Fibroblast activation protein inhibitor (FAPI) PET/CT in gastric cancer

Tadashi Watabe[1,2], M.D., Ph.D. Frederik L. Giesel [2,3] M.D., MBA.

[1]Department of Nuclear Medicine and Tracer Kinetics, Graduate School of Medicine, Osaka University

[2]Institute for Radiation Sciences, Osaka University

[3]Department of Nuclear Medicine, Medical Faculty, Heinrich-Heine-University and University Hospital Duesseldorf, Germany

Corresponding author:

Tadashi Watabe (Assistant Professor)

2-2 Yamadaoka, Suita, Osaka 565-0871, Japan

Tel: +81-6-6879-3461; Fax: +81-6-6879-3469

E-mail: watabe@tracer.med.osaka-u.ac.jp

ORCID: 0000-0001-8658-2395

Second author:

Frederik L. Giesel

frederik.giesel@med.uni-duesseldorf.de

Schanzenstrasse 78, 40549 Duesseldorf, Germany

Disclosure Statement

The authors have nothing to disclose.

Keywords: fibroblast activation protein, positron emission tomography, gastric cancer

Key Points

(3-5 bulleted sentences indicating the main takeaways/defining elements of the article)

- The utility of FDG PET is rather limited in gastric cancer owing to the physiological accumulation and existence of cases with low uptake.
- FAPI-PET shows higher accumulation in the primary site and metastatic lesions than does FDG-PET, especially in detection of peritoneal carcinomatosis.
- In the case of gastric signet ring cell carcinoma, FAPI-PET showed excellent performance since uptake is usually weak on FDG-PET in this cohort.

Synopsis (100 words or less)

Like other major cancers, gastric cancer expresses fibroblast activation protein (FAP) in cancer-associated fibroblasts. Many recent studies have reported the utility and superiority of FAPI-PET over FDG-PET in gastric cancers, from initial staging to recurrence detection. FAPI-PET shows higher accumulation in primary sites and metastatic lesions than does FDG-PET, especially for the detection of peritoneal carcinomatosis. In the case of gastric signet ring cell carcinoma, FAPI-PET showed excellent performance, as uptake is usually weak on FDG-PET in this cohort. Although there is a need to be careful about the pitfalls, FAPI-PET is very useful modality in the diagnosis and treatment planning of gastric cancer.

Abbreviation/Glossary list (most important abbreviations in article)

cancer-associated fibroblasts (CAFs)

fibroblast activation protein (FAP)

fibroblast activation protein inhibitor (FAPI)

fluorodeoxyglucose (FDG)

gastric signet ring cell carcinoma (SRCC)

Introduction

The tumor microenvironment is closely related to cancer invasion and metastasis. Cancer-associated fibroblasts (CAFs) are a major component of the cancer stroma and play an important role in cancer growth and progression.[1] CAFs express fibroblast activation protein (FAP), and FAP expression levels have been reported to correlate with prognosis in cancer patients.[1] In addition, FAP expression has been confirmed in various cancer types, with minimal expression in normal organs.[2,3] FAP inhibitor (FAPI), a ligand of FAP, is attracting attention as an excellent positron emission tomography (PET) probe that can accurately detect many types of cancer compared to the conventional glucose analog of [^{18}F]fluorodeoxyglucose (FDG). ^{68}Ga-labeled FAPI ([^{68}Ga]FAPI-04 or [^{68}Ga]FAPI-46) and ^{18}F-labeled FAPI ([^{18}F]FAPI-74) are mainly available for clinical use.[4-6] Recently, the number of published papers reporting the usefulness of FAPI-PET has increased, and clinical trials are being conducted in Europe, the United States, China, and elsewhere. It is expected that FAPI-PET will be utilized more commonly in cancer diagnosis and treatment in the future.

In this chapter, we focus on FAPI-PET imaging of gastric cancer based on recent reports and our experience.

Current status of FDG-PET imaging in Gastric Cancer

In current clinical practice, [^{18}F]FDG PET is the standard of care for the diagnosis of initial staging, evaluation of treatment response, and detection of recurrent lesions in cancer patients. However, the utility of [^{18}F]FDG PET is limited in gastric cancer compared to that in other malignancies. The disadvantages of FDG-PET in gastric cancers are as follows: 1) physiological accumulation is often observed in the stomach, 2) gastric cancer lesions sometimes show faint

uptake, and 3) thickening of the stomach wall is difficult to detect on computed tomography (CT) unless gastric distension protocols are used, which leads to difficulty in identifying matched lesions on PET/CT.[7] In particular, gastric signet ring cell carcinoma (SRCC) shows low FDG uptake and low sensitivity for its detection on [^{18}F]FDG PET/CT.[8] Due to the above background, the use of FDG-PET in gastric cancer is relatively limited compared to other cancers in oncology.

FAP expression in gastric cancer

FAP is reported to be expressed in the CAFs of more than 90% of human epithelial cancers.[9] FAP has also been identified as a novel biomarker that significantly contributes to the poor prognosis of stomach adenocarcinoma, and increased FAP expression is related to a more advanced tumor stage.[10] It has been suggested that there is a close relationship between FAP expression and the state of the tumor microenvironment. According to the Human Protein Atlas website, among major cancers, gastric cancer exhibits mid-level FAP RNA expression and the second highest FAP protein expression, followed by breast cancer and pancreatic cancer.[11] Considering these reports and atlas information, gastric cancer can be a good indication for FAPI-PET imaging.

