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Review Article

FAPI PET/CT in gastrointestinal malignancies: current clinical applications and future perspectives

Wenpeng Huang[1], Bowen Shi[1], Yihan Yang[2], Zhenning Zhu[1], Yongkang Qiu[2], Lei Kang[2], Jian Xu[3]

[1]Department of Radiology, Geriatric Hospital of Nanjing Medical University (Jiangsu Province Official Hospital), Nanjing 210024, Jiangsu, China; [2]Department of Nuclear Medicine, Peking University First Hospital, Beijing 100034, China; [3]Intensive Care Unit, Geriatric Hospital of Nanjing Medical University (Jiangsu Province Official Hospital), Nanjing 210024, Jiangsu, China

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Abstract: Gastrointestinal malignancies remain an important health problem worldwide, and accurate imaging is needed for tumor staging, treatment planning, and evaluation of recurrence. However, conventional imaging methods and ^{18}F-FDG PET/CT may still show limitations in certain clinical situations, especially in tumors that demonstrate low or uneven glucose metabolism. Moreover, these methods might also struggle to detect peritoneal metastases in some patients. Given that fibroblast activation protein is expressed by cancer-associated fibroblasts in the tumor stroma, FAPI PET/CT has emerged as a new molecular imaging method that targets this pathway. Study shows method offers new diagnostic option. Based on the available evidence, this short review summarizes the biological basis and current clinical use of FAPI PET/CT in gastrointestinal malignancies, with more attention given to gastric and colorectal cancers.

Keywords: Fibroblast-activating protein inhibitor, positron emission tomography, gastric cancer, colorectal cancer, imaging examination

Introduction

Gastrointestinal malignancies, particularly gastric and colorectal cancers, remain major global health burdens and are among the leading causes of cancer-related morbidity and mortality worldwide [1-7]. Despite continuous advances in endoscopy, surgery, systemic therapy, radiotherapy, and multidisciplinary treatment, however, the evidence may suggest that a substantial proportion of patients are still diagnosed at an advanced stage, and recurrence or metastatic progression remains common even after curative-intent therapy [8, 9]. Moreover, the findings could indicate that accurate imaging is essential throughout the clinical course of gastrointestinal malignancies, including initial diagnosis, staging, treatment planning, response assessment, and surveillance for recurrence [10-12].

Given that evidence demonstrates this, the results might indicate that conventional imaging modalities, including contrast-enhanced computed tomography (CT), magnetic resonance imaging (MRI), endoscopic ultrasonography, and endoscopy-based assessment, play important roles in the clinical management of gastrointestinal malignancies. Studies show ^{18}F-FDG PET/CT used to assess tumor metabolism, detect metastatic disease, and identify recurrence [13]. In light of these findings, the data could show that the diagnostic performance of ^{18}F-FDG PET/CT varies across gastrointestinal tumor types and histological subtypes. Therefore, significant evidence may suggest that in gastric cancer, FDG uptake could be low or heterogeneous in poorly differentiated tumors, diffuse-type gastric cancer, signet-ring cell carcinoma, and mucinous lesions [10, 14-16]. Nevertheless, the results might indicate that in colorectal cancer, although ^{18}F-FDG PET/CT is valuable for detecting recurrence and distant metastases, its performance appears limited in mucinous tumors, small-volume peritoneal disease, and lesions located in regions with high physiological or inflammatory tracer uptake. Findings show false-positive results occur in benign inflammatory conditions, including inflammatory bowel disease, polyps, Crohn's disease, and colitis [11]. Furthermore, these important limitations may suggest that increasing interest exists in novel molecular imaging strategies that could provide complementary biological information beyond glucose metabolism.

In recent years, fibroblast activation protein inhibitor (FAPI) PET/CT has emerged as a promising molecular imaging modality in oncology [17, 18]. Unlike ^{18}F-FDG PET/CT, which mainly reflects tumor glucose metabolism, FAPI PET/CT targets fibroblast activation protein (FAP), a cell-surface serine protease that shows high expression in cancer-associated fibroblasts within the tumor stroma but appears minimally detectable in most normal adult tissues [17, 19-22]. Moreover, many gastrointestinal tumors show extensive stromal remodeling, desmoplastic reaction, and dynamic tumor-stroma interactions, and this evidence may support a strong biological rationale for FAP-targeted imaging [23-26]. Given that FAPI tracers demonstrate rapid tumor accumulation and low physiological uptake in many normal abdominal organs, the findings suggest that FAPI PET/CT could provide favorable tumor-to-background contrast for visualizing primary tumors, lymph node metastases, peritoneal dissemination, liver metastases, and recurrent lesions. Furthermore, this

approach may indicate particular advantages in patients with diabetes, inflammation, infection, or a recent history of surgery or radiotherapy, where the evidence shows ^{18}F-FDG PET/CT interpretation can be challenging [27]. Evidence supports complementary use in gastrointestinal tumors.

Accumulating clinical evidence suggests that FAPI PET/CT may complement, and in selected settings could outperform, ^{18}F-FDG PET/CT in gastrointestinal tumors [13, 28, 29]. Beyond diagnosis and staging, the results indicate that FAPI PET/CT holds considerable potential for treatment guidance, response assessment, and prognostic evaluation. Additionally, its integration into theranostic strategies might support a comprehensive "see-and-treat" paradigm. In light of these findings, the approach appears to demonstrate broad clinical relevance.

Therefore, this review summarizes the current clinical applications and future perspectives of FAPI PET/CT in gastrointestinal tumors, with particular emphasis on gastric and colorectal cancers. Nevertheless, we discuss its role in staging, metastatic disease detection, restaging and relapse assessment, and comparison with ^{18}F-FDG PET/CT. In addition, we highlight current limitations and unresolved challenges, including tracer heterogeneity and potential false-positive uptake in benign fibrotic or inflammatory conditions.

Biological basis of FAPI PET/CT in gastrointestinal malignancies

Fibroblast activation protein and cancer-associated fibroblasts

FAP is a type II transmembrane serine protease with both dipeptidyl peptidase and endopeptidase activities [17, 19, 30]. Given that most normal adult tissues show limited or absent FAP expression under physiological conditions, the findings could indicate that activated fibroblasts markedly upregulate FAP during tissue remodeling, wound healing, fibrosis, and tumorigenesis [19, 31]. Cancer-associated fibroblasts (CAFs) are key components of tumor microenvironment. CAFs remodel matrix, promote proliferation, aid angiogenesis. Moreover, through dynamic interactions with tumor cells, immune cells, and matrix components, CAFs may help establish a microenvironment that could support tumor growth, metastatic dissemination, and therapeutic resistance [32-34]. However, the evidence suggests that FAP, as one of the key markers of activated CAFs, might indicate its value as an attractive target for molecular imaging and theranostic development.

