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Evaluation of ^{68}Ga-FAPI PET/CT and ^{18}F-FDG PET/CT for the diagnosis of recurrent colorectal cancers

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ABSTRACT

Objective: The present study aimed to compare the diagnostic value of gallium-68-labeled fibroblast activation protein inhibitor positron emission tomography/computed tomography (^{68}Ga-FAPI PET/CT) and fluorine-18-labeled fluorodeoxyglucose PET/CT (^{18}F-FDG PET/CT) for detecting recurrent colorectal cancers (CRCs).
Materials and Methods: Fifty-six patients (age: 18–80 years, 31 men and 25 women) with suspected recurrent CRC were enrolled and underwent ^{18}F-FDG PET/CT and ^{68}Ga-FAPI PET/CT sequentially within 1 week. The maximum standard uptake value (SUVmax), tumor-to-background ratio (TBR), and diagnostic accuracy were estimated and compared between the two modalities by using Student's *t*-test. The Wilcoxon signed-rank test was used to compare peritoneal carcinoma index (PCI) scores between the two imaging modalities.
Results: ^{68}Ga-FAPI PET/CT showed higher sensitivity for detecting recurrence (93 % vs. 79 %); lymph node metastasis (89 % vs. 78 %), particularly peritoneal lymph node metastasis (92 % vs. 63 %); and metastatic implantation on the intestinal wall (100 % vs. 25 %) compared to ^{18}F-FDG PET/CT. However, ^{68}Ga-FAPI PET/CT showed lower sensitivity for detecting bone metastasis (67 % vs. 100 %). The mean SUVmax values of peritoneal metastases and metastatic implantation on the intestinal wall were 4.28 ± 2.70 and 7.58 ± 1.66 for ^{18}F-FDG PET/CT and 5.66 ± 1.97 and 6.70 ± 0.25 for ^{68}Ga-FAPI PET/CT, respectively. Furthermore, ^{68}Ga-FAPI PET/CT showed significantly higher TBR for peritoneal metastatic lesions (4.22 ± 1.47 vs. 1.41 ± 0.89, $p < 0.0001$) and metastatic implantation on the intestinal wall (5.63 ± 1.24 vs. 2.20 ± 0.5, $p = 0.02$) compared to ^{18}F-FDG PET/CT. For the same patient, ^{68}Ga-FAPI PET/CT yielded a more accurate PCI score and a greater area under the curve value for the receiver operating characteristic curve ($p < 0.01$) than ^{18}F-FDG PET/CT.
Conclusion: ^{68}Ga-FAPI PET/CT was superior to ^{18}F-FDG PET/CT for detecting recurrence and peritoneal metastases. Hence, we propose the combination of these two modalities for better clinical diagnosis and management of patients with CRC.

Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed cancer and the second leading cause of cancer-related death worldwide [1,2]. Over 95 % of colorectal tumors tend to be adenocarcinoma, and signet ring cell carcinoma (SRCC) is a rare pathological subtype of

Abbreviations: ^{18}F-FDG, ^{18}F-fluorodeoxyclucose; CRC, colorectal cancer; CRS, cytoreductive surgery; FAPI, fibroblast activation protein inhibitor; HIPEC, hyperthermic intraperitoneal chemotherapy; PCI, peritoneal carcinoma index; PET/CT, positron emission tomography/computed tomography; PSDSS, peritoneal surface disease severity score; SRCC, signet ring cell carcinoma.

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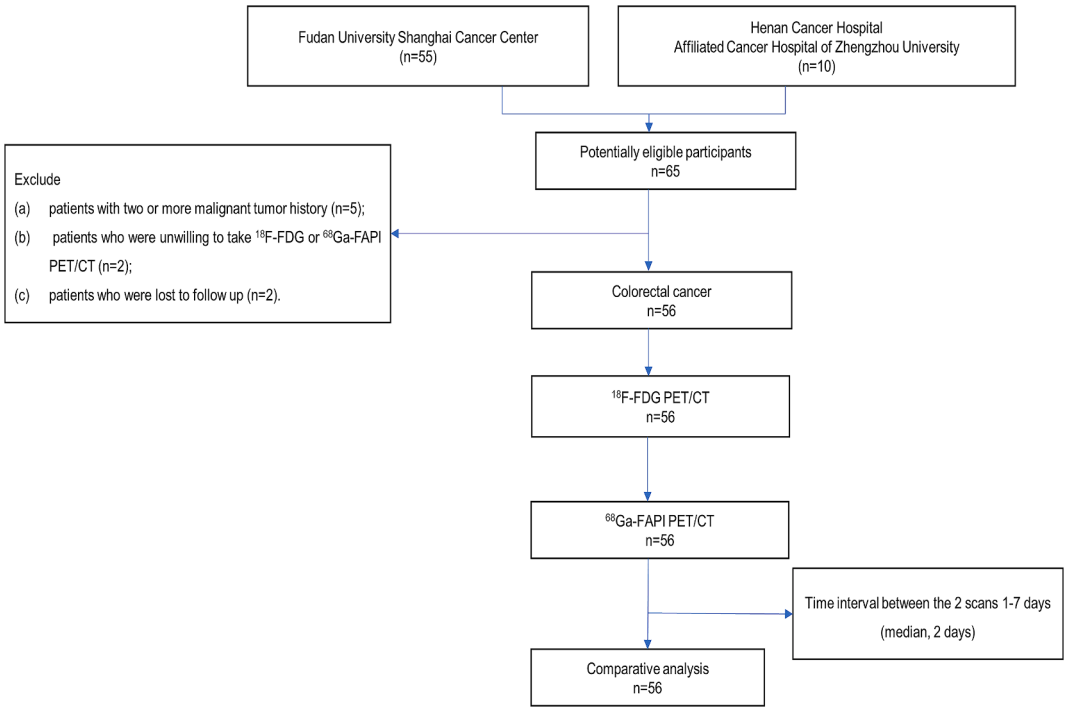