Clinical applications of FAPI-PET in gastric cancer

Many recent studies have reported the utility and superiority of FAPI-PET in gastric cancers compared with FDG-PET (Table 1). For example, Pang *et al.* reported the superiority of [^{68}Ga]FAPI-04 in 20 gastric cancer patients (11 patients for initial staging and 9 for recurrence detection: moderately or poorly differentiated adenocarcinoma [n = 11] and SRCC [n = 9]) (Fig.

1 and Fig. 2).[12] Moreover, FAPI uptake was higher with [^{68}Ga]FAPI-04 PET/CT than with [^{18}F]FDG PET/CT in primary lesions (gastric cancer:12.7 vs 3.7, respectively, p = 0.003). In addition, [^{68}Ga]FAPI-04 PET also detected more lymph node and peritoneal metastases, particularly in SRCC cases.

Furthermore, Qin *et al.* evaluated 20 patients with histologically proven gastric carcinomas (14 patients for initial staging and 6 for recurrence detection: poorly differentiated adenocarcinoma [n = 10], SRCC [n = 4], etc.). They reported that [^{68}Ga]FAPI-04 PET was superior to [^{18}F]FDG PET in the detection of primary tumors with higher uptake (100% [14/14] vs. 71.4% [10/14]; P=0.034) and metastases in the peritoneum, abdominal lymph nodes, liver, and bones (Fig. 3).[13] However, the detection ability of [^{68}Ga]FAPI-04 PET for ovarian metastases was not better than that of [^{18}F]FDG.

Kuten *et al.* performed a head-to-head prospective comparison between [^{68}Ga]FAPI-04 PET and [^{18}F]FDG PET in 13 patients with gastric adenocarcinoma (most of them were poorly differentiated adenocarcinomas) who presented for either initial staging (n = 10) or restaging (n = 3).[14] All 10 primary gastric tumors were FAPI-positive (100% detection rate), whereas only five were also FDG-positive (50%). The tumor-to-background ratio was significantly higher for FAPI (mean:12.9 [range: 2.2–23.9]) than for FDG (4.5 [0.8–9.7]). Although the detection rates of regional lymph node involvement were comparable, FAPI showed a superior detection rate for peritoneal carcinomatosis (100% vs. none).

Jiang *et al.* evaluated 38 patients with therapy-naive gastric cancer with histopathologic confirmation (31 with adenocarcinoma and seven with SRCC). For detection of the primary lesion, the sensitivities of [^{68}Ga]FAPI-04 PET and [^{18}F]FDG PET were 100% (38/38) and 82% (31/38), respectively (p = 0.016).[15] Four cases of adenocarcinoma and three cases of SRCC were

missed on [^{18}F]FDG PET. The mean SUVmax of FAPI was higher in T2–4 tumors (9.7 ± 4.4) than in T1 tumors (3.1 ± 1.5) ($p = 0.0002$). For the detection of metastatic lesions, the sensitivities of [^{68}Ga]FAPI-04 PET and [^{18}F]FDG PET in the 10 patients with regional lymph node metastasis and distant metastasis were 6/10 and 5/10, respectively. These data suggested that it is essential to improve the detection rate of metastatic lesion by FAPI-PET in order to avoid invasive staging, such as diagnostic laparoscopy.

Fu *et al.* retrospectively compared [^{68}Ga]Ga-FAPI-04/[^{18}F]FAPI-42 PET/CT with [^{18}F]FDG PET/CT in 61 patients with an initial gastric cancer.[16] The pathological types of the disease were highly and/or moderately differentiated adenocarcinoma (n = 10), moderately and poorly differentiated adenocarcinoma (n = 8), poorly differentiated adenocarcinoma without SRCC (n= 13), poorly differentiated adenocarcinoma containing SRCC (n = 21), SRCC (n = 7), and other types (n = 2). Lesions containing SRCC occurred in 45.9% (28/61) of patients. For primary lesions, higher uptake of FAPI than of FDG was observed (median SUVmax, 14.60 vs 4.35, $p < 0.001$), resulting in higher positive detection using FAPI-PET than FDG-PET (95.1% vs. 73.8%, $p < 0.001$), particularly for tumors with SRCC (96.4% vs. 57.1%, $p < 0.001$). FAPI PET/CT detected more positive lymph nodes than did FDG PET/CT (637 vs. 407). However, both modalities underestimated N staging compared with pathological N staging. FAPI PET/CT showed a higher sensitivity (92.3% vs. 53.8%, $p = 0.002$) and peritoneal cancer index score (18 vs. 3, $p < 0.001$) in peritoneum metastasis and other suspected metastases than did FDG PET/CT. Lin *et al.* evaluated 56 patients with histologically proven gastric carcinomas, including 45 patients for staging and 11 patients for restaging after surgery, of which 17 (37.8%) contained SRCC. [17] [^{68}Ga]FAPI-04 PET/CT was comparable to [^{18}F]FDG in detecting primary tumors and lymph node (LN) metastases, whereas FAPI outperformed FDG in detecting peritoneal (159 vs.