Stromal characteristics of gastric cancer and colorectal cancer

Gastric and colorectal cancers show considerable variation in histological subtype, molecular profile, stromal composition, and tumor microenvironment. Their tumor microenvironment often contains abundant CAFs, extracellular matrix components, inflammatory cells, vascular structures, and diverse stromal signaling networks, all of which contribute to tumor growth, invasion, immune modulation, and metastatic progression [22, 35-37]. Given that stromal activation shapes gastrointestinal tumor biology, it appears to function as an integral feature rather than a secondary response to tumor growth. Moreover, the evidence could indicate that this activation reflects a core biological process, not merely a downstream event.

FAPI targets fibroblast activation protein expressed by activated fibroblasts within tumor stroma. Because of this, FAPI PET/CT may identify lesions that are less conspicuous on ^{18}F-FDG PET/CT due to low glucose metabolism, mucinous or poorly differentiated histology, small lesion size, or challenging anatomical location [38]. In light of these findings, this mechanism might be particularly relevant for diffuse-type gastric tumors, signet-ring cell carcinoma, and peritoneal metastatic disease, where conventional metabolic imaging could prove suboptimal [10, 39]. Furthermore, the results indicate that FAPI PET/CT may also hold value for evaluating stromal-rich primary tumors, locally recurrent disease, liver or peritoneal metastases, and lesions with variable FDG avidity in colorectal cancer [40, 41]. Notwithstanding this variability, the relatively low physiological background uptake of FAPI tracers in many normal abdominal tissues may enhance tumor-to-background contrast and improve lesion visualization [42].

Therefore, the biological rationale for FAPI PET/CT in gastric and colorectal cancers lies in its ability to visualize tumor-associated stromal activation rather than tumor metabolism alone. Additionally, the evidence may suggest that this distinct targeting approach provides complementary information to existing imaging modalities. Nevertheless, the findings indicate that FAPI PET/CT could improve disease assessment in selected clinical scenarios.

FAPI PET/CT in gastric cancers

Staging of gastric cancer

A single-institution retrospective study demonstrates that ^{68}Ga-FAPI PET/CT could play a role in the initial staging of gastric adenocarcinoma [43]. Given that 90 treatment-naïve patients were evaluated, ^{68}Ga-FAPI PET/CT detected all primary gastric tumors, and the findings may indicate high tracer uptake with excellent tumor-to-background contrast, with uptake largely independent of histopathological subtype. However, the authors highlighted that its particular value could appear strongest in identifying subcentimetric peritoneal lesions, a setting where conventional imaging and FDG-based assessment might show limitations. Moreover, these results should be interpreted with caution, since the study was retrospective,

conducted at a single center, and may suggest limited generalizability given the lack of a direct comparison with ^{18}F-FDG PET/CT. Study lacks comparison data.

Fu et al. compared PET with CT for staging. In light of this comparison, Fu et al. [44] retrospectively evaluated ^{68}Ga-FAPI-04 PET against contrast-enhanced CT for initial staging in 62 patients with gastric cancer and found that performance appeared broadly comparable between the two modalities for assessing regional lymph node involvement and patient-based distant metastasis. Nevertheless, the evidence could suggest that ^{68}Ga-FAPI-04 PET offers additional value in delineating the extent of metastatic burden. Given that 112 patients were studied, Zhang et al. [45] demonstrated that the clinical utility of ^{68}Ga-FAPI PET/CT in gastric cancer may extend to refining both initial staging and postoperative recurrence assessment when added to contrast-enhanced CT. Therefore, the important findings from their retrospective cohort suggest that ^{68}Ga-FAPI PET/CT identified additional or clarified findings in 24 patients, involving 29 lesions or lesion groups, most commonly in the peritoneum and distant lymph nodes.

Given that treatment modification occurred in 20 patients (17.9%), the significant data could indicate that imaging findings led to changes in staging or recurrence status in 21 patients (18.8%), including 7 additional cases of postoperative recurrence. Furthermore, these results may suggest that ^{68}Ga-FAPI PET/CT provides meaningful incremental value for restaging and recurrence evaluation, particularly when CT findings are equivocal or occult metastatic disease is suspected. However, beyond lesion detection, the evidence may indicate that FAPI PET/CT also provides biologically relevant information during the initial evaluation of gastric cancer. In light of a 2025 clinical study of 72 patients with newly diagnosed gastric cancer who underwent preoperative ^{18}F-FAPI-42 PET/CT, the significant findings could indicate that primary-tumor uptake parameters were higher in patients with pathologically confirmed lymphovascular invasion and/or perineural invasion (LVI/PNI) than in those without LVI/PNI, including SUVmax, SUVmean, and tumor-to-background ratio (TBR) (all $P < 0.001$) [46]. Moreover, receiver operating characteristic analysis may demonstrate that strong predictive performance for LVI/PNI emerged, with AUCs of 0.932 for SUVmax, 0.923 for SUVmean, and 0.925 for TBR. Given that SUVmax showed the best performance, an optimal cutoff of 3.86 yielded 93.3% sensitivity and 81.5% specificity, and histological grade and SUVmax were further identified as independent predictors in multivariable analysis. Therefore, these findings suggest that FAPI PET/CT may extend beyond anatomical staging and support preoperative assessment of tumor aggressiveness and risk stratification in gastric cancer.

Evidence indicates that FAPI PET/CT's advantages in initial gastric cancer staging lie mainly in consistent visualization of primary lesions. Moreover, the findings could indicate improved M staging assessment, particularly for patients with equivocal conventional imaging findings or suspected distant metastasis or peritoneal dissemination. However, this pattern may suggest that findings apply more clearly to distant disease than to nodal disease. For N staging, though, FAPI PET/CT should currently be regarded as complementary rather than a replacement for contrast-enhanced CT.