Fig. 1. Flowchart of patient enrolment. A total of 56 patients were finally included, and they underwent paired ^{18}F-FDG PET/CT and ^{68}Ga-FAPI PET/CT. FAPI=fibroblast activation protein inhibitor, ^{18}F=fluorine-18, FDG=fluorodeoxyglucose, ^{68}Ga = gallium-68.

Table 1
Patient characteristics.

Characteristics	Value
Patients	56
Age (y)	
Median	52
Interquartile range	36–65
Gender	
Men	31
Women	25
Patient status	
Resection surgery	38
Chemotherapy	15
Chemotherapy after surgery	2
Targeted therapy after surgery	1
Histology	
Colorectal adenocarcinoma	5
Colorectal adenocarcinoma with mucinous component	5
Colorectal adenocarcinoma with signet-ring cell carcinoma	5
Colorectal mucinous carcinoma	27
Colorectal signet-ring cell carcinoma	14

Table 2.1
Comparative results for tumor recurrence detection.

Lesions	No. of Patients	^{18}F-FDG PET/CT				^{68}Ga-FAPI PET/CT			
		Negative		Positive		Negative		Positive	
		T	**F**	**T**	**F**	**T**	**F**	**T**	**F**
Recurrence	14	36	3	11	6	42	1	13	0
Metastatic lesions									
Lymph node	9	47	2	7	0	46	1	8	1
Peritoneal	37	21	13	22	0	19	3	34	0
Bone and visceral metastases									
Liver	7	49	1	6	0	49	1	6	0
Lung	5	51	3	2	0	51	3	2	0
Bone	4	52	0	3	1	52	1	2	1
Intestinal wall implantation	4	52	3	1	0	52	0	4	0
Ovary	5	51	0	5	0	51	0	5	0

*^{18}F-FDG:^{18}F-fluorodeoxyclucose; PET/CT: positron emission tomography/computed tomography; FAPI: fibroblast activation protein inhibitor.

adenocarcinoma [3]. Compared to adenocarcinoma that does not secrete mucus, mucinous adenocarcinoma and SRCC [4] have a high degree of malignancy, poor prognosis, and distinct pathological characteristics. Although colonoscopy is the gold standard for screening CRCs [5], it was ineffective in reducing the risk of CRCs and related death [6]. Positron emission tomography/computed tomography (PET/CT) is a promising multimodal molecular imaging technique for the early detection of lesions and diagnosis of primary tumors. ^{18}F-fluorodeoxyglucose (^{18}F-FDG) is the most commonly used probe in PET/CT [7,8]. However, there is a wide overlap in ^{18}F-FDG uptake by benign and malignant lesions, which impedes the differentiation of low-grade tumors from benign lesions [9,10]. Furthermore, CRC subtypes such as SRCC and mucinous adenocarcinoma could show low ^{18}F-FDG uptake, leading to false-negative detection of CRC lesions [11,12]. The evaluation of ^{18}F-FDG uptake of intestinal lesions is also hindered by the physiological uptake of ^{18}F-FDG in the intestine. Hence, novel radiopharmaceuticals are required that can better detect SRCC and mucinous adenocarcinoma in patients with CRC.