47, P < 0.001) and bone metastases (64 vs. 55, p = 0.003) on lesion-based analysis. Compared with [^{18}F]FDG PET, FAPI PET showed higher SUVmax (10.3 vs. 8.1, p = 0.004) and tumor to background ratio (TBR) (11.6 vs. 5.8, p < 0.001) in the primary tumor, and higher TBR in LN involvement (8.0 vs. 3.7, p < 0.001) and peritoneal metastases (8.1 vs. 3.2, p < 0.001). The specificity and positive predictive value of FAPI were significantly higher than those of FDG (100.0% vs. 97.7%, p < 0.001; 100.0% vs. 57.1%, p = 0.001, respectively) in determining LN status. The excellent specificity and positive predictive value of FAPI-PET indicated that it can lead to the proper staging and appropriate patient management. The FAPI was comparable to FDG in evaluating N-staging (47.1% vs. 23.5%, p = 0.282). FAPI PET/CT detected more positive recurrent lesions in all restaging patients and showed a clearer tumor delineation.

Chen *et al.* evaluated 34 patients with histologically confirmed SRCCs and showed excellent performance of [^{68}Ga]FAPI-04 PET compared with [^{18}F]FDG PET.[18] [^{68}Ga]FAPI-04 PET showed higher SUVmax and TBR values than did [^{18}F]FDG PET in the primary tumors (SUVmax: 5.2 vs. 2.2, p = 0.001; TBR: 7.6 vs. 1.3, p < 0.001), involved lymph nodes (SUVmax: 6.8 vs. 2.5, p < 0.001; TBR: 5.8 vs. 1.3, p < 0.001), and bone and visceral metastases (SUVmax: 6.5 vs. 2.4, p < 0.001; TBR: 6.3 vs. 1.3, p < 0.001). In diagnostic performance, [^{68}Ga]FAPI-04 PET exhibited higher sensitivity than [^{18}F]FDG PET for detecting primary tumors (73% [16/22] vs. 18% [4/22], p < 0.001), local recurrence (100% [7/7] vs. 29% [2/7], p = 0.071), lymph node metastases (77% [59/77] vs. 23% [18/77], p < 0.001), and distant metastases (93% [207/222] vs. 39% [86/222], p < 0.001).

Kratochwil *et al.* reported FAPI uptake in 28 different kinds of cancer, with a SUVmax value of approximately 5.0 in gastric cancer (n = 3); which belongs to the relatively low uptake group compared to many other types of cancer.[3] However, the reported value in the other studies was

approximately 10–15 in SUVmax on average, which is also higher than FDG uptake. Previous reports by Kratochwil *et al.* might have underestimated the FAPI uptake in gastric cancer due to the limited number of included patients. In addition, a pre-test selection bias may have also be in operation here with many clinicians not using FDG PET/CT for other than intestinal type adenocarcinoma because of recognised limitations in diffuse gastric cancer (SRCC).

In the interpretation of FAPI-PET images, there is a need to be careful about specificity. There are several pitfalls of noncancer uptake in benign lesions. A previous study reported that benign uptake occurs in bone degeneration, wound healing, the endometrium, and inflammation including pancreatitis and pneumonia.[19,20] Benign tumors sometimes showed high FAPI uptakes in renal angiomyolipoma, thyroid adenoma, necrotizing granuloma, and splenic hemangioma.[20] In one study, the specificity of [^{68}Ga]FAPI PET/CT was not higher than that of [^{18}F]FDG (82% [46 of 56] vs. 89% [50 of 56], respectively; p = 0.50).[12] In another, the specificity of FAPI-PET was lower than that of [^{18}F]FDG PET (46% vs. 71%) for bone and visceral metastases because more false-positive lesions were observed on [^{68}Ga]FAPI PET (including myelofibrosis [n = 6/24], arthritis [n = 2/24], granulomatous disease [n = 2/24], uterine fibroid [n = 1/24], pneumonia [n = 1/24], and esophagitis [n = 1/24]).[18] However, in the study of Lin *et al.,* the specificity for metastatic disease was superior.[17] Therefore, there is a need for careful interpretation regarding the possibility of benign or inflammatory uptake on FAPI-PET to maintain a high positive predictive value, particularly if avoidance of invasive staging or curative treatment would be considered based on PET/CT findings.

Regarding the labeling radionuclide for FAPI, the short half-life of ^{68}Ga (68 min) can be a limitation for its production and delivery. ^{18}F-labeling (half-life=110 min) will enable large-scale production like [^{18}F]FDG and will have wider availability. Evaluation using [^{18}F]FAPI-74 also

shows excellent performance in gastric cancer. A case study presentation using [^{18}F]FAPI-74 is shown in Fig 4.

Conclusion

The utility of FAPI-PET imaging in gastric cancer is summarized in this chapter. FAPI-PET shows higher accumulation in primary sites and metastatic lesions than does FDG-PET, especially for the detection of peritoneal carcinomatosis. In the case of gastric SRCC, FAPI-PET showed excellent performance because uptake is usually weak on FDG-PET in this cohort of patients. It is highly expected that FAPI-PET will be increasingly utilized in the diagnosis and treatment planning of gastric cancer.

