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Review Article

The comparative utility of FAPI-based PET radiotracers over [^{18}F]FDG in the assessment of malignancies

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Abstract: Fibroblast activation protein (FAP) is a type II transmembrane serine protease overexpressed in cancer-associated fibroblasts (CAFs) and has been associated with poor prognosis. PET/CT imaging with radiolabeled FAP inhibitors (FAPI) is currently being studied for various malignancies. This review identifies the uses and limitations of FAPI PET/CT in malignancies and compares the advantages and disadvantages of FAPI and ^{18}F-fluorodeoxyglucose ([^{18}F]FDG). Due to high uptake, rapid clearance from the circulation, and limited uptake in normal tissue, FAPI tumor-to-background contrast ratios are equivalent to or better than [^{18}F]FDG in most applications. In several settings, FAPI has shown greater uptake specificity than [^{18}F]FDG and improved sensitivity in detecting lymph node, bone, and visceral tissue metastases. Therefore, FAPI PET/CT may be complementary in distinguishing pathological lesions with conventional imaging, determining the primary site of malignancy, improving tumor staging, and detecting disease recurrence, especially in patients with inconclusive [^{18}F]FDG PET/CT findings. Nevertheless, FAPI has limitations, including certain settings with non-specific uptake, modified uptake with age and menopause status, challenges with clinical access, and limited clinical evidence.

Keywords: Fibroblast activation protein (FAP), fibroblast activation protein inhibitor (FAPI), positron emission tomography (PET), [^{18}F]-fluorodeoxyglucose ([^{18}F]FDG), cancer, malignancy, diagnosis

Introduction

Molecular imaging allows for visualizing and characterizing biological processes at the tissue level [1]. Positron emission tomography (PET), a molecular imaging modality, utilizes radionuclide-labeled biomarkers, also known as radiotracers, to evaluate tissue function. PET can identify functional changes earlier than structural imaging modalities and capture the functional state of tissues [2]. The most commonly used PET radiotracer is ^{18}F-fluorodeoxyglucose ([^{18}F]FDG), a glucose analog. [^{18}F]FDG uptake directly correlates with cellular metabolic rate and GLUT transporter expression [3], making [^{18}F]FDG PET/CT valuable for imaging malignant, infectious, and inflammatory processes due to increased [^{18}F]FDG uptake in cells with elevated glycolytic activity, such as cancer cells or activated granulocytes [4, 5]. However, [^{18}F]FDG lacks optimal specificity for malignancies, resulting in low tumor-to-background ratios (TBRs) and low sensitivity for certain cancers [6]. To address these limitations, researchers have focused on developing new radiotracers, including radiolabeled fibroblast activation protein inhibitors (FAPIs) [6, 7].

Fibroblast activation protein (FAP) is a 760-amino-acid, type II transmembrane glycoprotein that belongs to the serine protease family. It is expressed in stromal fibroblasts in more than 90% of epithelial malignancies and malignant cells in glioblastoma, breast, colorectal, cervical, pancreatic, and oral squamous cell carcinomas [8-10]. Overexpression of FAP is linked to increased local tumor invasiveness, lower survival, and poor prognosis [9-11]. Activated fibroblasts and FAPs are only expressed in reactive tumor stroma or fibrosis. The normal stroma contains only a small number of quiescent fibroblasts with low or undetectable FAP expression [12]. This selective expression makes FAP an excellent biomarker for identifying and targeting tumors. One of the promising applications of targeting FAP is through the use of FAP inhibitors (FAPI). These inhibitors can be radiolabeled and used in PET imaging for targeted imaging of various cancers (**Figure 1**) [13-15].

While most radiotracers are utilized only diagnostically due to notable physiological uptake, the highly selective expression of FAP allows for paired theragnostic approaches. Much of the current work in FAPI research is performed with quinoline-based, small-molecule FAPI deriva-