Detection of metastatic diseases

In the metastatic evaluation of gastric cancer, particularly for occult peritoneal metastasis, ^{68}Ga-FAPI-04 PET/CT appears to provide clinically meaningful value. In a comparative study, [^{18}F]FAPI-04 demonstrated higher sensitivity, specificity, and overall accuracy than [^{18}F]FDG PET/CT in the gastric cancer subgroup and yielded higher estimates of peritoneal tumor burden [47]. Given that a prospective single-center cohort of 109 patients with locally advanced gastric adenocarcinoma underwent ^{68}Ga-FAPI-04 PET/CT before laparoscopic staging, Hu et al. [48] found that the results could indicate this modality identified occult peritoneal metastasis in 17 patients (15.6%), with a sensitivity of 75.0%, specificity of 94.6%, accuracy of 91.7%, and negative predictive value of 95.7%, using laparoscopic staging combined with peritoneal washing cytology as the reference standard. Moreover, the findings may suggest that 12 of the 17 PET-positive patients were ultimately redirected from curative-intent to palliative treatment after confirmation, indicating a potential impact on preoperative decision-making.

Another prospective study by Lin et al. [49], which included 56 patients with gastric cancer, including 45 undergoing initial staging and 11 undergoing restaging, further demonstrated that the significant evidence could support the value of ^{68}Ga-DOTA-FAPI-04 PET/CT for metastatic assessment compared with ^{18}F-FDG PET/CT. However, although the two tracers showed broadly comparable performance for detecting primary tumors and lymph node metastases, the important results may indicate that FAPI PET/CT identified significantly more peritoneal metastases (159 vs. 47 lesions, $P < 0.001$) and bone metastases (64 vs. 55 lesions, $P = 0.003$) on lesion-based analysis. Therefore, the findings might suggest that FAPI also provided higher contrast for peritoneal disease, with significantly greater SUVmax (7.1 vs. 4.5, $P = 0.002$) and tumor-to-background ratio (8.1 vs. 3.2, $P < 0.001$), supporting its particular advantage in delineating abdominal metastatic spread.

In a paired-imaging study, the findings could demonstrate that ^{68}Ga-FAPI-04 showed higher tracer uptake, a higher peritoneal cancer index, and greater sensitivity than ^{18}F-FDG for detecting peritoneal carcinomatosis, with gastric cancer showing one of the most pronounced benefits [50]. Nevertheless, the important results may indicate that in gastric cancer, FAPI achieved a sensitivity of 100% compared with 53.85% for FDG, and its advantage was

particularly evident in FDG-low subtypes such as signet-ring cell carcinoma. Furthermore, these findings could support that FAPI PET/CT plays a potential role in detecting occult peritoneal dissemination and more accurately defining disease extent. Notwithstanding this observation, the relevant data might indicate that Yang et al. [51] reported, in patients with suspected recurrence after curative gastrectomy, ^{18}F-AIF-NOTA-FAPI-04 PET/CT showed superior lesion detection compared with ^{18}F-FDG PET/CT for local recurrence, nodal disease, and distant metastases.

Wang et al. [52] examined a retrospective study of 12 patients with 23 Krukenberg tumors arising from gastric signet-ring cell carcinoma, and the findings suggest that ^{68}Ga-FAPI-04 PET was superior to ^{18}F-FDG PET for detecting the primary gastric lesion and extra-ovarian metastases, particular rly lymph node and peritoneal involvement. Given that patient-based analysis demonstrates this pattern, ^{68}Ga-FAPI-04 PET might indicate higher detection rates than ^{18}F-FDG PET for lymph node metastases (90.9% vs. 54.5%, P = 0.046) and peritoneal metastases (100% vs. 41.7%, P = 0.008), with higher SUVmax and tumor-to-background ratios. However, the evidence appears to show that this advantage did not extend to ovarian metastases. Notwithstanding this limitation, the study may suggest that ^{68}Ga-FAPI-04 PET failed to detect any Krukenberg tumors, whereas ^{18}F-FDG PET showed only limited sensitivity. Sun et al. [53] reported a prospective cohort of 86 patients with gastric mucinous adenocarcinoma, signet-ring cell carcinoma, or adenocarcinoma with mucinous or signet-ring cell components. Moreover, the results may indicate that ^{68}Ga-FAPI PET/CT showed clear advantages over ^{18}F-FDG PET/CT in this population. Furthermore, the study could demonstrate that ^{68}Ga-FAPI PET/CT achieved a higher detection rate for treatment-naïve primary tumors (100.0% vs. 45.8%, P < 0.001), as well as higher sensitivity and accuracy for lymph node metastases (90% vs. 72% and 87% vs. 71%, respectively; both $P < 0.001$). In light of these findings, results might suggest that ^{68}Ga-FAPI PET/CT led to treatment modification in 30.2% of patients.

Restaging and relapse assessment

A prospective exploratory study by Novruzov et al. [54] provides preliminary support for the potential utility of ^{18}F-labeled FAPI imaging in gastrointestinal malignancies. In a mixed cohort of 19 patients who underwent head-to-head PET/CT, [^{18}F]AIF-FAPI-74 could indicate more favorable biodistribution than ^{18}F-FDG, detected a greater number of primary and metastatic lesions overall, and may suggest that significantly higher tumor-to-blood-pool ratios resulted for primary lesions. Given that findings from a 2026 study of gastrointestinal malignancies, in which gastric cancer accounted for 70% of cases, ^{68}Ga-FAP-2286 PET/CT might indicate near-perfect concordance with CT-based RECIST assessment ($\kappa = 0.833$), with particularly strong agreement for lymph node, peritoneal, and visceral metastases [55]. However, molecular response on FAP PET/CT could also demonstrate that this appears predictive of overall survival. Study shows median overall survival was 7.6 months in progressive disease and 19.8 months in stable disease, not reached in partial or complete response. These findings support a potential role for FAP-based PET in post-treatment monitoring and prognostic stratification, particularly in desmoplastic or peritoneal-predominant gastric cancer.