Clinics Care Points – ***Bulleted list of evidence-based pearls and pitfalls relevant to the point of care***

1) FAPI-PET should be considered for pretreatment evaluation of gastric cancers if FDG-PET shows weak uptake.
2) If the histological type is gastric signet-ring cell carcinoma, FAPI-PET is strongly recommended.
3) FAPI-PET is useful for the detection of peritoneal carcinomatosis in gastric cancer.

References

1. Kobayashi H, Enomoto A, Woods SL, Burt AD, Takahashi M, Worthley DL. Cancer-associated fibroblasts in gastrointestinal cancer. Nat Rev Gastroenterol Hepatol 2019;16:282-95.
2. Giesel FL, Kratochwil C, Lindner T, et al. 68Ga-FAPI PET/CT: Biodistribution and Preliminary Dosimetry Estimate of 2 DOTA-Containing FAP-Targeting Agents in Patients with Various Cancers. J Nucl Med 2019;60:386-92.
3. Kratochwil C, Flechsig P, Lindner T, et al. 68Ga-FAPI PET/CT: Tracer Uptake in 28 Different Kinds of Cancer. J Nucl Med 2019;60:801-5.
4. Loktev A, Lindner T, Burger EM, et al. Development of Fibroblast Activation Protein-Targeted Radiotracers with Improved Tumor Retention. J Nucl Med 2019;60:1421-9.
5. Giesel FL, Adeberg S, Syed M, et al. FAPI-74 PET/CT Using Either ^{18}F-AlF or Cold-Kit ^{68}Ga Labeling: Biodistribution, Radiation Dosimetry, and Tumor Delineation in Lung Cancer Patients. J Nucl Med 2021;62:201-7.

6. Naka S, Watabe T, Lindner T, et al. One-pot and one-step automated radio-synthesis of [18F]AlF-FAPI-74 using a multi purpose synthesizer: a proof-of-concept experiment. EJNMMI Radiopharm Chem 2021;6:28.
7. Le Roux PY, Duong CP, Cabalag CS, et al. Incremental diagnostic utility of gastric distension FDG PET/CT. Eur J Nucl Med Mol Imaging. 2016 Apr;43(4):644-53.
8. Dondi F, Albano D, Giubbini R, Bertagna F. 18F-FDG PET and PET/CT for the evaluation of gastric signet ring cell carcinoma: a systematic review. Nucl Med Commun 2021;42:1293-1300.
9. Zhi K, Shen X, Zhang H, Bi J. Cancer-associated fibroblasts are positively correlated with metastatic potential of human gastric cancers. J Exp Clin Cancer Res. 2010 Jun 8;29(1):66.
10. Lyu Z, Li Y, Zhu D, et al. Fibroblast Activation Protein-Alpha is a Prognostic Biomarker Associated With Ferroptosis in Stomach Adenocarcinoma. Front Cell Dev Biol 2022;10:859999.
11. The Human Protein Atlas https://www.proteinatlas.org/ENSG00000078098-FAP/pathology
12. Pang Y, Zhao L, Luo Z, et al. Comparison of ^{68}Ga-FAPI and ^{18}F-FDG Uptake in Gastric, Duodenal, and Colorectal Cancers. Radiology 2021;298:393-402.
13. Qin C, Shao F, Gai Y, et al. ^{68}Ga-DOTA-FAPI-04 PET/MR in the Evaluation of Gastric Carcinomas: Comparison with ^{18}F-FDG PET/CT. J Nucl Med 2022 Jan;63(1):81-88.
14. Kuten J, Levine C, Shamni O, et al. Head-to-head comparison of [68Ga]Ga-FAPI-04 and [18F]-FDG PET/CT in evaluating the extent of disease in gastric adenocarcinoma. Eur J Nucl Med Mol Imaging 2022;49:743-50.

15. Jiang D, Chen X, You Z, et al. Comparison of [^{68} Ga]Ga-FAPI-04 and [^{18}F]-FDG for the detection of primary and metastatic lesions in patients with gastric cancer: a bicentric retrospective study. Eur J Nucl Med Mol Imaging 2022;49:732-42.
16. Fu L, Huang S, Wu H, et al. Superiority of [68Ga]Ga-FAPI-04/[18F]FAPI-42 PET/CT to [18F]FDG PET/CT in delineating the primary tumor and peritoneal metastasis in initial gastric cancer. Eur Radiol 2022;32:6281-90.
17. Lin R, Lin Z, Chen Z, et al. [68Ga]Ga-DOTA-FAPI-04 PET/CT in the evaluation of gastric cancer: comparison with [18F]FDG PET/CT. Eur J Nucl Med Mol Imaging 2022;49:2960-71.
18. Chen H, Pang Y, Li J, et al. Comparison of [^{68}Ga]Ga-FAPI and [^{18}F]FDG uptake in patients with gastric signet-ring-cell carcinoma: a multicenter retrospective study. Eur Radiol 2022.
19. Kessler L, Ferdinandus J, Hirmas N, et al. Pitfalls and Common Findings in ^{68}Ga-FAPI PET: A Pictorial Analysis. J Nucl Med 2022;63:890-6.
20. Hotta M, Rieger AC, Jafarvand MG, et al. Non-oncologic incidental uptake on FAPI PET/CT imaging. Br J Radiol 2022:20220463.