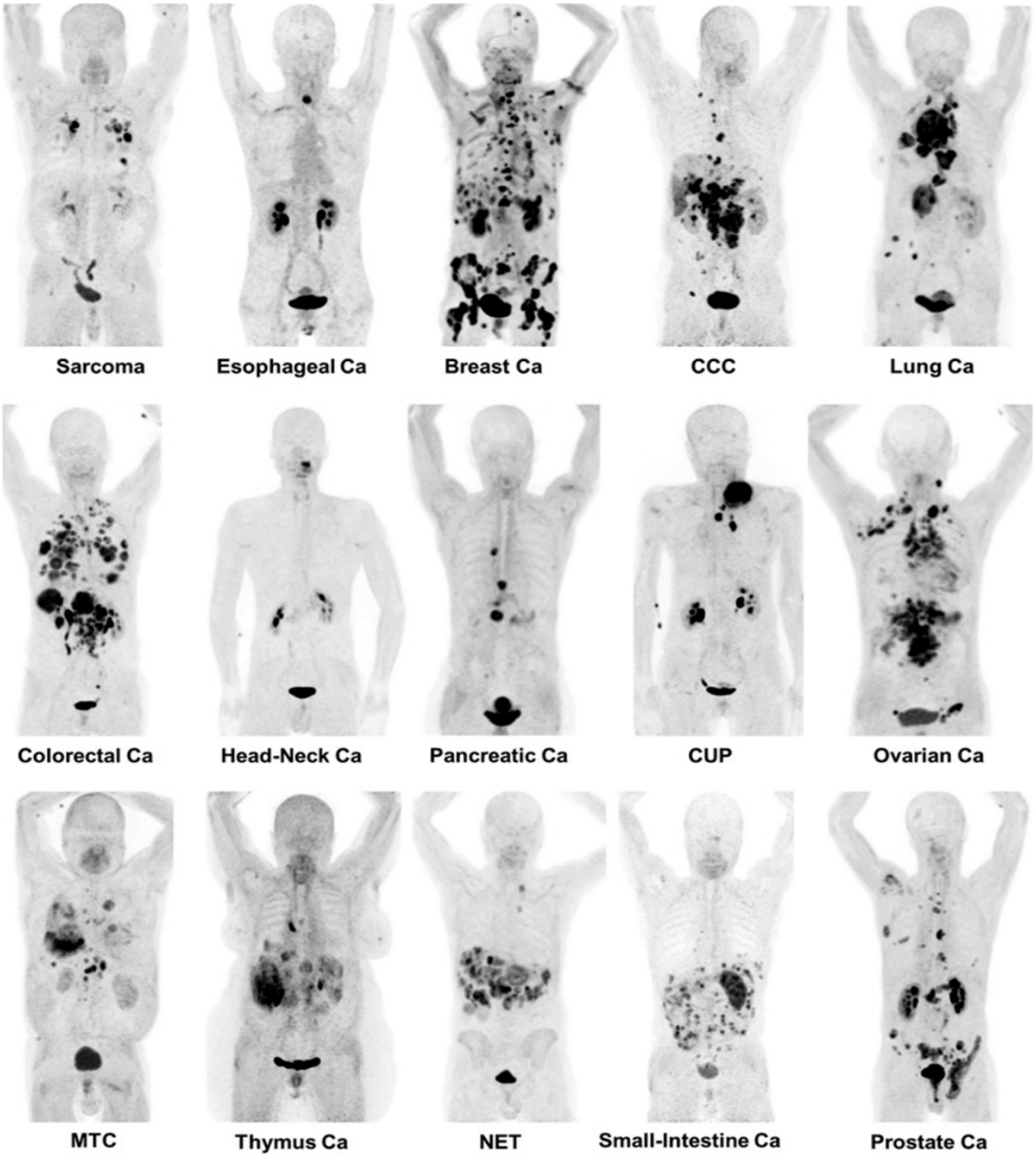

Figure 1. Maximum-intensity projection images of [^{68}Ga]Ga-FAPI PET/CT scans demonstrating 15 distinct histologically proven tumor types, with the tumors sorted based on their uptake levels in descending order. Abbreviations used to represent specific tumor entities: Ca (cancer), CCC (cholangiocellular carcinoma), CUP (carcinoma of unknown primary), MTC (medullary thyroid cancer), and NET (neuroendocrine tumor). Adapted from Journal of Nuclear Medicine [15]. © by the Society of Nuclear Medicine and Molecular Imaging, Inc.

tives with a high affinity for FAP and a superior pharmacokinetics [10]. To utilize their unique imaging properties, FAPI has been labeled with ^{68}Gallium (^{68}Ga) and ^{18}FIuorine (^{18}F). The chemical structures of some FAPI compounds are shown in **Figure 2** [16].

The first FAPI tracers introduced in clinical research were labeled with ^{68}Ga, which has a relatively short half-life of 68 minutes; this limited the accessibility of [^{68}Ga]Ga-FAPI in centers without onsite production [10]. ^{18}F has a longer half-life of 109.8 minutes and is easier to produce, which

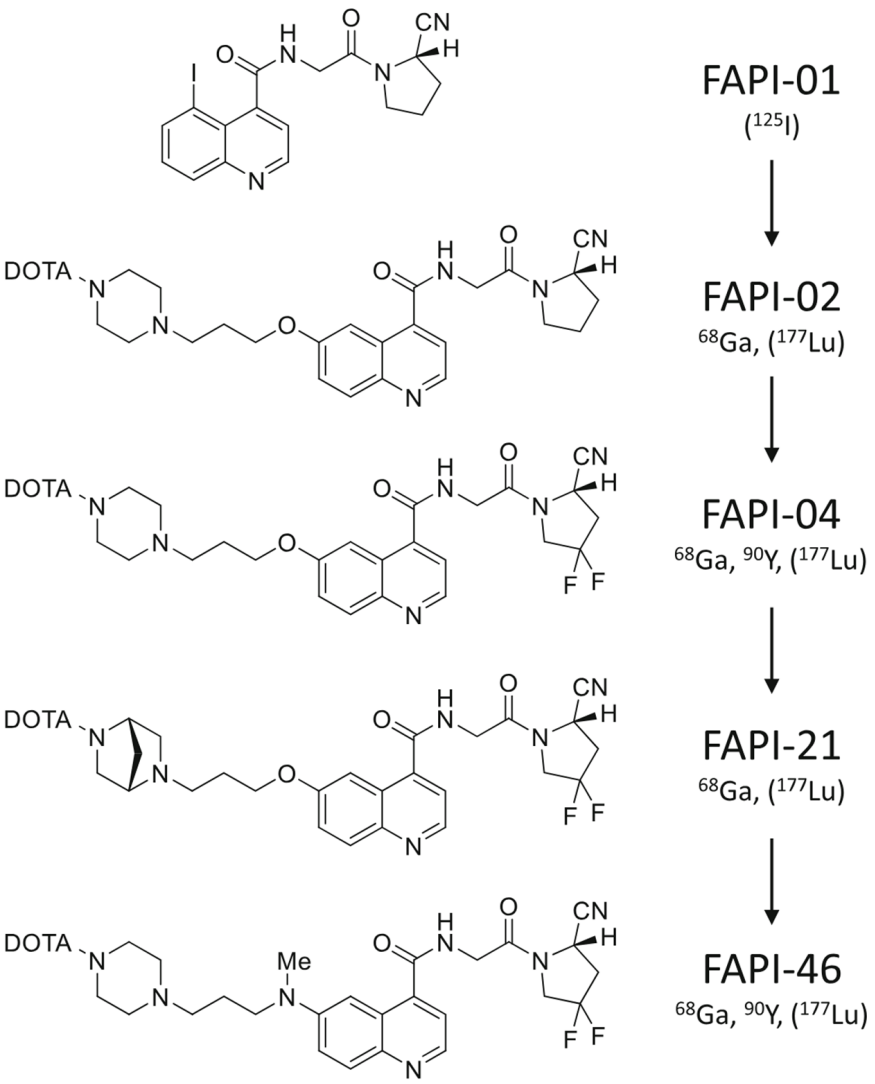

Figure 2. The chemical structures of a few FAPI compounds have been studied in preclinical and/or clinical studies. Adapted without any changes from EJNMMI Radiopharmacy and Chemistry [16] under the Creative Commons Attribution 4.0 International License (CC BY). https://creativecommons.org/licenses/by/4.0/.

allows for longer distance transit of higher quantities [10]. Another benefit of [^{18}F]FAPI may be a higher resolution on PET imaging due to the lower positron energy of ^{18}F compared to ^{68}Ga [10]. As such, ^{18}F-labeled FAPI appears to be more favorable for clinical applications.