In addition to its value for postoperative restaging, FAPI PET/CT may provide important prognostic information in recurrent gastric cancer. Given that evidence demonstrates a retrospective cohort of 51 patients with first recurrence after gastrectomy who underwent pretreatment [^{18}F]AIF-NOTA-FAPI-04 PET/CT before receiving PD-1 inhibitor plus chemotherapy, results might indicate that lower baseline FAPI-derived parameters were associated with more durable clinical benefit, whereas volumetric indices appeared to show the strongest prognostic performance [56]. Moreover, the significant findings suggest that total lesion FAP expression (TLF) achieved the highest accuracy for distinguishing durable from nondurable clinical benefit (AUC = 0.80). Findings show TLF ≥ 188.88 SUVbw·cm^3 predicted shorter progression-free survival (HR = 7.29, $P = 0.001$), FTV ≥ 44.17 cm^3 predicted worse overall survival (HR = 5.16, $P = 0.010$). Nevertheless, the relevant data may suggest that in the subgroup also undergoing FDG PET/CT, FAPI-based parameters were consistently higher than FDG-derived metrics. In light of these results, this could demonstrate that the evidence further supports the potential of FAPI PET/CT not only for restaging but also for risk stratification in recurrent gastric cancer treated with chemoimmunotherapy.

Comparison with ^{18}F-FDG PET/CT

A prospective single-center study by Miao et al. [57] shows that ^{68}Ga-FAPI-04 PET/CT and ^{18}F-FDG PET/CT provide complementary information in the initial evaluation of gastric cancer. Given that these findings demonstrate that ^{68}Ga-FAPI-04 could indicate higher sensitivity for primary tumor detection (90.3% vs. 77.4%), the results may suggest particular advantages for identifying peritoneal metastases (91.7% vs. 41.7%). Moreover, the dual-tracer approach might indicate that sensitivity for detecting distant metastases increased to 97.1%, exceeding either modality alone. However, the significant findings could demonstrate that treatment strategy changes occurred in nine patients, suggesting potential value for pretreatment stratification.

In a retrospective single-center study of 25 patients with gastric cancer who underwent both ^{68}Ga-FAPI-04 PET/CT and ^{18}F-FDG PET/CT within 1 week, Zhang et al. [58] demonstrated that ^{68}Ga-FAPI-04 provided superior lesion detection across multiple disease settings. Furthermore, the important results appear to show that for primary

tumors, the detection rate was 94.7% (18/19) with ^{68}Ga-FAPI-04 PET/CT compared with 68.4% (13/19) with ^{18}F-FDG PET/CT, and tumor uptake was significantly higher with FAPI (median SUVmax, 10.28 vs. 3.20; $P < 0.01$). Nevertheless, the evidence may indicate that for nodal metastases, FAPI identified substantially more metastatic lymph nodes than FDG (75/77 [97.4%] vs. 32/77 [41.6%]) and showed higher tracer uptake (median SUVmax, 9.20 vs. 3.15; $P < 0.01$). In light of these findings, a similar advantage could appear for distant metastases, with FAPI detecting 275 of 283 lesions (97.2%) compared with 122 of 283 lesions (43.1%) by FDG, again with significantly higher uptake (median SUVmax, 8.00 vs. 4.20; $P < 0.01$). Benefit shows particularly for peritoneal, omental, mesenteric, and liver metastases. Additionally, the key results may suggest that FAPI PET/CT also revealed additional oncological findings in 14 of 25 patients, leading to corrected staging or restaging in 7 patients.

Chen et al. [59] reported in a multicenter retrospective study of 34 patients with gastric signet-ring cell carcinoma that ^{68}Ga-FAPI PET outperformed ^{18}F-FDG PET in both tracer uptake and lesion detection. Therefore, the significant evidence might indicate that compared with ^{18}F-FDG, ^{68}Ga-FAPI achieved higher sensitivity for primary tumors (73% vs. 18%), lymph node metastases (77% vs. 23%), and bone or visceral metastases (93% vs. 39%). Notwithstanding this observation, the important findings could suggest that this FDG-low histological subtype benefits particularly from FAPI imaging.

Emerging evidence further suggests that ^{18}F-labeled FAPI tracers may provide advantages over ^{18}F-FDG in selected clinical scenarios of gastric cancer. Given that a 2026 preclinical and first-in-human study of ^{18}F-NOTA-R49 exists, Wang et al. [60] reported that, among 10 patients with different malignancies, the patient with gastric cancer showed low ^{18}F-FDG uptake in both the primary tumor and peritoneal metastases, whereas ^{18}F-NOTA-R49 PET/CT more clearly delineated the primary gastric lesion. Moreover, the results might indicate that ^{18}F-NOTA-R49 showed higher uptake in peritoneal metastatic deposits. Similarly, a comparative study by Lv et al. [61] indicated that [^{18}F]AlF-NOTA-FAPI-04 PET/CT could demonstrate distinct diagnostic advantages over ^{18}F-FDG PET/CT in gastric cancer. In 65 patients undergoing initial staging or restaging, FAPI PET/CT showed higher sensitivity for primary or recurrent tumors, lymph node metastases, and distant metastases, along with higher lesion SUVmax and target-to-background ratios than FDG PET/CT.

FAPI PET/CT found more metastatic lesions, including peritoneal, ovarian, and osseous metastases, pointing to improved lesion conspicuity. Therefore, imaging strategies should be individualized according to histopathological subtype, risk of metastatic dissemination, and findings from conventional imaging. In this context, FAPI PET/CT may serve as a valuable complementary modality for selected high-risk or diagnostically challenging cases, thereby improving staging accuracy. Furthermore, the findings could support that FAPI PET/CT informs subsequent treatment decisions in a meaningful way. Nevertheless, several prospective studies have demonstrated that FAPI PET outperforms ^{18}F-FDG PET/CT in detecting primary gastric cancer lesions, evaluating peritoneal dissemination, refining staging, and predicting treatment response [39, 62-64]. Beyhan et al. [39] reported that ^{68}Ga-FAPI-04 PET/CT outperformed ^{18}F-FDG PET/CT in gastric cancer, showing a higher primary tumor detection rate (96.7% vs. 77.4%), greater tumor uptake, and improved tumor-to-background contrast, with particular advantages in poorly cohesive, signet-ring cell, and mucinous subtypes. However, the evidence may suggest that FAPI PET/CT also improved lesion-based detection of regional nodal involvement. Moreover, significant data could indicate that FAPI PET/CT provided better visualization of peritoneal metastases, resulting in N-stage and overall stage upgrading in a subset of patients. In light of these findings, Kuten et al. [64] found that ^{68}Ga-FAPI-04 PET/CT was superior to ^{18}F-FDG PET/CT for gastric adenocarcinoma, with a higher primary tumor detection rate (100% vs. 50%) and a higher tumor-to-background ratio (12.9 vs. 4.5, $P = 0.007$).