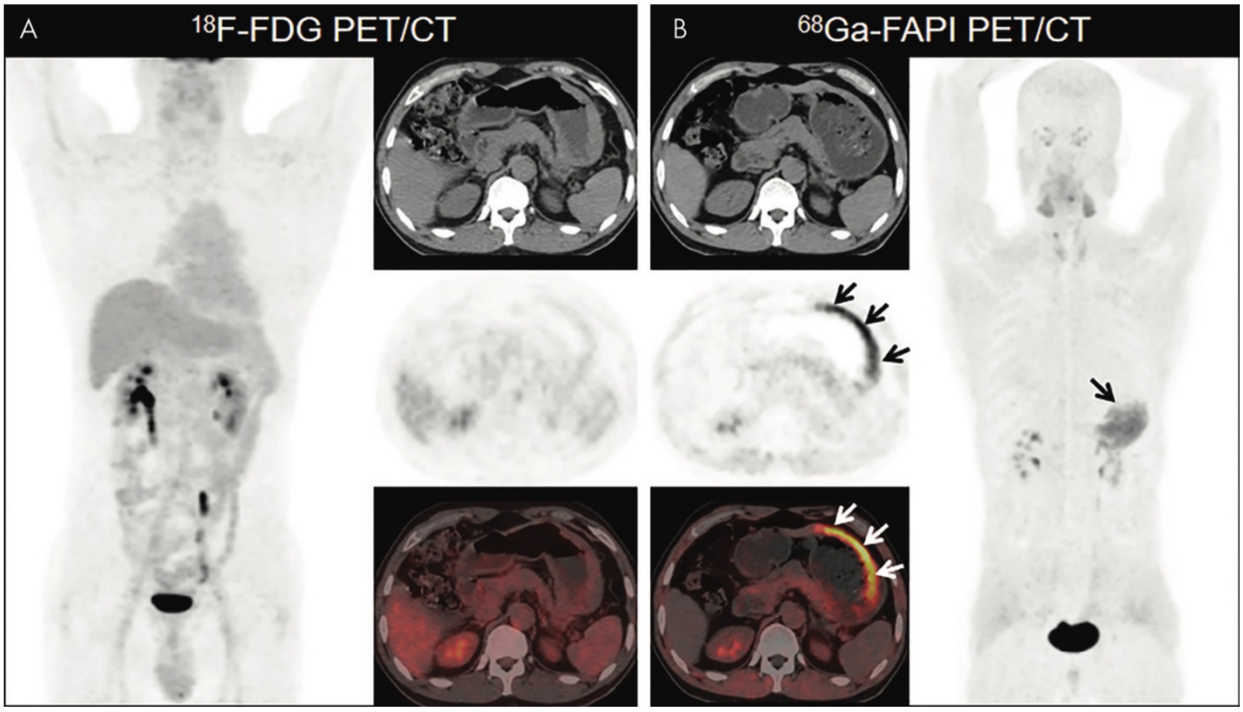


Fig 1. Images from a 55-year-old man with known gastric signet ring cell carcinoma who underwent [^{18}F]FDG PET/CT for initial staging. *A*, Images from [^{18}F]FDG PET/CT demonstrating normal findings (left image: anterior maximum intensity projection image obtained using [^{18}F]FDG PET; right upper image: axial unenhanced CT image; right middle image: axial PET image; right lower image: axial fused PET/CT image). *B*, Images obtained during [^{68}Ga]FAPI PET/CT performed for further evaluation revealed intense [^{68}Ga]FAPI uptake along the gastric wall (arrows) (maximum standardized uptake value, 11) (right image: anterior maximum intensity projection image obtained using [^{18}F]FDG PET; left upper image: axial unenhanced CT image; left middle image: axial PET image; left lower image: axial fused PET/CT image). No distant metastasis was observed.

(cited from reference No.12 according to the open-access policy)