Initial studies have claimed that FAPI radiotracers may replace [^{18}F]FDG for oncological and non-oncological conditions [17, 18], but controversies remain [19]. Research comparing the clinical applicability and efficacy of various FAPI-based PET radiotracers to that of [^{18}F]FDG is still limited. This literature review aims to identify the potential advantages and known limitations of FAPI PET/CT in malignant disorders and the comparative performance of FAPI-based radiotracers vs. [^{18}F]FDG PET/CT. While FAPI, as a theragnostic agent, also has therapeutic value, we will mainly focus on its diagnostic performance in this review.

Comparing FAPI PET/CT and [^{18}F]FDG PET/CT

The studies included in this review comparing FAPI PET/CT and [^{18}F]FDG PET/CT in malignancies were evaluated based on their performance in four main categories: tracer uptake, tumor-to-background ratio (TBR), detection of primary tumors, and detection of metastases. The results are summarized in **Table 1**.

Higher tumor uptake of FAPI tracers than [^{18}F]FDG

A majority (24/34) of the studies we reviewed reported a higher tumor uptake of FAPI tracers than [^{18}F]FDG.

Although there were variations in uptake among different cancer types, FAPI uptake was equal to or comparable to [^{18}F]FDG in a majority of the cancers. Some examples of cancers that demonstrated higher uptake of FAPI than [^{18}F]FDG include breast cancer, gastric adenocarcinoma, gastrointestinal signet cell carcinoma, and other gastrointestinal malignancies. FAPI also showed significantly higher uptake than [^{18}F]FDG in brain metastases. However, the uptake of FAPI was comparable to [^{18}F]FDG in squamous cell carcinoma, prostate cancer, hepatocellular carcinoma, and hepatic metastases due to breast cancer. Notably, the uptake of FAPI was lower than [^{18}F]FDG in nasopharyngeal carcinoma and hematological malignancies such as lymphoma and multiple myeloma. FAPI PET/CT could also be beneficial in differentiating autoimmune pancreatitis and pancreatic cancer, with FAPI exhibiting uniformly higher uptake throughout the pancreas in autoimmune pancreatitis, unlike [^{18}F]FDG PET/CT.

Kuyumcu et al. did an intraindividual comparison of [^{18}F]FDG and [^{68}Ga]Ga-FAPI-04 uptake among seven patients with various histopathologically proven tumors. They demonstrated the uptake of [^{68}Ga]Ga-FAPI-04 was superior to or equal to [^{18}F]FDG in the metastatic lesions (**Figure 3**) [53].

While comparing [^{68}Ga]Ga-FAPI PET/CT and [^{18}F]FDG PET/CT in 48 patients with breast cancer, [^{68}Ga]Ga-FAPI PET/CT detected additional lesions due to higher tracer uptake, resulting in upstaging in half of the patients in the

Table 1. The main results of studies reviewed to compare [^{18}F]FDG and FAPI radiotracers in various cancers