^{68}Ga-labeled fibroblast activation protein inhibitor (^{68}Ga-FAPI) is a novel probe that targets fibroblast activated protein (FAP) [13], which is frequently overexpressed in various types of cancer but rarely in healthy tissues. Recently, ^{68}Ga-FAPI PET/CT has been confirmed to be a promising molecular imaging tool [14], with a significant value in tumor diagnosis [15]. Compared to ^{18}F-FDG, ^{68}Ga-FAPI is physiologically less absorbed by normal organs, has higher tumor-to-background ratio (TBR), and is rapidly cleared through the kidney, which makes it more advantageous for use in abdominal and pelvic imaging [16]. ^{18}F-FDG PET/CT shows lower sensitivity for the most commonly involved sites of peritoneal carcinoma, such as the omentum, mesentery, bowel wall, and pelvis [17,18]. In contrast, ^{68}Ga-FAPI PET/CT shows a superior diagnostic efficacy for lesions in these sites [19]. Thus, we hypothesized that

Table 2.2
Comparative results for tumor recurrence detection.

Lesions	*^{18}F-FDG PET/CT			*^{68}Ga-FAPI PET/CT		
	Sensitivity	Specificity	Accuracy	Sensitivity	Specificity	Accuracy
Recurrence	79 %	86 %	84 %	93 %	100 %	98 %
Metastatic lesions						
Lymph node	78 %	100 %	96 %	89 %	98 %	96 %
Peritoneal	63 %	100 %	77 %	92 %	100 %	95 %
Bone and visceral metastases						
Liver	86 %	100 %	98 %	86 %	100 %	98 %
Lung	40 %	100 %	95 %	40 %	100 %	95 %
Bone	100 %	98 %	98 %	67 %	98 %	96 %
Intestinal wall implantation	25 %	100 %	95 %	100 %	100 %	100 %
Ovary	100 %	100 %	100 %	100 %	100 %	100 %

* ^{18}F-FDG:^{18}F-fluorodeoxyclucose; PET/CT: positron emission tomography/computed tomography; FAPI: fibroblast activation protein inhibitor.

^{68}Ga-FAPI PET/CT could outperform ^{18}F-FDG PET/CT in detecting relapsed CRC.

The present study aimed to evaluate and compare the diagnostic value of ^{68}Ga-FAPI-PET/CT and ^{18}F-FDG PET/CT for detecting SRCC and mucinous adenocarcinoma in patients with non-FDG-avid CRC.

Materials and methods

Patient selection

This retrospective study was conducted at Fudan University Shanghai Cancer Center and Henan Cancer Hospital affiliated Cancer Hospital of Zhengzhou University from August 2020 to May 2022; the study was approved by the ethics committee of Hospital A (approval ID: 2012229-2) and conducted in accordance with the Declaration of Helsinki 1964 and its subsequent amendments or comparable ethical standards. All participating subjects signed an informed consent form. Fifty-six adult patients (age: 18–80 years) with histopathologically confirmed diagnosis of CRC were included in this study. The inclusion criteria were as follows: (a) patients who underwent paired ^{18}F-FDG PET/CT and ^{68}Ga-FAPI PET/CT; (b) patients with a history of CRC; (c) patients with suspected CRC recurrence and/or metastasis; (d) patients with 6 months of follow-up by CT and/or MRI; and (e) patients willing to provide informed consent. Exclusion criteria were as follows: (a) patients with a history of two or more malignant tumors; (b) patients who were unwilling to undergo ^{18}F-FDG PET/CT or ^{68}Ga-FAPI PET/CT; and (c) patients who were lost to follow-up.

Radiopharmaceutical synthesis

^{18}F-FDG was synthesized automatically at our institution by using the Explora FDG4 module and a cyclotron (Siemens, Knoxville, TN, USA). DOTA-FAPI-04 (Jiangsu Huayi Technology Co., Ltd., Jiangsu, China) was radiolabeled with ^{68}Ga solution (eluted from the ^{68}Ge generator IGG100, Eckert & Ziegler, Berlin, Germany) as reported by Lindner et al. [20]. After pH adjustment with sodium acetate, the FAPI-04 precursor and ^{68}Ga were chelated. The reaction mixture was heated at 95 °C for 10 min, and the integrity of the reaction was confirmed by radio-liquid chromatography. Solid-phase extraction of the ^{68}Ga-labeled compounds was performed prior to PET. The stability of these compounds was confirmed by incubating FAPI-04 in human serum at 37 °C. The radiochemical purity of both ^{18}F-FDG and ^{68}Ga-FAPI was greater than 95 %, which is considered usable.

PET/CT image acquisition and preprocessing of images

^{68}Ga-FAPI PET/CT and ^{18}F-FDG PET/CT were performed within 1 week. Under fasting condition, ^{18}F-FDG was injected intravenously with a rest period of approximately 60 min, followed by PET/CT imaging. For ^{68}Ga-FAPI PET/CT, patients were injected with the radiotracer at the dose of 2 MBq/kg and rested for approximately 60 min before the scan. The scan was performed with the patient in the supine head-up position, and the scanning area ranged from the skull base to one-third of the femur. After the examination area was selected, a CT scan was performed followed by a PET scan.