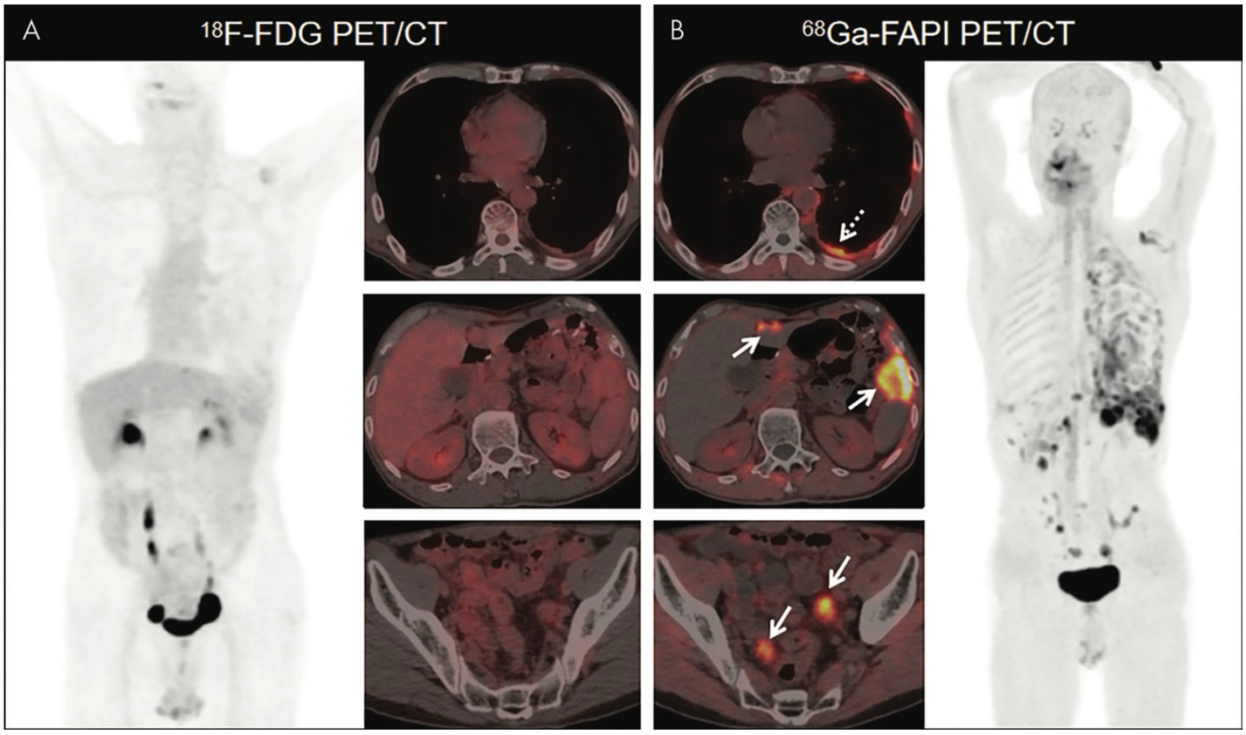


Fig 2. Images from a 66-year-old man who had undergone radical gastrectomy for gastric adenocarcinoma presented with abdominal pain and elevated tumor marker levels. *A*, Images from [^{18}F]FDG PET/CT show thickened pleura and multiple nodules in the peritoneum and mesentery, with low-to-moderate [^{18}F]FDG activity in these lesions (left image: anterior maximum intensity projection image from [^{18}F]FDG PET; right images: axial fused PET/CT images). *B* Images from [^{68}Ga]FAPI PET/CT show much higher tracer uptake in the thickened pleura (dashed arrow) and peritoneal nodules (solid arrows) (right image: anterior maximum intensity projection image from [^{18}F]FDG PET; left images: axial fused PET/CT images). A subsequent biopsy of the pleura and peritoneal nodules revealed metastatic gastric adenocarcinoma (poorly differentiated).

(cited from reference No.12 according to the open-access policy)

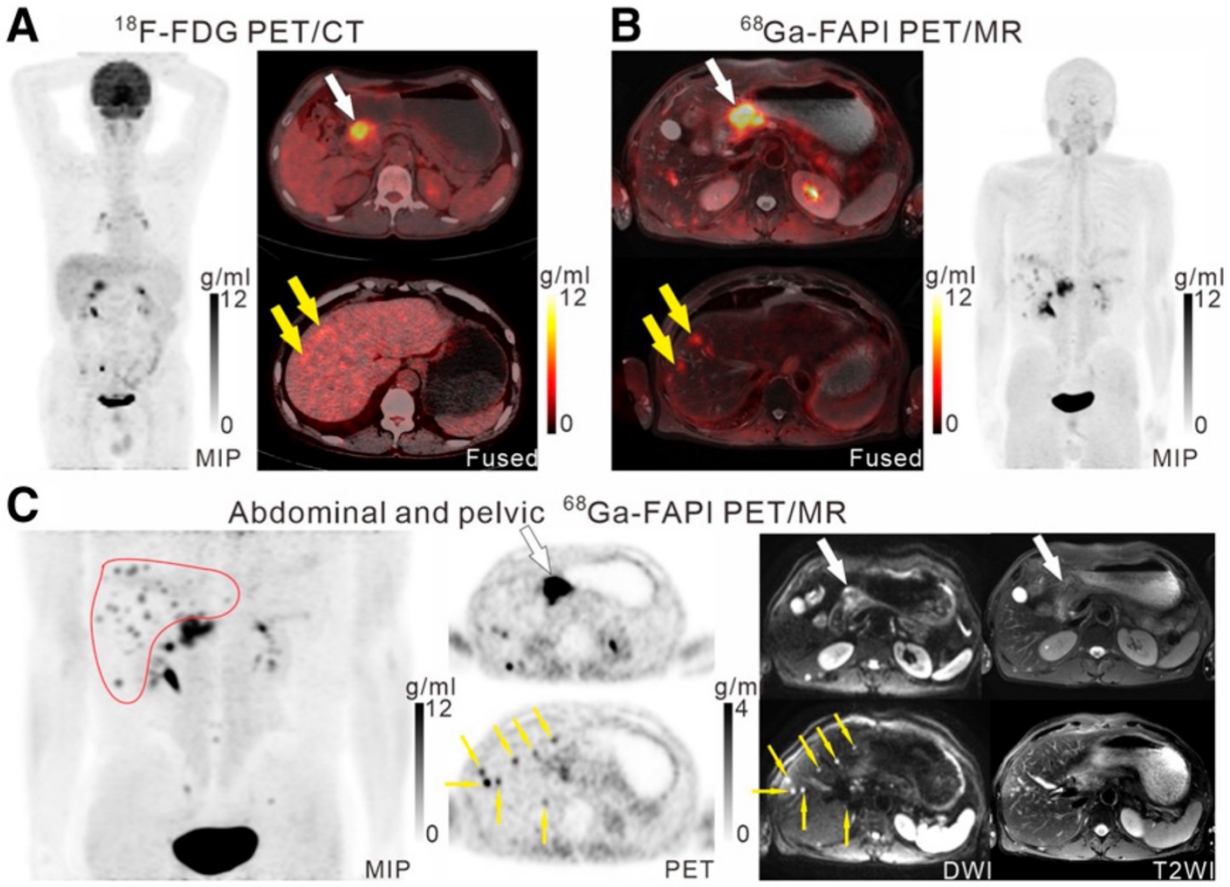
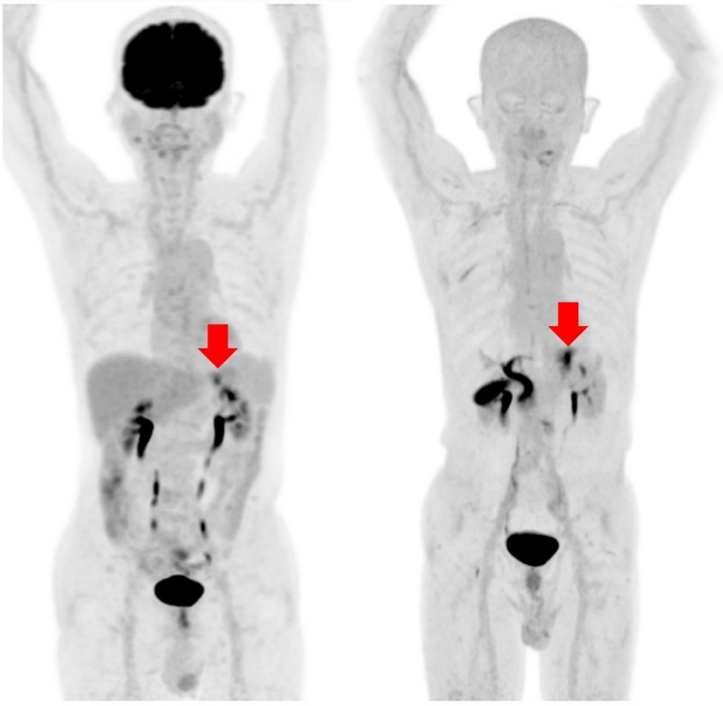