S.N.	Type of cancer	Authors/Year published	Type of study (number of patients)	Type of FAPI tracer studied	Uptake of FAPI tracer vs. [^{18}F]FDG	TBR of radiolabeled FAPI tracer compared to [^{18}F]FDG	Superiority of FAPI tracer vs. [^{18}F]FDG in the detection of primary tumors	Superiority of FAPI tracer vs. [^{18}F]FDG in the detection of metastatic tumors
1	Breast cancer	Komek et al. (2021) [20]	Prospective study (20)	[^{68}Ga]Ga-FAPI-04	Significantly higher	Significantly higher	Superior	Superior
2	Breast cancer	Elboga et al. (2021) [21]	Retrospective study (48)	[^{68}Ga]Ga-FAPI-04	Significantly higher	Significantly higher	Superior	Superior
3	Gastric carcinoma	Qin et al. (2022) [22]	Prospective study (20)	[^{68}Ga]Ga-FAPI-04	Significantly higher	Significantly higher	Superior	Superior
4	Gastric cancer	Jiang et al. (2022) [23]	Retrospective study (38)	[^{68}Ga]Ga-FAPI-04	Significantly higher	N/A	Superior	Superior
5	Gastric adenocarcinoma	Kuten et al. (2022) [24]	Prospective study (13)	[^{68}Ga]Ga-FAPI-04	Not significantly different	Significantly higher	Superior	Superior
6	Primary gastric lymphoma	Wang et al. (2021) [25]	Case study (1)	[^{68}Ga]Ga-NOTA-FAPI-04	Significantly higher	N/A	Superior	Not reported
7	Esophageal carcinoma	Rao et al. (2021) [26]	Case study (1)	[^{68}Ga]Ga-FAPI-04	Significantly higher	N/A	Not reported	Not reported
8	Signet ring cell carcinoma of sigmoid colon	Fu et al. (2021) [27]	Case study (1)	[^{68}Ga]Ga-FAPI-04	Significantly higher	Significantly higher	Superior	Superior
9	Appendiceal mucinous adenocarcinoma	Qiu & Chen et al. (2021) [28]	Case study (1)	[^{68}Ga]Ga-FAPI	Significantly higher	N/A	Superior	Superior
10	Hepatocellular carcinoma	Wang et al. (2021) [29]	Retrospective study (25)	[^{68}Ga]Ga-FAPI-04	Similar	Significantly higher	Superior	Not reported
11	Cholangiocarcinoma	Siripongsatian et al. (2021) [30]	Case study (1)	[^{68}Ga]Ga-FAPI-46	Significantly higher	Significantly higher	Superior	Superior
12	Gastrointestinal system cancer	Sahin et al. (2021) [31]	Prospective study (31)	[^{68}Ga]Ga-FAPI-04	Not significantly higher	N/A	Not reported	Superior
13	Head and neck cancer	Gu et al. (2022) [32]	Prospective study (18)	[^{68}Ga]Ga-FAPI-04	Significantly higher	Significantly higher	Superior	Similar
14	Head and neck cancer	Syed et al. (2020) [33]	Prospective cohort study (14)	[^{68}Ga]Ga-FAPI	Significantly higher	Significantly higher	Superior	Not reported
15	Nasopharyngeal carcinoma	Qin et al. (2021) [34]	Prospective study (15)	[^{68}Ga]Ga-FAPI-04	Lower	N/A	Same	Superior
16	Alveolar soft part sarcoma	Zhou et al. (2021) [35]	Case study (1)	[^{68}Ga]Ga-FAPI-04	Significantly higher	Significantly higher	Superior	Superior
17	Solitary fibrous tumor	Wang et al. (2021) [36]	Case study (1)	[^{68}Ga]Ga-FAPI	Significantly higher	N/A	Superior	Superior
18	Neuroendocrine tumor	Wang et al. (2021) [37]	Case study (1)	[^{68}Ga]Ga-FAPI-04	Significantly higher	Significantly higher	Superior	Superior
19	Squamous cell carcinoma	Linz et al. (2021) [38]	Pilot study (10)	[^{68}Ga]Ga-FAPI-04	Statistically insignificant	N/A	Same	Similar
20	Prostate Cancer	Xu et al. (2021) [39]	Case study (1)	[^{68}Ga]Ga-FAPI-04	Similar	N/A	Similar	Similar
21	Prostate Cancer	Khreish et al. (2020) [40]	Case study (1)	[^{68}Ga]Ga-FAPI-04	Significantly higher	N/A	Similar	Similar
22	Various Cancer	Lan et al. (2022) [41]	Prospective study (123)	[^{68}Ga]Ga-FAPI-04	Significantly higher	N/A	Superior	Superior
23	Various Cancer	Giesel et al. (2021) [14]	Retrospective study (71)	[^{68}Ga]Ga-FAPI-02 [^{68}Ga]Ga-FAPI-04 [^{68}Ga]Ga-FAPI-46 [^{68}Ga]Ga-FAPI-74	N/A	N/A	Superior	Superior
24	Various Cancer	Zhao et al. (2021) [42]	Retrospective study (46)	[^{68}Ga]Ga-FAPI-04	Significantly higher	N/A	N/A	Superior
25	Various Cancer	Ballal et al. (2020) [43]	Prospective study (54)	[^{68}Ga]Ga-DOTA.SA.FAPi	Significantly higher	Significantly higher	Not significant	Superior
26	Various Cancer	Guo et al. (2021) [44]	Retrospective study (34)	[^{68}Ga]Ga-FAPI-04	Significantly higher	N/A	Superior	Superior
27	Cervical Cancer	Wegen et al. (2023) [45]	Retrospective study (7)	[^{68}Ga]Ga-FAPI-46	N/A	Significantly higher	N/A	Superior
28	Gastric, duodenal and colorectal cancer	Liu et al. (2023) [46]	Prospective study (41)	[^{68}Ga]Ga-FAPI-04	Significantly higher for nodal metastasis	N/A	Not Significant	Superior
29	Breast cancer	Zheng et al. (2023) [47]	Prospective study (34)	[^{68}Ga]Ga-FAPI	Significantly higher	Significantly higher	Superior	Superior
30	Ovarian cancer	Zheng et al. (2023) [48]	Retrospective (27)	[^{68}Ga]Ga-FAPI-04	Not significantly higher	Significantly higher	Superior	Superior
31	Gastric signet-ring-cell carcinoma	Chen et al. (2023) [49]	Retrospective (34)	[^{68}Ga]Ga-FAPI	Significantly higher	Significantly higher	Superior	Superior
32	Bladder cancer	Novruzov et al. (2022) [50]	Retrospective (8)	[^{68}Ga]Ga-DOTA-FAPI	Significantly higher	Significantly higher	Superior	Superior
33	Head and neck cancer	Wegen et al. (2022) [51]	Retrospective (15)	[^{68}Ga]Ga-DOTA-FAPI-46	Significantly higher	Significantly higher	Comparable	Comparable
34	Nasopharyngeal Carcinoma	Zheng et al. (2022) [52]	Retrospective (47)	[^{68}Ga]Ga-FAPI	N/A	N/A	Superior	Inferior
	Total	34 studies reviewed	803 patients in total		24/34 studies had higher uptake of FAPI PET tracer than [^{18}F]FDG	18/34 studies had higher TBR for FAPI tracer than [^{18}F]FDG. TBR was not reported in the remaining 16 studies.	23/34 studies had superior detection of primary tumors than [^{18}F]FDG	24/34 studies had superior detection of metastatic tumors than [^{18}F]FDG

