

Staging of a patient with rectal mucinous carcinoma. (a) Mean intensity projection images of ^{18}F -FDG and ^{68}Ga -FAPI PET/CT scans. (b) Axial CT, PET, and fused images at the level of primary lesion (red line in a) and two metastatic lymph nodes (blue line in a) are shown. In contrast to ^{18}F -FDG PET/CT, ^{68}Ga -FAPI PET/CT allowed the discrimination of the primary lesion (red arrows) and lymph nodes metastases (blue arrows) due to the higher uptake of tracer

Figure 3

Staging of a patient with colon cancer and metastatic lymph nodes. (a) Mean intensity projection images of ^{18}F -FDG and ^{68}Ga -FAPI PET/CT scans. (b) Axial CT, PET, and fused images at different levels of metastatic lymph nodes (blue, black, and green lines in a) are shown. The uptake of ^{68}Ga -FAPI is higher in both the diaphragmatic (blue arrows) and retroperitoneal (black and green arrows) metastatic lymph nodes compared to that of ^{18}F -FDG

Figure 4

A patient with rectal cancer and peritoneal metastasis. (a) Mean intensity projection images of ^{18}F -FDG and ^{68}Ga -FAPI PET/CT scans. (b) Axial CT, PET, and fused images at the level of liver metastasis (blue line in a) are shown. Pelvic perineal carcinoma is distinctly observed in the ^{68}Ga -FAPI PET/CT scans because of the high tracer uptake compared with the ^{18}F -FDG PET/CT scans

Figure 5

Staging of a patient with colon cancer and with metastatic perineal carcinoma. (a) Mean intensity projection images of ^{18}F -FDG and ^{68}Ga -FAPI PET/CT scans. (b) Axial CT, PET, and fused images at different levels of metastatic peritoneal lesions (blue, black, and green lines in a) are shown. The ^{68}Ga -FAPI uptake is higher than that of ^{18}F -FDG in perineal carcinomas

Figure 6

A patient with colon cancer that has metastasized to the liver. (a) Mean intensity projection images of ^{18}F -FDG and ^{68}Ga -FAPI PET/CT scans. (b) Axial CT, PET, and fused images at level of liver metastasis (blue line in a) are shown. (c and d) Images of enhanced MRI scan, T₂WI (delay phase) and DWI. The metastatic lesion in the right liver lobe is clearly revealed in ^{68}Ga -FAPI PET/CT images (blue arrows) but is absent in ^{18}F -FDG PET/CT images, which was confirmed by enhanced MRI scan and was clearly shown (blue arrows)

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