Fig 3. Images from a 61-year-old man (patient 7) with moderately differentiated gastric adenocarcinoma. In addition to the primary tumor (A, white arrow, SUVmax = 11.0), two foci of elevated activity in the liver were noted on the [^{18}F]FDG PET/CT images (*A*, yellow arrows, SUVmax = 5.8). On the [^{68}Ga]FAPI PET/MR images, the primary tumor had more intense uptake (*B* and *C*, white arrows, SUVmax = 14.2), and the 2 hepatic lesions had more prominent [^{68}Ga]FAPI accumulation (*B*, yellow arrows, SUVmax = 7.6). Additionally, multiple foci of increased [^{68}Ga]FAPI activity were also revealed in the liver (*C*, red outline, yellow arrows), which corresponded to multiple high signals on DWI (yellow arrows), suggesting multiple hepatic metastases.

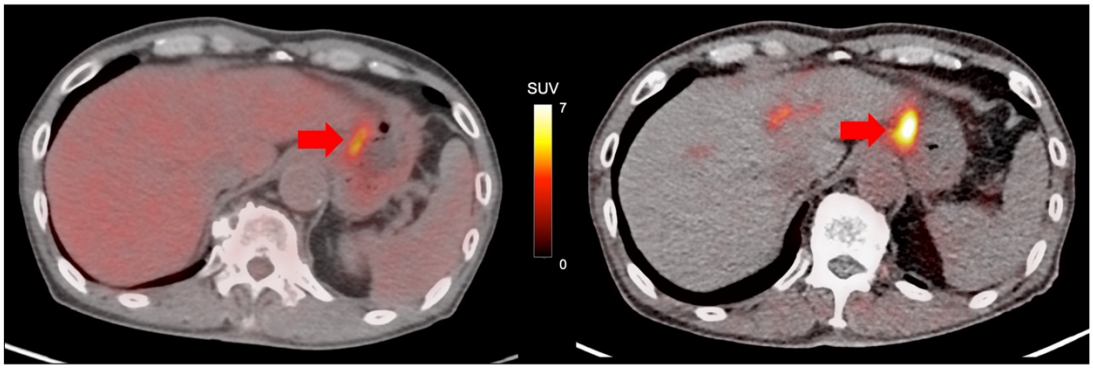
(cited from reference No.13 according to the open-access policy)