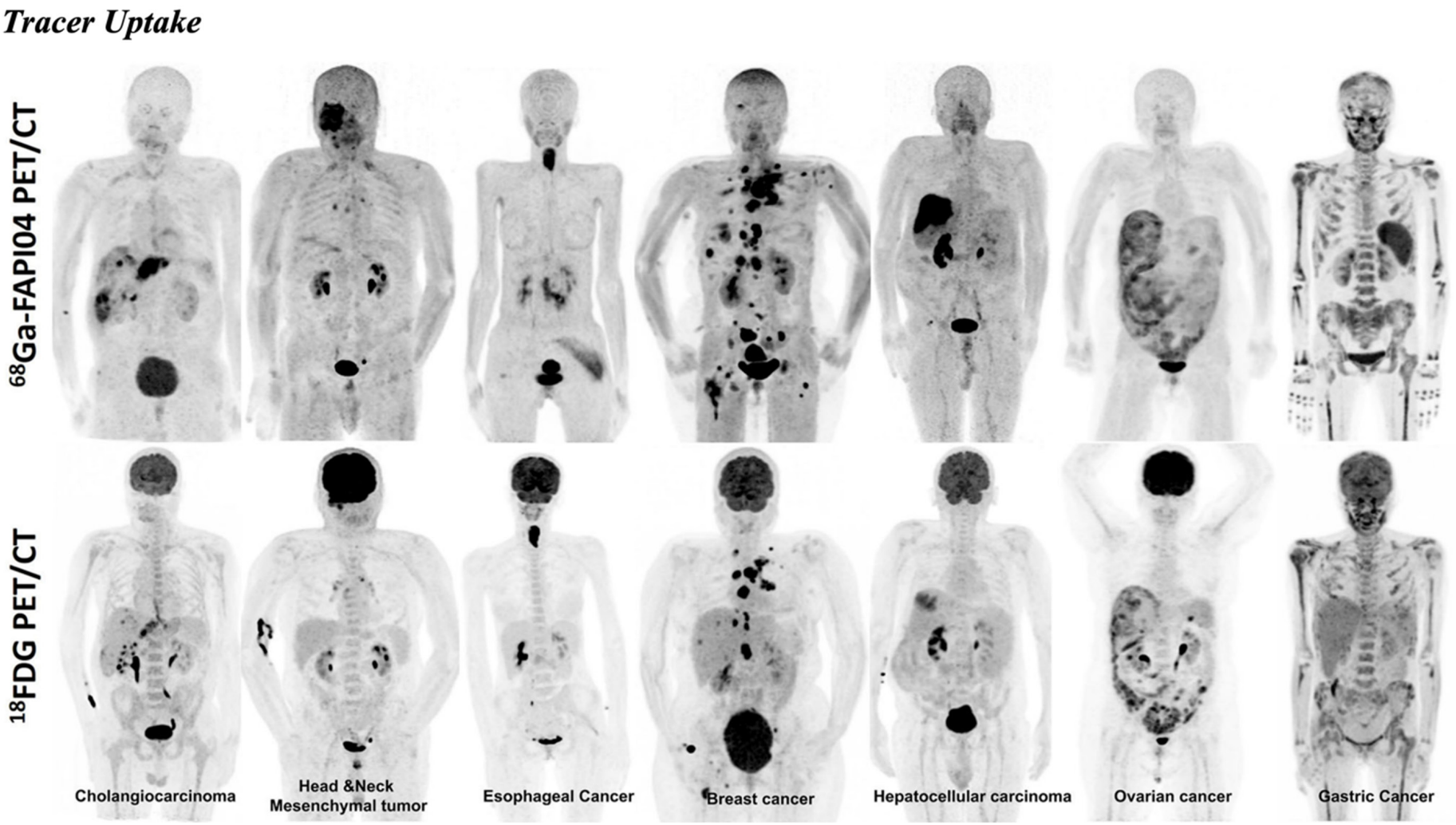

Figure 3. Intraindividual comparison of [^{18}F]FDG and [^{68}Ga]Ga-FAPI-04 PET maximum-intensity projection images of seven patients with various histopathologically proven tumors. The uptake of [^{68}Ga]Ga-FAPI-04 was superior to or equal to [^{18}F]FDG in the metastatic lesions. Adapted without any changes from Frontiers in Oncology [53] under the Creative Commons Attribution 4.0 International License (CC BY). https://creativecommons.org/licenses/by/4.0/.