All images were acquired using a Biograph mCT Flow^{TM} scanner (Siemens Medical Solutions, Knoxville, TN, USA). The PET image dataset was reconstructed using the CT data for attenuation correction according to previously reported guidelines [21]. Reconstruction was performed using the ordered subset expectation maximization algorithm with 2 iterations/21 subsets and Gaussian filtering with a cross-axis resolution of 5 mm at full-width half-maximum. Attenuation correction was performed using low-dose unenhanced CT data. Quantitative assessment of the standardized uptake value (SUV) was applied to regions of interest.

PET/CT image analysis

The images were independently analyzed by Assistant Director and Head of Nuclear Medicine Department, with each having more than 10 years of work experience, by using the visual method combined with the semiquantitative method; consensus was reached through consultation in the case of disagreement. The visual method involved the comparative analysis of PET, CT, and PET/CT fusion images from frame to frame, combined with determination of the morphology and metabolic activity of the lesions to confirm the presence of CRC metastasis. The semiquantitative method involved manual delineation of the region of interest (ROI) of suspected metastases at higher metabolic sites to obtain their SUVmax values. For multiple suspected metastases in one organ, only the average value of the five most metabolically active SUVmax values was considered.

Statistical analysis

The abdomen and pelvic cavity were divided into 13 regions. Lesion size score (LS) was classified into four grades: LS0, no tumor; LS1, tumor < 0.5 cm; LS2, 0.5 cm $<$ tumor < 5 cm; LS3, tumor > 5 cm or fused into a mass. The peritoneal carcinoma index (PCI) score was calculated as the sum of LS values per domain.

SPSS 25.0 was used for statistical analysis (IBM, Armonk, NY, USA). Continuous variables were expressed as mean $\pm$ SD, minimum, median, and maximum. The two-sample *t*-test was used to compare ^{18}F-FDG and ^{68}Ga-FAPI uptake in metastatic lesions. The Wilcoxon signed-rank test was used for comparing PCI scores between the two imaging modalities.