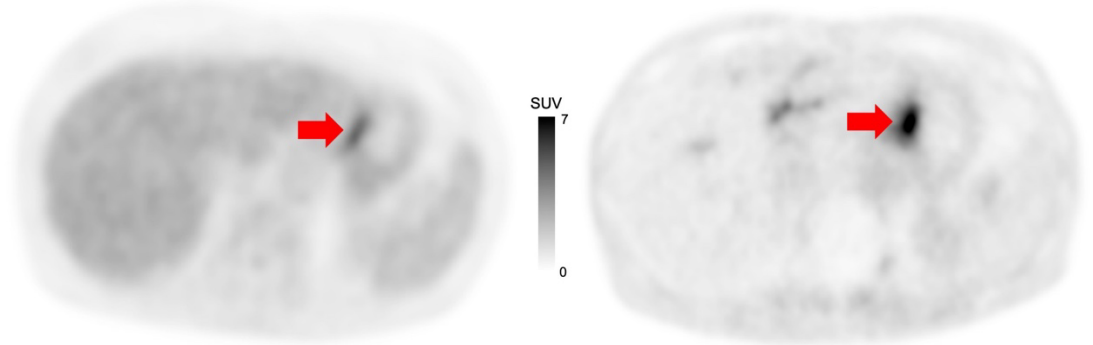
A



FDG-PET FAPI-PET

B





FDG-PET FAPI-PET

Fig 4. A 73-year old male patient with gastric cancer underwent [^{18}F]FAPI-74 PET and [^{18}F]FDG PET after three courses of preoperative chemotherapy (docetaxel, oxaliplatin, and S-1). [^{18}F]FDG PET showed mild uptake in the stomach (SUVmax = 5.5), and [^{18}F]FAPI-74 PET showed more intense and extensive uptake in the corresponding area (SUVmax = 8.2) (red arrows) without metastatic lesions: *A*) MIP (maximum intensity projection) images and *B*) axial PET/CT fusion and PET images. The patient underwent a robot-assisted total gastrectomy and lymphadenectomy. The pathological diagnosis was residual poorly differentiated adenocarcinoma without lymph node metastasis. [^{18}F]FAPI-74 PET clearly detected residual active lesions with higher uptake compared to [^{18}F]FDG-PET. [^{18}F]FAPI-74 PET scan was performed in a clinical research. The study protocol was approved by the Institutional Review Board of Osaka University Hospital. Written informed consent was obtained from the patient.

Reference No.	Year	Author	Journal	Total	Primary staging	PET probe	Primary tumor		
							Detection	SUVmax (FDG vs. FAPI)	Number (FDG vs. FAPI)
12	2021	Pang Y, et al.	Radiology	35	19	[^{68}Ga]FAPI-04	FDG < FAPI	3.7 vs. 12.7 (median)	4 vs. 11
13	2022	Qin C, et al.	J Nucl Med	20	14	[^{68}Ga]FAPI-04	FDG < FAPI	6.2 vs. 11.3 (mean)	10 vs. 14
14	2022	Kuten J, et al.	Eur J Nucl Med Mol Imaging	13	10	[^{68}Ga]FAPI-04	FDG < FAPI	4.5 vs. 12.9 (mean)	10 vs. 10
15	2022	Jiang D, et al.	Eur J Nucl Med Mol Imaging	38	38	[^{68}Ga]FAPI-04	FDG < FAPI	4.5 vs. 11.0* (mean)	12 vs. 17*
16	2022	Fu L, et al.	European Radiology	61	61	[^{68}Ga]FAPI-04 and [^{18}F]FAPI-42	FDG < FAPI	4.4 vs. 14.6 (mean)	45 vs. 58
17	2022	Lin R, et al.	Eur J Nucl Med Mol Imaging	56	45	[^{68}Ga]FAPI-04	FDG < FAPI	8.1 vs. 10.3 (mean)	44 vs. 45
18	2022	Chen H, et al.	European Radiology	34	22	[^{68}Ga]FAPI-04	FDG < FAPI	2.2 vs. 5.2 (median)	4 vs. 16

Reference No.	LN metastasis			Other metastasis		
	Detection	SUVmax (FDG vs. FAPI)	Number (FDG vs FAPI)	Detection	SUVmax of peritoneal metastases (FDG vs. FAPI)	Number of peritoneal metastases (FDG vs. FAPI)
12	FDG < FAPI**	2.4 vs. 6.7 (median)	48 vs. 96	FDG < FAPI**	3.6 vs. 8.4 (median)	51 vs. 93
13	FDG < FAPI	6.6 vs. 9.9 (mean)	33 vs. 45	FDG < FAPI	7.6 vs. 8.4 (mean)	14 vs. 42

14	FDG = FAPI	4.9 vs. 6.5 (mean)	16 vs. 17	FDG < FAPI	2.0 vs. 10.7 (mean)	2 vs. 2
15	FDG = FAPI	N.A.	5 vs. 6		N.A.	
16	FDG < FAPI	2.8 vs. 8.7 (mean)	407 vs. 637	FDG < FAPI	2.5 vs. 9.9 (mean)	14 vs. 24
17	FDG = FAPI	7.6 vs. 7.4 (mean)	16 vs. 20	FDG < FAPI	6.0 vs. 8.2 (mean)	47 vs. 159
18	FDG < FAPI	2.5 vs. 6.8 (median)	38 vs. 83	FDG < FAPI	2.3 vs. 6.3 (median)	20 vs. 59

Table 1. Summary of recent papers that reported the utility and superiority of FAPI-PET in gastric cancers compared to FDG-PET (*in primary tumors greater than 4 cm, **including duodenal and colorectal cancers).