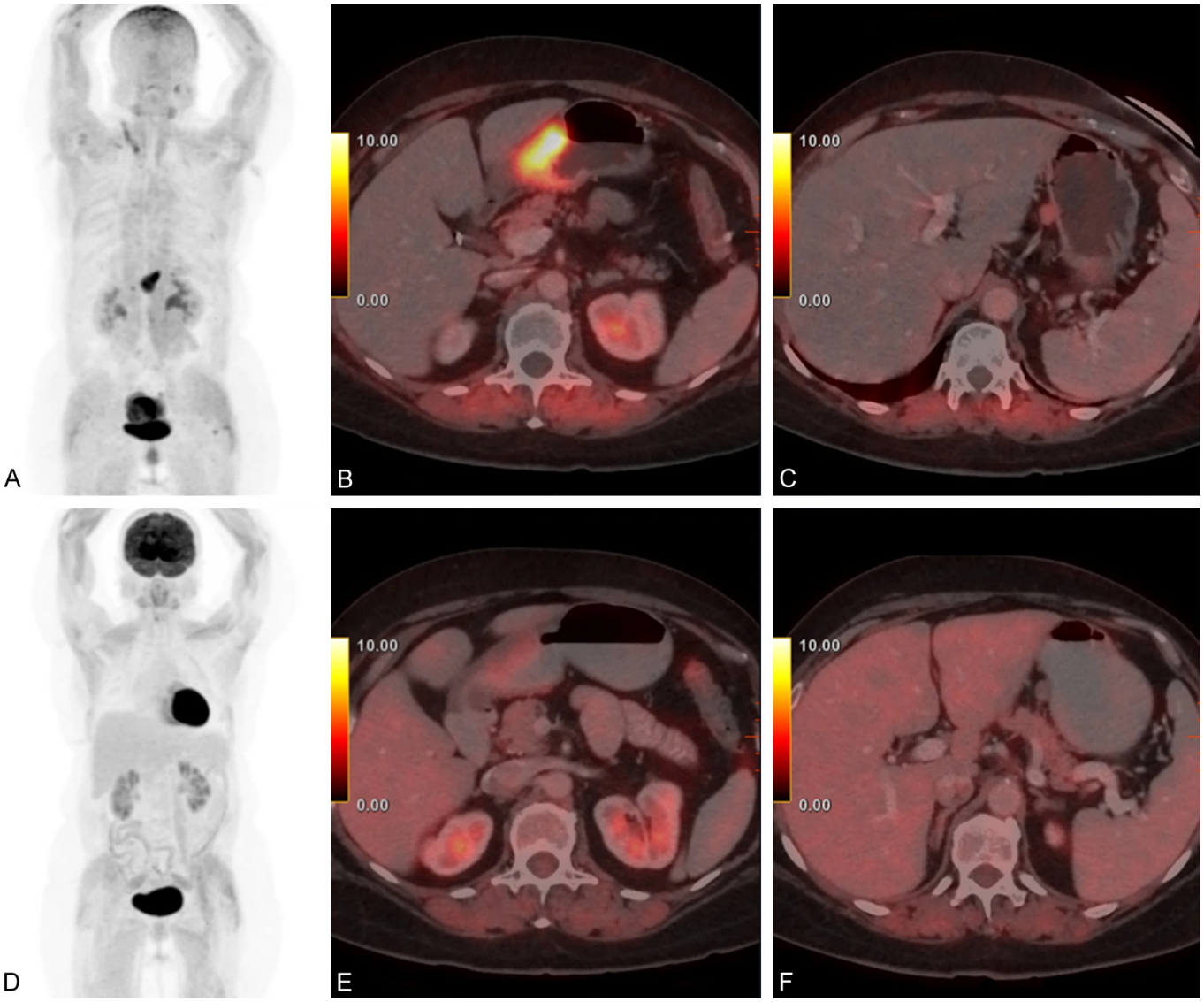

Figure 4. The staging PET/CT scans with [^{68}Ga]Ga-FAPI-04 (A-C) and [^{18}F]FDG (D-F) of a 65-year-old female patient with poorly differentiated gastric adenocarcinoma showed that the primary tumor was positive for [^{68}Ga]Ga-FAPI-04 and negative for [^{18}F]FDG (SUVmax 11.8 and 2.3, respectively). A perigastric lymph node also demonstrated an SUVmax of 0.3 with [^{68}Ga]Ga-FAPI-04 and 2.3 with [^{18}F]FDG. Adapted without any changes from the European Journal of Nuclear Medicine and Molecular Imaging [24] under the Creative Commons Attribution 4.0 International License (CC BY). https://creativecommons.org/licenses/by/4.0/.

post-chemotherapy group [21]. In a prospective study of 20 women with primary and recurrent breast cancer, [^{18}F]FDG and FAPI PET/CT scans were performed; FAPI imaging showed greater SUVmax than [^{18}F]FDG for primary breast tumors, lymph nodes, lung metastases, and bone metastases. However, the SUVmax of hepatic metastases did not differ between these imaging techniques [20]. For gastric cancer, although the difference in SUVmax of [^{68}Ga]Ga-FAPI-04 and [^{18}F]FDG was not statistically significant, the higher tumor-to-background ratio for [^{68}Ga]Ga-FAPI-04 led to a 100% detection rate of all ten primary gastric tumors (vs. 50% for [^{18}F]FDG) and peritoneal carcinomatosis (none for [^{18}F]FDG) (**Figures 4** and **5**) [23, 24].

In another multicenter retrospective study including 34 patients with gastrointestinal signet cell carcinoma (GSCC), [^{68}Ga]Ga-FAPI-04 had a clearly higher SUVmax compared to [^{18}F]FDG in primary tumors, lymph nodes and distal metastases [49]. However, in other prospective studies with 13 gastric adenocarcinomas [24] and 31 patients with gastrointestinal malignancies [31], [^{68}Ga]Ga-FAPI-04 uptake was not significantly different from [^{18}F]FDG [24, 31]. [^{68}Ga]Ga-FAPI-04 and [^{18}F]FDG also had comparable SUVmax for hepatocellular carcinoma in a retrospective study of 25 patients [29]. Nonetheless, [^{68}Ga]Ga-FAPI-04 uptake was also similar to [^{18}F]FDG in a pilot study done on 10 patients with squamous cell carcinoma [38] and a case of prostate cancer [39]. Among the studies done in patients with multiple cancers, [^{68}Ga]Ga-FAPI-04 uptake was higher for most cancers except for lymphoma and multiple myeloma, suggesting the limited usefulness of FAPI in hematological malignancies [24]. Similarly, FAPI uptake was lower than [^{18}F]FDG in a study on nasopharyngeal carcinoma [34]. It was statisti-