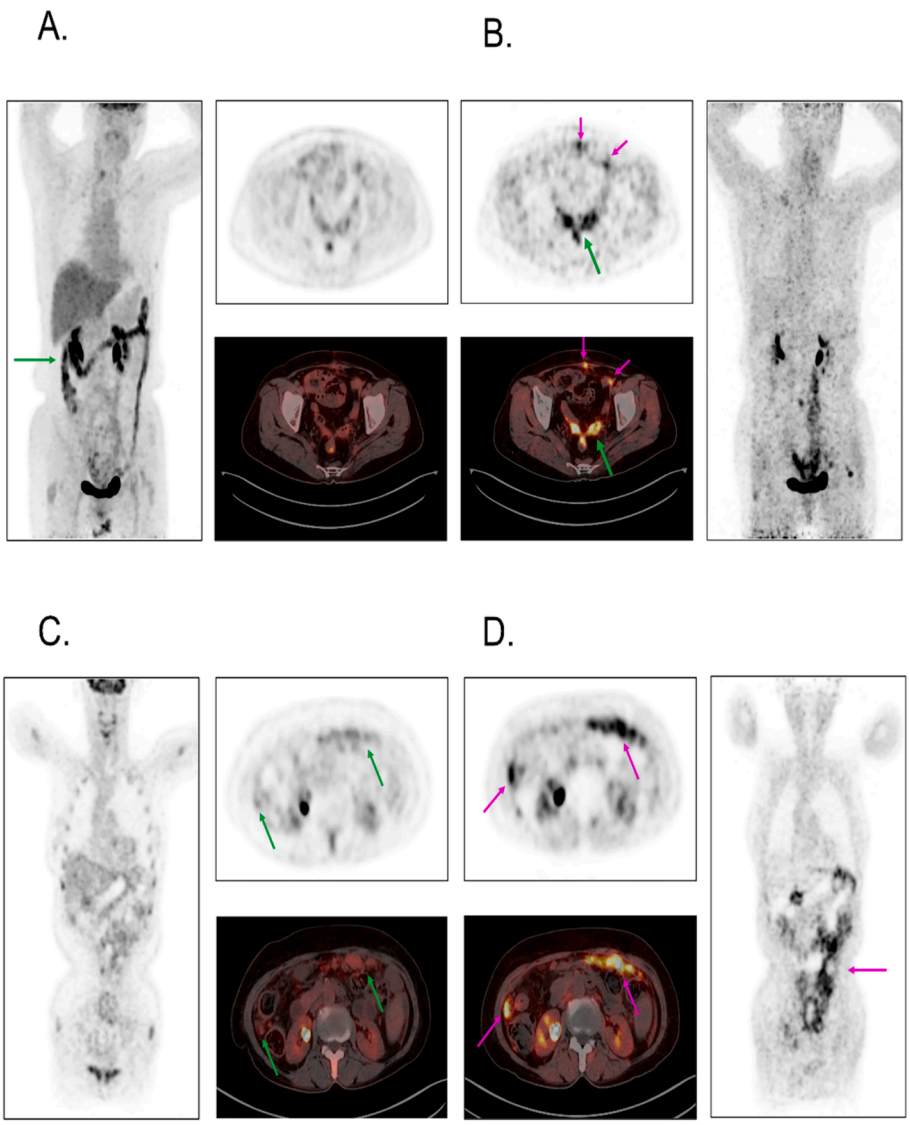

Fig. 2. Representative images of adenocarcinoma in two patients. A & B: The pathological feature of adenocarcinoma with a signet ring cell in a 68-year-old female patient who underwent ^{18}F-FDG PET/CT and ^{68}Ga-FAPI PET/CT sequentially. A: ^{18}F-FDG PET/CT shows high intestinal uptake (green arrow), while no tracer uptake was detected in the lesion. B: ^{68}Ga-FAPI PET/CT shows significantly high tracer uptake in parts of the bowel wall (green arrow) and peritoneum (magenta arrow). C & D: A 58-year-old woman with biopsy-confirmed moderately differentiated mucinous adenocarcinoma underwent ^{18}F-FDG PET/CT and ^{68}Ga-FAPI PET/CT for detecting recurrence. C: ^{18}F-FDG PET/CT images show low tracer uptake in the metastatic lesions (green arrow). D: ^{68}Ga-FAPI PET/CT images show intense tracer uptake in the peritoneum (magenta arrow). A subsequent colonoscopy biopsy confirmed the presence of colorectal signet ring cell carcinoma in the lesions. A & C: left image: anterior maximum intensity projection image obtained by ^{18}F-FDG PET; right upper image: axial PET image; right lower image: axial fused PET/CT image. B & D: left upper image: axial PET image; left lower image: axial fused PET/CT image; right image: anterior maximum intensity projection image obtained by ^{68}Ga-FAPI PET. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Peritoneal surface disease severity score (PSDSS) was determined according to the PSDSS scoring standard, and the diagnostic efficacy was compared by generating the receiver operating characteristic (ROC) curve by MedCalc software. A p-value of <0.05 was considered statistically significant.

Results

Patients

A total of 65 patients from our center and Henan Cancer Hospital (Affiliated Cancer Hospital of Zhengzhou University) were enrolled in the study. Fifty-six patients were selected for further analysis based on the inclusion and exclusion criteria (Fig. 1). Patient characteristics are shown in Table 1. The median age of the patients was 52 years (range: 36–65 years). Thirty-one patients were men (55.4 %) and 25 patients were women (44.6 %). Among all the patients, the most common pathological tumor type was mucinous colorectal carcinoma in 27 patients (48.2 %) and SRCC in 14 patients (25 %). Ten patients (17.9 %) had adenocarcinoma with a mucinous (5 of 10) or signet ring cell (5 of 10) component, and only 5 patients (8.9 %) had simple adenocarcinoma.

Comparison of ^{18}F-FDG PET/CT and ^{68}Ga-FAPI PET/CT for detecting metastatic lesions

Table 2.1 shows the characteristics of metastatic lesions. Based on the results of CT, MRI, colonoscopy, or surgical pathology at 1 year, 14 patients had primary tumor recurrence, 9 had lymph node metastasis, and 5 had ovarian metastasis. Peritoneal metastases were the most common metastatic lesions and occurred in 63.8 % of patients with

Table 3
Comparison of ^{68}Ga-FAPI and ^{18}F-FDG uptake in colorectal cancer lesions.

Lesions	^{18}F-FDG PET/CT		^{68}Ga-FAPI PET/CT		*P* Value
	SUV_{max}	TBR	SUV_{max}	TBR	
Recurrence	6.57 ± 5.22	2.16 ± 1.72	7.87 ± 3.59	5.87 ± 2.67	0.37
Lymph node	4.86 ± 2.90	1.60 ± 0.95	6.85 ± 2.82	5.11 ± 2.10	0.17
Peritoneal	4.28 ± 2.70	1.41 ± 0.89	5.66 ± 1.97	4.22 ± 1.47	<0.0001
Bone and visceral metastases					
Liver	5.50 ± 1.61	1.81 ± 0.53	6.42 ± 4.85	4.80 ± 3.62	0.70
Lung	2.70	0.89	1.40	1.00	N/A
Bone	4.00	1.12 ± 0.12	3.40 ± 0.35	3.00	0.62
Intestinal wall implantation	7.58 ± 1.66	2.20 ± 0.5	6.70 ± 0.25	5.63 ± 1.24	0.02
Ovary	4.58 ± 2.26	1.50 ± 0.74	5.32 ± 2.02	3.98 ± 1.52	0.6