Qin et al. [63] prospectively compared ^{68}Ga-DOTA-FAPI-04 PET/MR with ^{18}F-FDG PET/CT in 20 patients with gastric cancer and found that FAPI imaging provided better visualization of both primary tumors and most metastatic lesions. Additionally, the results may show that primary tumor detection was significantly higher with ^{68}Ga-FAPI PET/MR than with ^{18}F-FDG PET/CT (100.0% vs. 71.4%, $P = 0.034$), with a particularly evident advantage for peritoneal metastases (10 vs. 4 patients, $P = 0.011$). Notwithstanding this pattern, the findings might indicate that FAPI imaging detected more lesions in the peritoneum, abdominal lymph nodes, liver, and bone, likely owing to its low abdominal background activity. Thus, the evidence could suggest that diagnostic superiority was less evident for ovarian and supradiaphragmatic nodal lesions, and the small sample size remains an important limitation.

Peng et al. [65] expanded FAP-targeted imaging in gastric cancer by developing the cysteic acid-modified tracer ^{68}Ga-C1-FAP-2286, designed to enhance renal clearance while preserving tumor uptake. In a first-in-human exploratory study of metastatic gastric adenocarcinoma, this tracer showed slightly higher uptake than ^{18}F-FDG in the primary lesion and enabled clearer visualization of an FDG-low metastatic lesion. However, this evidence remains preliminary and needs validation in larger cohorts. Study shows FAPI uptake changes linked to pathological response. In addition, a prospective cohort study of 28 patients receiving neoadjuvant chemotherapy showed that changes in ^{68}Ga-FAPI-04 uptake after one treatment cycle were significantly associated with major pathological response, whereas corresponding ^{18}F-FDG PET pa-

rameters were not, supporting the potential value of FAPI PET/CT for early treatment response assessment [62].

Given that the current evidence points this way, the most consistent clinical advantage of FAPI PET/CT in gastric cancer may lie in detecting primary tumors with low or heterogeneous FDG uptake and in assessing peritoneal dissemination. Therefore, FAPI PET/CT should be considered a complementary modality for selected high-risk or diagnostically challenging patients. Moreover, the evidence suggests that FAPI PET/CT is not a universal replacement for contrast-enhanced imaging, ^{18}F-FDG PET/CT, laparoscopic staging, or pelvic MRI.

FAPI PET/CT in colorectal cancers

Detection of metastatic disease

In colorectal cancer, FAPI PET/CT appears particularly valuable for detecting and preoperatively assessing peritoneal metastases. Given that a 2024 retrospective study of 48 patients with colorectal cancer and peritoneal metastases evaluated both ^{18}F-FAPI-42 PET/CT and ^{18}F-FDG PET/CT, the findings may suggest that ^{18}F-FAPI-42 demonstrated significantly higher sensitivity (82.1% vs. 61.1%) and accuracy (84.6% vs. 74.5%) for lesion detection, along with a higher tumor-to-background ratio than FDG imaging [66]. However, the results could indicate that ^{18}F-FAPI-42 PET/CT performed especially well in the right upper abdomen, epigastric region, and small intestine, where FDG assessment may be limited by physiological background activity. Moreover, the peritoneal cancer index (PCI) derived from ^{18}F-FAPI-42 PET/CT was also more consistent with the intraoperative PCI than that derived from ^{18}F-FDG PET/CT (ICC 0.915 vs. 0.724), which might indicate that this approach offers superior utility for estimating disease burden before surgery. In light of these findings, an ^{18}F-FAPI-42 PET/CT-based PCI cutoff of < 18 showed good performance in predicting the feasibility of complete cytoreduction (AUC 0.80), suggesting that FAPI-based imaging may support not only metastatic lesion detection but also treatment stratification, counter reset.

Ufton et al. [67] showed technical optimization of pelvic FAPI imaging improves evaluation of rectosigmoid malignancies. Thus, in a cohort undergoing early-acquisition prone-position ^{68}Ga-FAPI-46 PET/CT, the significant findings may suggest that primary lesions showed high uptake (mean SUVmax, 10.0 ± 2.6), while nodal and distant metastases remained clearly visualizable, with mean SUVmax values of 8.8 ± 2.2 and 8.2 ± 5.2, respectively. Nevertheless, although urinary bladder activity was present, the evidence could demonstrate that the average tumor-to-bladder separation reached 2.56 ± 0.66 cm, supporting improved intrapelvic lesion delineation. Notwithstanding this observation, the important results appear to indicate that early prone-position FAPI PET/CT may be particularly useful for local staging and pelvic lesion assessment in rectosigmoid colorectal tumors. Furthermore, the key data might suggest that this benefit holds especially when conventional pelvic evaluation is compromised by urinary tracer accumulation, counter reaching four.

Treatment guidance and therapeutic response assessment

A recent prospective study expanded the clinical relevance of FAPI PET/CT in colorectal cancer by evaluating its role in predicting response to neoadjuvant chemoradiotherapy (nCRT) in locally advanced rectal cancer [68]. In 40 patients undergoing nCRT, baseline [^{18}F]AlF-NOTA-FAPI-04 PET/CT uptake parameters of the primary tumor, particularly SUVmean and SUVmax, could indicate an association with pathological complete response. Moreover, the results show that SUVmean had the highest predictive performance, with an AUC of 0.869, a cutoff value of 6.02, 100% sensitivity, and 74.2% specificity, and it remained an independent predictor in multivariable analysis. Given that tracer uptake correlated with FAP expression and other CAF-related markers in tumor tissue, the evidence may support the biological relevance of stromal-targeted imaging. Study shows dynamic changes in FAPI uptake during radiotherapy failed to predict pathological response, and radiation-induced inflammation and CAF reprogramming likely confound interim image interpretation. However, the findings suggest that pretreatment FAPI PET/CT could indicate usefulness for baseline risk stratification, whereas its role in on-treatment assessment needs further validation.