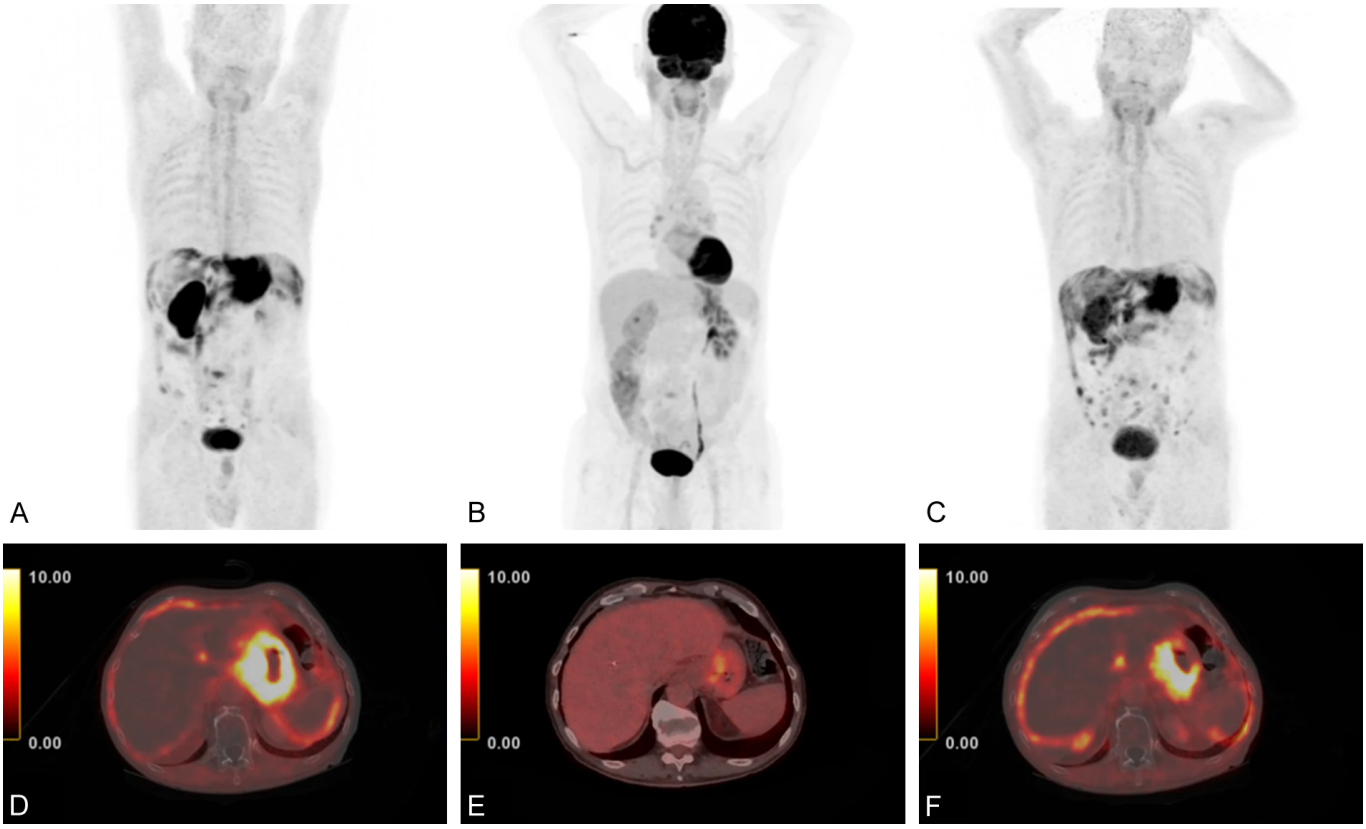

Figure 5. Staging FAPI (A, D) and FDG (B, E) PET/CT scans of a 78-year-old male with poorly differentiated gastric adenocarcinoma demonstrated an intense FAPI uptake in the primary tumor and peritoneal carcinomatosis compared to FDG (SUVmax 23 and 6.8 for the primary tumor; tumor-to-background ratio 11.5 and 3.8; SUVmax 7.5 and 2.3 for peritoneal carcinomatosis, respectively). Follow-up FAPI PET/CT (C, F) conducted after four months of chemotherapy indicated disease progression. Adapted without any changes from the European Journal of Nuclear Medicine and Molecular Imaging [24] under the Creative Commons Attribution 4.0 International License (CC BY). https://creativecommons.org/licenses/by/4.0/.

cally insignificant for primary tumors but significantly lower for lymph nodes [34].

[^{18}F]FDG PET/CT confers difficulties in differentiating autoimmune pancreatitis from pancreatic cancer, especially in focal autoimmune pancreatitis when there is no evidence of inflammation in other organs (such as salivary glands, orbit, thyroid, lung, retroperitoneal, kidney, and lymph nodes). [^{68}Ga]Ga-FAPI targets FAP, which is abundant in tumor stroma and inflammatory tissue with substantial fibroblast proliferation, such as plasma cell-mediated sclerosing inflammation. In a case report, pancreatic inflammation appeared similar to focal malignant lesions on [^{18}F]FDG PET/CT [54]. However, [^{68}Ga]Ga-FAPI-04 PET/CT revealed uniformly higher uptake throughout the pancreas, ruling out possible malignancy and confirming immunoglobulin G4-related disease (IgG4-RD). Hence, it demonstrated that [^{68}Ga]Ga-FAPI-04 PET/CT is more sensitive than [^{18}F]FDG PET/CT for IgG4-RD and may assist in improving the distinction between pancreatitis and pancreatic cancer (**Figures 6** and **7**) [54, 55].

As ^{68}Ga-labeled FAPI agents are becoming popular in various preclinical and clinical imaging studies, there is a growing tendency to modify the FAPI tracers and identify their specific usefulness. The biodistribution, pharmacokinetics, and dosimetry of [^{68}Ga]Ga-DOTA.SA.FAPI, another modified FAPI tracer, was compared to [^{18}F]FDG PET/CT among fifty-four patients with 14 types of cancer (including 37% breast, 24% lung, 7.4% head and neck (H&N), and 31.6% with other histologies). Standardized uptake values corrected for lean body mass (SUL) were used to quantify tracer uptake. In patient-based comparisons, both radiotracers showed concordance for detecting primary malignancy, pleural thickening, bone and liver metastases, and second primary malignancy. Lymph nodes (7.5%), lung nodules (5.6%), and brain metastases (2%), however, showed discrepancies. Among the primary disease sites, patients with H&N cancer had the highest SULpeak and SULavg [^{68}Ga]Ga-DOTA.SA-FAPI, similar to those of [^{18}F]FDG. On the other hand, lung cancer had the lowest uptake for both radiotracers. Unlike [^{18}F]FDG, [^{68}Ga]Ga-DOTA.SA.FAPI had a significantly higher ratio of SULpeak (and SULavg) for brain metastases compared to normal brain parenchyma, increasing its usefulness in diagnosing brain metastases. However, except for brain metastases, the radiotracers had equivalent SULpeak and SULavg in all other regions of metastases without any significant differences. Thus, [^{68}Ga]Ga-DOTA.SA.FAPI could be a promising FAPI agent with performance comparable to the standard-of-care radiotracer, [^{18}F]FDG, in diagnosing various cancers [43].