*^{18}F-FDG:^{18}F-fluorodeoxyclucose; PET/CT: positron emission tomography/computed tomography; FAPI: fibroblast activation protein inhibitor; SUV_{max}: maximum standard uptake value; TBR: tumor-to-background ratio.
TBR=tSUVmax/bSUVmean; tSUVmax is the maximum SUV of a tumor lesion; bSUVmean is the mean SUV of a muscle.

tumor recurrence. Regarding bone and visceral metastases, liver metastases, lung metastases, bone metastases, and metastatic implantation on the intestinal wall were detected in 7, 5, 4, and 4 patients, respectively.

Among 14 patients with primary tumor relapse, the sensitivity of ^{18}F-FDG PET/CT and ^{68}Ga-FAPI PET/CT was 79 % (11 of 14) and 93 % (13 of 14), respectively. ^{68}Ga-FAPI PET/CT showed higher specificity (100 % [42 of 42] vs. 86 % [36 of 42]) and higher TBR (5.87 ± 2.67 vs. 2.16 ± 1.72, p = 0.37) compared to ^{18}F-FDG PET/CT (Table 2.2).

^{68}Ga-FAPI PET/CT was more sensitive than ^{18}F-FDG PET/CT in detecting lymph node metastasis, particularly peritoneal metastasis and bowel implants (89 % vs. 78 %, 92 % vs. 63 %, and 100 % vs. 25 %, respectively; Table 2.2 & Fig. 2). However, the sensitivity of ^{68}Ga-FAPI PET/CT for bone metastases appeared to be lower than that of ^{18}F-FDG PET/CT (67 % vs. 100 %, Table 2.2).

Lung metastatic lesions showed low uptake of both tracers. The mean SUVmax values of peritoneal metastases were 4.28 ± 2.70 and 5.66 ± 1.97 for ^{18}F-FDG PET/CT and ^{68}Ga-FAPI PET/CT, respectively. The mean SUVmax values for intestinal wall implantation were 7.58 ± 1.66 and 6.70 ± 0.25 for ^{18}F-FDG PET/CT and ^{68}Ga-FAPI PET/CT, respectively. ^{68}Ga-FAPI PET/CT showed significantly higher TBR for peritoneal metastases (4.22 ± 1.47 vs. 1.41 ± 0.89, p < 0.0001) and intestinal wall implantation (5.63 ± 1.24 vs. 2.20, p = 0.02) compared to ^{18}F-FDG PET/CT (Table 3 & Fig. 2). Progression-free survival curve of patients with recurrence detected by ^{68}Ga-FAPI PET/CT was higher than those detected by ^{18}F-FDG PET/CT (Supplemental Fig. 2, p = 0.147).

Comparison of the performance of ^{18}F-FDG PET/CT and ^{68}Ga-FAPI PET/CT for analyzing peritoneal metastases and prognosis

To compare the prognostic performance, a lesion-by-lesion analysis of peritoneal metastases was performed for ^{68}Ga-FAPI PET/CT and ^{18}F-FDG PET/CT (Fig. 3A). Among 37 patients with peritoneal metastases, PCI scores of 12 patients were zero measured by ^{18}F-FDG PET/CT imaging while were two points higher on average measured by ^{68}Ga-FAPI. The highest PCI score was 23 with ^{68}Ga-FAPI PET/CT; however, the PCI score of the same patient assessed by ^{18}F-FDG PET/CT was only 8. Three patients who underwent ^{68}Ga-FAPI PET/CT had PCI scores above 10; however, none of the patient who underwent ^{18}F-FDG PET/CT had a PCI score above 10. Overall, the heatmap showed a significantly higher PCI score with ^{68}Ga-FAPI PET/CT than with ^{18}F-FDG PET/CT (p < 0.05, Fig. 3B). The PSDSS scores were calculated according to the PSDSS scoring standard (Supplemental Table). The AUC values of the ROC curve generated for the PSDSS scores were 0.91 and 0.71 (^{68}Ga-FAPI PET/CT vs. ^{18}F-FDG PET/CT) (Fig. 3C, p = 0.0005), which demonstrated that the former modality showed better prognostic performance.