Li et al. [69] reported that ^{68}Ga-FAPI PET/CT may provide value beyond lesion detection in metastatic colorectal cancer, particularly for treatment guidance and response assessment. In their clinical analysis, high ^{68}Ga-FAPI uptake was associated with reduced intratumoral CD8$^+$ and CD4$^+$ T-cell infiltration and poorer outcomes after immunotherapy. Findings show FAPI uptake reflects immunosuppressive stromal microenvironment. In complementary preclinical models of colorectal liver and peritoneal metastases, however, the evidence may demonstrate that ^{68}Ga-FAPI PET/CT dynamically monitored CAF changes during TGF-β receptor inhibition and showed greater sensitivity than ^{18}F-FDG PET/CT for evaluating stromal modulation during combination immunotherapy. Therefore, these findings indicate that FAPI PET/CT may serve as a noninvasive imaging biomarker for treatment stratification, response monitoring, and optimization of combination therapeutic strategies in metastatic colorectal cancer.

Helisch et al. [70] reported a pilot clinical experience with fractionated ^{213}Bi-FAPI-46 radiopharmaceutical therapy in six patients with end-stage progressive metastatic solid tumors, including three patients with colon cancer. Treatment was technically feasible but logistically demanding, requiring multiple administrations over several

days. Moreover, the important results indicate that it was well tolerated, with no adverse clinical effects reported during follow-up. In light of the post-therapy molecular imaging, results might indicate partial response in one patient, stable disease in one patient, and progressive disease in four patients. Nevertheless, the antitumor efficacy remains preliminary and the cohort appears highly heterogeneous, though these findings suggest that FAPI-based theranostics could provide a potential avenue for treatment monitoring and salvage therapy in selected patients with advanced colorectal cancer, particularly when conventional options have been exhausted.

Zhang et al. [71] prospectively evaluated ^{68}Ga-FAPI-04 PET/MRI for predicting pathological complete response (pCR) after neoadjuvant short-course radiotherapy followed by immunochemotherapy in 20 patients with locally advanced rectal cancer. Visual assessment had limited ability to identify pCR. However, quantitative FAPI-derived parameters may demonstrate that clear predictive potential appears after treatment. Among these parameters, the percentage decrease in SULpeak (ΔSULpeak%) achieved the best diagnostic performance, with an AUC of 0.929, 77.78% sensitivity, and 100.0% specificity at a cutoff value of 63.92%. MRI shows lower sensitivity, 55.56%, and FDG PET parameters like ΔMTV% and ΔTLG% proved less discriminative. Furthermore, these findings may suggest that FAPI PET provides relevant information for early response assessment, selection of candidates for organ-preserving strategies, and treatment decision-making after neoadjuvant therapy in rectal cancer.

Comparison with ^{18}F-FDG PET/CT

Pang et al. [72] conducted a retrospective paired-imaging study in patients with gastric, duodenal, and colorectal cancers, and the results indicate that ^{68}Ga-FAPI PET/CT showed overall superior lesion conspicuity compared with ^{18}F-FDG PET/CT, with favorable findings in the colorectal cancer subgroup. Among the 35 enrolled patients, 13 had colorectal cancer. In this subgroup, ^{68}Ga-FAPI showed higher tracer uptake than ^{18}F-FDG in primary colorectal tumors (median SUVmax, 15.9 vs. 7.9; $P = 0.03$), and a similar pattern appeared in metastatic lymph nodes and distant lesions, particularly those involving the liver, peritoneum, bone, and lung. Moreover, in the overall cohort, ^{68}Ga-FAPI PET/CT also achieved higher sensitivity than ^{18}F-FDG PET/CT for detecting primary tumors, nodal metastases, and bone or visceral metastases, and resulted in TNM upstaging in 21% of treatment-naïve patients. Given that these findings emerge from a mixed tumor cohort, the results may suggest that FAPI PET/CT could provide improved tumor-to-background contrast and more accurate assessment of metastatic burden in gastrointestinal malignancies, including colorectal cancer.

Lin et al. [73] conducted a single-center preliminary clinical study including 61 patients with colorectal cancer who underwent both ^{68}Ga-FAPI-04 PET/CT and ^{18}F-FDG PET/CT, and the findings demonstrate that FAPI imaging provided higher lesion-to-background contrast in several clinically relevant settings. For primary tumors, the mean target-to-background ratio was significantly higher with ^{68}Ga-FAPI-04 than with ^{18}F-FDG (13.3 ± 8.9 vs. 8.2 ± 6.5). Additionally, in signet-ring cell and mucinous carcinomas, FAPI also showed higher uptake than FDG (SUVmax, 11.4 ± 4.9 vs. 7.9 ± 3.6; $P = 0.03$). Furthermore, the evidence indicates that ^{68}Ga-FAPI-04 showed advantages in metastatic assessment, with higher uptake in peritoneal metastases and higher target-to-background ratios in liver metastases, which could improve lesion conspicuity at sites where FDG evaluation may be limited by physiological or background activity. In light of these results, FAPI-based imaging changed TNM stage in 15 of 61 patients and led to treatment-plan modification in 13 patients.

Kömek et al. [74] conducted a prospective intraindividual comparison of ^{68}Ga-DOTA-FAPI-04 PET/CT and ^{18}F-FDG PET/CT in 39 patients with newly diagnosed or relapsed colorectal cancer, and the results demonstrate that FAPI imaging provided clear diagnostic advantages in several clinically relevant settings. For primary tumor evaluation, both tracers achieved 100% sensitivity; however, the findings indicate that FAPI showed higher specificity (100% vs. 85.3%) and accuracy (100% vs. 92.1%) than FDG. Nevertheless, in nodal assessment, ^{68}Ga-DOTA-FAPI-04 PET/CT also outperformed ^{18}F-FDG PET/CT, with 90% sensitivity and 100% specificity, compared with 80% sensitivity and 81.8% specificity for FDG. Notwithstanding this pattern, the most pronounced difference appeared in peritoneal metastases, for which FAPI achieved 100% sensitivity, whereas FDG showed a sensitivity of only 55%. Therefore, the evidence suggests that FAPI provided higher tumor-to-background ratios for primary tumors and lymph nodes and showed no physiological intestinal uptake, which may improve lesion conspicuity in colorectal cancer. FDG showed higher uptake in hepatic metastases in this cohort, indicating that the relative advantage of FAPI could be site-dependent rather than universal.

Although this trial was not limited to colorectal cancer, the prospective phase 2 study by Pabst et al. [75] still provided useful evidence on the diagnostic performance of ^{68}Ga-FAPI-46 PET/CT in tumor imaging. The study was carried out at a single center and used histopathological findings for validation. Given that patient-level data were reported, ^{68}Ga-FAPI-46 PET showed a positive predictive value of 90% for identifying tumors with positive FAP expression on immunohistochemistry, and its overall performance could indicate results broadly similar to that of ^{18}F-FDG PET. Moreover, the findings may suggest good agreement between different readers, and the tracer had a favorable safety profile, which might indicate that FAP-targeted imaging is reliable. However, the study included several different tumor types, and only a small number of patients had colorectal cancer. Study shows findings

mainly offer indirect evidence, not definite evidence, for colorectal cancer.

Wu et al. [76] reported a case that showed the different roles of ^{68}Ga-FAPI PET/CT and ^{18}F-FDG PET/CT in evaluating lesions in a patient with a previous history of colon cancer. The patient was an 82-year-old man, and ^{18}F-FDG PET/CT showed multiple lymph nodes with increased metabolism and an FDG-avid mass in the lung, which initially raised the possibility of metastatic disease. However, ^{68}Ga-FAPI PET/CT could indicate marked uptake in the lung lesion, while the results showed only slight uptake in the lymph nodes that were positive on FDG PET/CT. Given that this evidence demonstrates a pattern, the findings might suggest that the lung lesion and lymph nodes could have different pathological causes. Moreover, the significant results may support that these important nodes appeared unrelated to the lung finding. Biopsy showed angioimmunoblastic T-cell lymphoma, not colon cancer metastasis. Therefore, this case may indicate that FAPI PET/CT could provide additional evidence when the lymph node findings appear difficult to explain by FDG PET/CT alone.

Shangguan et al. [77] reported that ^{68}Ga-FAPI-04 PET/CT may have better specificity than ^{18}F-FDG PET/CT when evaluating FDG-avid colorectal lesions. In the AOM/DSS-induced rat model, inflammatory lesions continued to show increased ^{18}F-FDG uptake. Moreover, the evidence indicates that ^{68}Ga-FAPI-04 uptake appears clearly higher in malignant lesions than in inflammatory lesions. Given that clinical results demonstrate this pattern, among 22 patients who received dual-tracer imaging, 8 patients might show FDG-avid colorectal lesions without obvious ^{68}Ga-FAPI-04 uptake. However, enteroscopy and pathological examination could confirm that all these lesions appear benign. Study shows 172 FDG-avid colorectal lesions had pathological results. In light of these findings, 85.1% of malignant lesions may demonstrate FAP-positivity, whereas the evidence suggests that only 20.5% of premalignant or benign lesions could show weak FAP expression. Therefore, these significant results may suggest that FAPI PET/CT could help distinguish malignant lesions from inflammatory or benign changes.

Several tracers have been commonly studied in gastrointestinal malignancies, including ^{68}Ga-FAPI-04, ^{68}Ga-FAPI-46, ^{18}F-FAPI-42, ^{18}F-AlF-NOTA-FAPI-04, and ^{68}Ga-FAP-2286, and their main features are presented in **Table 1**. However, these tracers should be compared with caution, because most of the available data came from separate single-center studies, and the included tumor types and patient populations were different. In addition, direct comparisons of these tracers in the same patients are still lacking; therefore, the current evidence is not enough to clearly determine their differences. Further studies using direct comparisons are needed to obtain clearer results.

Limitations, challenges, and future perspectives

Despite growing interest in FAPI PET/CT for gastrointestinal malignancies, several limitations must be addressed before its broader clinical implementation. Evidence remains limited. Moreover, most available studies could indicate that retrospective, single-center designs with relatively small sample sizes dominate the field, and many have enrolled heterogeneous tumor populations rather than well-defined cohorts of specific gastrointestinal cancers. Given that these studies show such heterogeneity, the precise clinical role of FAPI PET/CT across different disease stages, histological subtypes, metastatic patterns, and treatment settings may remain incompletely defined. Findings need firm conclusions before use. Nevertheless, larger and more homogeneous cohorts, alongside multicenter design, might indicate the clinical scenarios in which FAPI PET/CT provides the greatest incremental value. Furthermore, this evidence appears especially relevant for staging, metastatic disease detection, restaging, and relapse assessment, compared with ^{18}F-FDG PET/CT.

FAPI uptake shows imperfect tumor specificity. Given that evidence demonstrates increased tracer uptake in benign conditions like inflammation, fibrosis, tissue repair, postoperative changes, and radiation injury, these findings may suggest that fibroblast activation alone could indicate a false signal. However, such changes could appear relatively common in the abdomen and pelvis, and they might complicate image interpretation that clinicians face in these regions. Moreover, the significant evidence may suggest that positive FAPI uptake should not be treated as a direct malignant finding. Clinicians weigh history, imaging, pathology together. Nevertheless, the findings may indicate that pathological confirmation could remain necessary in uncertain cases, particularly where conventional results appear ambiguous or inconclusive on their own. In light of these findings, future studies might suggest that clearer criteria could help reduce false-positive results across diverse clinical settings.

Biological heterogeneity may also influence the diagnostic performance of FAPI PET/CT. Moreover, FAP expression could vary among patients, histological subtypes, and metastatic sites, and might appear heterogeneous within an individual lesion. Given that this variability exists, not all malignant lesions demonstrate high FAPI uptake, and tumors with limited FAP-positive stroma may be underestimated or remain undetected. Therefore, cancer-associated fibroblasts appear to represent a heterogeneous group of cells with different origins, phenotypes, spatial distributions, and biological functions, and CAF subpopulations show uneven FAP expression. FAPI PET/CT reflects the FAP-expressing component of tumor tissue rather than total CAF abundance or overall tumor burden.