Discussion

CRC is one of the five leading cancer burdens worldwide [22,23]. Among patients diagnosed to have colon cancer, 20 % patients show metastatic lesions, and 40 % patients show tumor relapse after prior treatment for local disease [24]. Peritoneum is one of the most common sites of metastasis [25,26]. Approximately 7 ~ 30 % of metastatic CRC

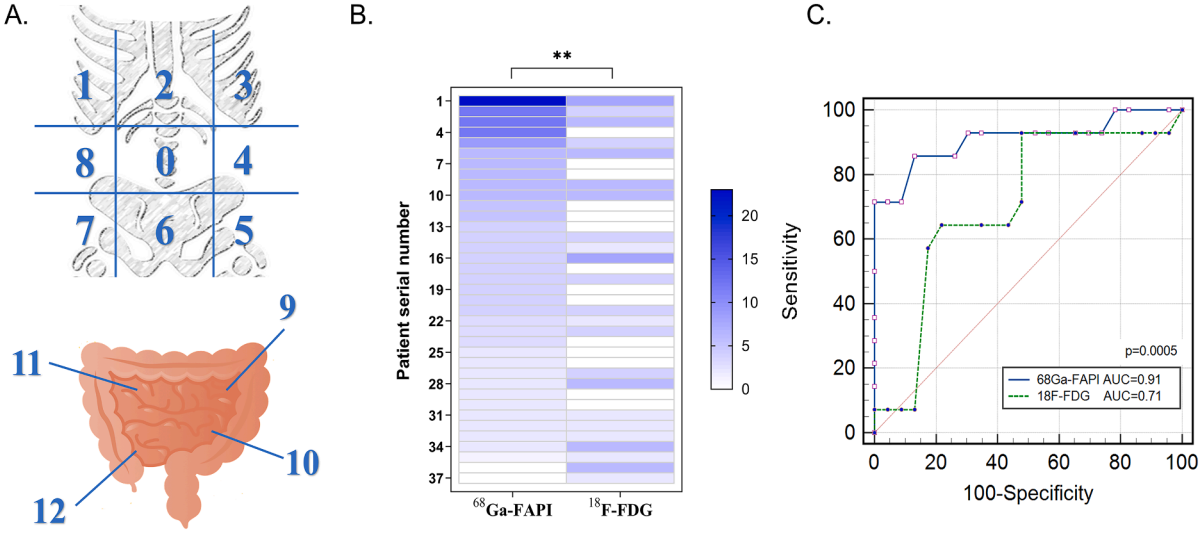

Fig. 3. Evaluation index of peritoneal diagnosis. A: The abdomen and pelvic cavity were divided into 13 regions as follows: 0, central; 1, right upper; 2, epigastrium; 3, left upper; 4, left flank; 5, left lower; 6, pelvis; 7, right lower; 8, right flank; 9, upper jejunum; 10, lower jejunum; 11, upper ileum; 12, lower ileum. B: PCI scores analyzed by ^{18}F-FDG PET/CT and ^{68}Ga-FAPI PET/CT are shown on the heatmap (p < 0.05). Lesion size score (LS) was classified into four grades. LS0, no tumor; LS1, tumor < 0.5 cm; LS2, 0.5 cm < tumor < 5 cm; LS3, tumor > 5 cm or fused into a mass. The PCI score is the sum of the LS scores for each area. C: The ROC curve generated for the PSDSS score. PCI: peritoneal carcinoma index (PCI); PSDSS: peritoneal surface disease severity score.

have peritoneal spread, and 4 ~ 19 % of patients show peritoneal metastasis during the follow-up period after radical resection [27]. Moreover, patients with peritoneal spread demonstrate a poor prognosis [28]. Additional studies have indicated that recurrent peritoneal metastasis following radical treatment is particularly aggressive.

The noninvasive ^{18}F-FDG PET/CT examination has been proved to be useful in tumor diagnosis, staging, and therapy response assessment of various cancers. Gade et al. demonstrated that ^{18}F-FDG PET has high accuracy for diagnosing recurrent CRC [29]. The National Comprehensive Cancer Network has recommended the use of ^{18}F-FDG PET/CT for diagnosing peritoneal disease of small bowel adenocarcinoma [30,31]. However, because of low FDG avidity or disturbance due to physiological activity, this technique has certain limitations in evaluating some gastrointestinal cancer types such as mucinous adenocarcinoma or SRCC. Koppula et al. demonstrated that mucinous and signet ring cell variants of adenocarcinoma and their metastatic forms may show low metabolic activity, mainly because mucinous adenocarcinoma and SRCC show excessive mucin and mucus components with sparse vascularity [32].

FAP is a protein present in the tumor microenvironment and is overexpressed in various cancers, thus making it a potential target for tumor imaging and treatment. Given the limitations of ^{18}F-FDG PET/CT and the lack of uptake of a physiologic FAP-targeted tracer in the liver and intestinal loops, gastrointestinal cancer is one of the most attractive indications for FAP-targeted imaging. Our study found that, compared to the ^{18}F-FDG PET/CT scan, the ^{68}Ga-FAPI-04 PET/CT scan visualized lesions more clearly (Supplemental Fig. 1) and detected more lesions related to mucinous adenocarcinoma and SRCC, particularly for primary lesions and peritoneal metastases (Table 3, Fig. 3). A previous study [33] showed that the uptake of ^{68}Ga-FAPI-04 by the lesions was 3- to 6-fold higher than that of ^{18}F-FDG. Veldhuijzen et al. [34] concluded that FAPI-PET consistently provided higher SUVmax and TBRmax values for tumor detection than FDG-PET during preoperative staging with chemotherapy for patients with pancreatic cancer, gastric cancer, and cholangiocarcinoma; this indicated the possibility of more accurate target outlining for radiation therapy [35]. From the comprehensive perspective of sensitivity, specificity, and accuracy, our study revealed that the ^{68}Ga-FAPI-04 PET/CT scan surpassed the ^{18}F-FDG PET/CT scan in terms of avoidance of potentially false-positive pitfalls [16,36] and challenges [37] such as physiological uptake or inflammatory uptake during the imaging of colorectal mucinous carcinoma and SRCC.

There is yet no definite consensus regarding the appropriate treatment modality for patients with peritoneal metastases from CRC. The international guidelines have recommended cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) as the preferred treatment approach for peritoneal metastasis of CRC [38]. The Chinese Expert Consensus on the Diagnosis and Treatment of Peritoneal Metastases of Colorectal Cancer (2022 edition) recommends the selective use of CRS combined with HIPEC for treating patients with peritoneal metastases of resectable CRC on the basis of an adequate assessment of the degree of tumor load. Tumor load assessment of peritoneal metastases is mainly based on the PCI score and the PSDSS.

The PCI score can quantify the burden of peritoneal metastases in CRC, which can be used for screening patients suitable for treatment with the combination of CRS and HIPEC [25]. Patients with the total PCI score of $\leq$20 can undergo the combination therapy. A recent study found a linear relationship between the PCI score and patient survival; the higher the PCI score, the worse was the treatment prognosis [39]. Burnett et al. [40] retrospectively analyzed patients with peritoneal metastases from CRC who underwent tumor cytoreduction combined with peritoneal hyperthermia-irrigated chemotherapy; the median overall survival of patients with PCI $>$ 20 and those with PCI $\leq$ 20 was 19 and 62 months, respectively. Therefore, the accurate assessment of peritoneal involvement is critical for the efficient diagnosis and management of patients with peritoneal metastatic cancer.

The PSDSS is based on clinical symptoms, PCI score, and histopathological characteristics of the primary lesions. Therefore, changes in the PCI score will directly affect PSDSS grading. PSDSS is divided into four grades based on the total score: 2–3, grade I; 4–7, grade II; 8–10, grade III; and $>$10, grade IV; grades III and IV suggest poor prognosis [41]. The PSDSS can also be used to screen patients suitable to receive the combination treatment of CRS and HIPEC. Moreover, compared to ^{18}F-FDG PET/CT, ^{68}Ga-FAPI PET/CT yielded more definite PCI index and PSDSS staging, which enabled to better support the clinical management of recurrent CRC patients with peritoneal metastases.

In the present study, we retrospectively compared the efficacy of ^{18}F-FDG PET/CT and ^{68}Ga-FAPI-04 PET/CT for detecting recurrent CRCs. ^{68}Ga-FAPI-04 PET/CT showed better performance than ^{18}F-FDG PET/CT based on higher TBR and higher efficacy for evaluating SRCC and colorectal mucinous carcinoma, particularly in CRC patients with peritoneal metastasis. This presents a better adjunctive solution for monitoring and guiding the treatment of recurrent metastasis in patients with these pathological types. By using the combination of these two modalities, more metastatic lesions of SRCC and mucinous carcinoma could be detected, which could modify the target area of radiotherapy. This approach also has potential advantages in predicting the prognosis of patients with metastatic cancer (Supplemental Fig. 2).

The present study has some limitations. First, although subsequent CT, MRI, and other traditional imaging examinations can enable to determine whether the lesion is metastatic, the relevant pathological results were lacking, and the possibility of false-positive results cannot be excluded. Second, the study was inherently biased because of its retrospective nature and had a high attrition rate. Third, the sample size was small, and more patients should be enrolled for obtaining robust results. Lastly, changes in the treatment outcomes due to different imaging modalities were not compared. Therefore, more in-depth research should be conducted in future studies to fully utilize the advantages of FAPI PET/CT for peritoneal metastatic carcinoma diagnosis, treatment guidance, and prognosis prediction.

CRediT authorship contribution statement

Yue Xi: Formal analysis, Investigation, Methodology, Writing – original draft. **Yuyun Sun:** Data curation, Project administration, Writing – review & editing. **Bingxin Gu:** Validation, Visualization. **Linjie Bian:** Software. **Shaoli Song:** Conceptualization, Funding acquisition, Resources, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2024.100848.

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