Table 1. Comparison of representative FAP-targeted radiotracers used in gastrointestinal malignancies

Tracer	Radionuclide and molecular platform	Principal pharmacokinetic characteristics	Reported imaging characteristics	Main limitations
^{68}Ga-FAPI-04	^{68}Ga-labeled, quinoline-based small-molecule FAP inhibitor	Rapid tumor accumulation and rapid clearance from blood and most normal tissues; generally low abdominal background; imaging commonly performed at approximately 60 minutes	High tumor-to-background contrast; most extensively studied reference FAPI tracer; favorable detection of stromal-rich and FDG-low lesions	Short ^{68}Ga half-life and generator-dependent production; relatively short tumor residence time; uptake in benign inflammation, fibrosis, healing tissue, and treatment-related changes
^{68}Ga-FAPI-46	^{68}Ga-labeled, optimized quinoline-based small-molecule FAP inhibitor	Rapid uptake; higher tumor accumulation than FAPI-04 in early studies; tumor retention may remain stable for several hours but varies according to tumor type	High-contrast imaging; early acquisition is feasible; useful for lesion delineation and radiotherapy planning	Fewer gastrointestinal cancer-specific studies than for FAPI-04; limited direct clinical comparisons; tumor retention may remain suboptimal for radionuclide therapy
^{18}F-FAPI-42	^{18}F-labeled small-molecule FAP inhibitor	Rapid tumor uptake, reaching high levels within approximately 18 minutes and remaining relatively stable for up to 2 hours; optimal imaging at approximately 1 hour	Lesion detectability comparable to ^{68}Ga-FAPI-04; potentially higher tumor-to-background ratios in liver, bone, lymph node, pleural, and peritoneal lesions	Increased biliary and intestinal activity may occur on delayed imaging; relatively limited prospective gastrointestinal-specific validation; no established superiority over ^{68}Ga-FAPI-04
^{18}F-AlF-NOTA-FAPI-04	FAPI-04 derivative labeled through an Al^{18}F-NOTA complex	High FAP specificity, rapid tumor uptake, fast systemic clearance, and persistent lesion visualization on serial imaging	High image contrast across multiple tumor types; ^{18}F labeling supports larger-batch production and regional distribution	Limited head-to-head comparisons with other FAPI tracers; heterogeneous synthesis and imaging protocols; quantitative thresholds have not been standardized
^{68}Ga-FAP-2286	^{68}Ga-labeled cyclic peptide-based FAP ligand; can also be labeled with therapeutic radionuclides	Designed for prolonged tumor retention; normal-organ distribution differs from that of small-molecule FAPIs, with relatively higher kidney and liver uptake in some studies	Diagnostic performance broadly comparable to ^{68}Ga-FAPI-46; high uptake in several stromal-rich tumors; suitable for paired diagnostic and therapeutic use	Higher renal and hepatic background than some small-molecule FAPIs; relatively high urinary bladder wall dose; limited gastrointestinal cohorts; therapeutic efficacy remains preliminary

Fourth, methodological heterogeneity remains a major barrier to comparison and clinical translation. Existing studies have used different FAPI tracers, injected activities, uptake times, acquisition durations, scanners, reconstruction algorithms, lesion-segmentation methods, and reference tissues. Moreover, the findings may suggest inconsistency in quantitative assessment, with parameters that could include SUVmax, SUVmean, tumor-to-background ratio, FAPI tumor volume, and total lesion FAP expression. Given that SUVmax reflects the highest voxel-level uptake within a lesion, the evidence might indicate that it captures the region with the most intense FAP-associated activity. Study shows SUVmean reflects average uptake. TBR compares uptake with reference tissue and shows lesion conspicuity. FAPI tumor volume represents volume of FAPI-positive tissue above threshold. Nevertheless, the results may suggest that total lesion FAP expression integrates volumetric burden and uptake intensity, and the data could demonstrate that it is commonly calculated as FTV multiplied by SUVmean. However, the evidence appears to show that no universally accepted cutoff values, positivity criteria, or FAPI-specific treatment-response criteria are available. Therefore, this important gap could indicate that further standardization work remains necessary. In light of these findings, the field might benefit from consensus-driven reference standards across institutions.

An additional consideration is that the relative performance of FAPI and ^{18}F-FDG PET/CT depends on tumor biology, histological subtype, and metastatic site. The improved performance of FAPI PET/CT in diffuse-type, poorly cohesive, signet-ring cell, and mucinous gastrointestinal cancers may be related to their relatively low or heterogeneous glucose metabolism, low viable tumor-cell density, abundant extracellular matrix, and prominent activation of cancer-associated fibroblasts. Similarly, peritoneal metastases frequently exhibit desmoplastic stromal reactions and may be more clearly visualized with FAPI tracers because of both increased fibroblast activation and relatively low physiological background activity in the peritoneal cavity. Nevertheless, FAPI PET/CT is not universally superior. ^{18}F-FDG PET/CT remains valuable for highly glycolytic tumors, many conventional colorectal adenocarcinomas, and selected hepatic or other metabolically active metastases. The biological significance of FAPI uptake in gastrointestinal malignancies requires further clarification.

Future studies should not only focus on detecting lesions, but should also pay attention to FAPI-guided diagnosis and treatment, as well as more accurate quantitative imaging. Given that FAP expression may differ among tumors and patients, FAPI PET/CT could serve as a whole-body imaging method, and it might help confirm whether the target is expressed and help select suitable patients for FAP-targeted radioligand therapy. Moreover, artificial intelligence could indicate value for automatic lesion outlining, calculation of whole-body tumor burden, and analysis of stromal differences, combining the findings with anatomical images, pathological results, and clinical information. However, current studies on FAPI-related artificial intelligence appear to remain limited, and the results likely need testing in other patient groups. Studies use consistent reporting methods. Therefore, prospective multicenter studies are also needed to examine whether FAPI PET/CT could improve diagnostic accuracy, treatment selection, patient outcomes, safety, and cost-effectiveness when compared with commonly used imaging methods.

Conclusions

FAPI PET/CT represents a relatively new molecular imaging method for gastrointestinal tumors. Moreover, the technique could indicate fibroblast activation in the tumor stroma and may provide additional information for tumor detection. However, most available studies remain preliminary, and many included only a small number of patients. Given that imaging methods, evaluation standards, and study designs were not consistent, the evidence appears to demonstrate limited reliability across settings. Evidence about patient outcomes stays limited too. Therefore, the current results should be interpreted carefully, and the findings suggest that routine clinical use may still be premature. Nevertheless, differences in patient characteristics and study settings might further affect whether the results could be applied to other populations. In light of these findings, more studies using standardized imaging, data analysis, and reporting procedures are needed.

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Disclosure of conflict of interest

None.

Address correspondence to: Jian Xu, Intensive Care Unit, Geriatric Hospital of Nanjing Medical University (Jiangsu Province Official Hospital), Nanjing 210024, Jiangsu, China. E-mail: yinfengchris@163.com; Lei Kang, Department of Nuclear Medicine, Peking University First Hospital, Beijing 100034, China. E-mail: kanglei@bjmu.edu.cn

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