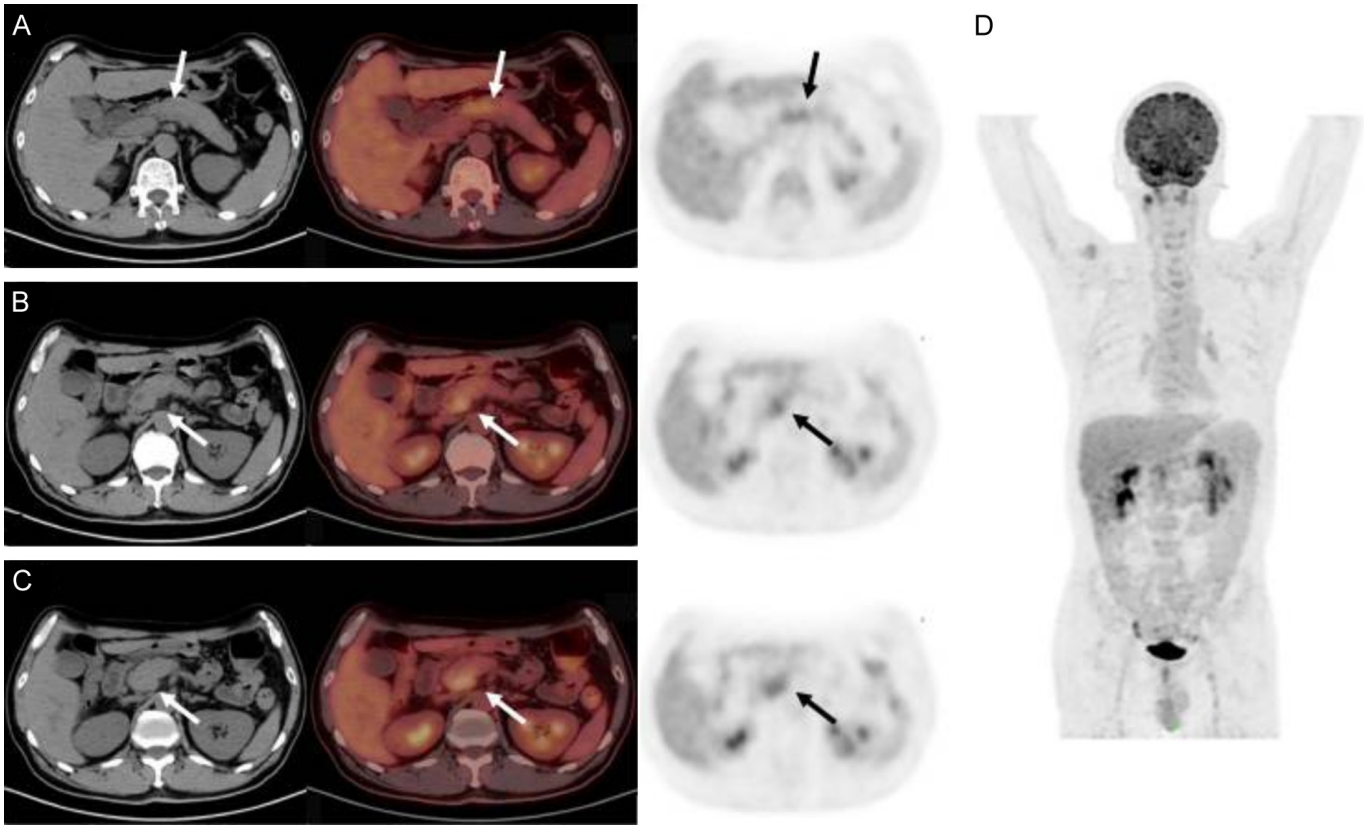

Figure 6. [^{18}F]FDG PET/CT images of IgG4-RD showed a mild increase in [^{18}F]FDG uptake in the uncinate process and neck of the pancreas, making it challenging to distinguish from pancreatic cancer. Adapted without any changes from the European Journal of Hybrid Imaging [55] under the Creative Commons Attribution 4.0 International License (CC BY). https://creativecommons.org/licenses/by/4.0/.

Higher tumor-to-background ratio with FAPI compared to [^{18}F]FDG

The target-to-background ratio (TBR) in PET imaging is a measure used to assess the contrast between the area of interest (the "target", such as a tumor or lesion) and the surrounding tissue (the "background") [56]. It is calculated as the ratio of the target region's PET signal intensity to the background region's PET signal intensity. A high TBR indicates a clear distinction between the target and the background, suggesting the target is well visualized against the surrounding tissue. This is particularly important in diagnostic imaging, as it affects the ability to accurately detect and characterize lesions or abnormalities. In clinical practice, a high TBR is desirable because it enhances the visibility of pathological regions, making it easier for radiologists to identify and assess tumors or other areas of interest (**Figure 8**) [57]. As noted in **Table 1**, 18 out of 34 studies reported higher TBRs with FAPI compared to [^{18}F]FDG, whereas TBR was not reported in the remaining 15 studies. Low levels of FAPI accumulation in physiological tissues are expected and allow for superior detection of primary and metastatic lesions in those organs compared to [^{18}F]FDG.

In a prospective study done among 20 women with primary and recurrent breast cancer, FAPI imaging showed higher TBR in breast, hepatic, bone, brain, and lung metastases compared to [^{18}F]FDG [20]. Giesel et al. found [^{68}Ga]Ga-FAPI ([^{68}Ga]Ga-FAPI-02, [^{68}Ga]Ga-FAPI-04, [^{68}Ga]Ga-FAPI-46, and [^{68}Ga]Ga-FAPI-74) had significantly lower SUVmax compared to [^{18}F]FDG in background tissues such as the brain, oral mucosa, blood pool, myocardium, liver, pancreas, and colon [14]. Therefore, lower levels of [^{68}Ga]Ga-FAPI uptake at tumor sites allow one to distinguish lesions from the background [14]. In a study of nasopharyngeal carcinoma by Qin et al., SUVmax in primary tumors was comparable between [^{68}Ga]Ga-FAPI-04 and [^{18}F]FDG, but the low levels of physiological uptake of [^{68}Ga]Ga-FAPI-04 in the brain allowed for superior tumor delineation and higher TBRs, such that [^{68}Ga]Ga-FAPI-04 led to the detection of the skull base and intracranial invasion, whereas [^{18}F]FDG imaging unable to capture this invasion [34]. Nonetheless, a study analyzed variables linked to [^{68}Ga]Ga-FAPI-04 uptake in hepatocellular carcinoma (HCC). In [^{68}Ga]Ga-FAPI-04 positive lesions, TBR was correlated with tumor size but not with other clinical and pathological characteristics [29].

Superior detection of primary tumors with FAPI compared to [^{18}F]FDG

[^{68}Ga]Ga-FAPI is a superior tracer to [^{18}F]FDG for the detection of various primary and metastatic tumors, including gastric, pancreatic, head and neck, and solitary fibrous tumors (**Figure 9**) [58]. FAPI PET/CT has shown the

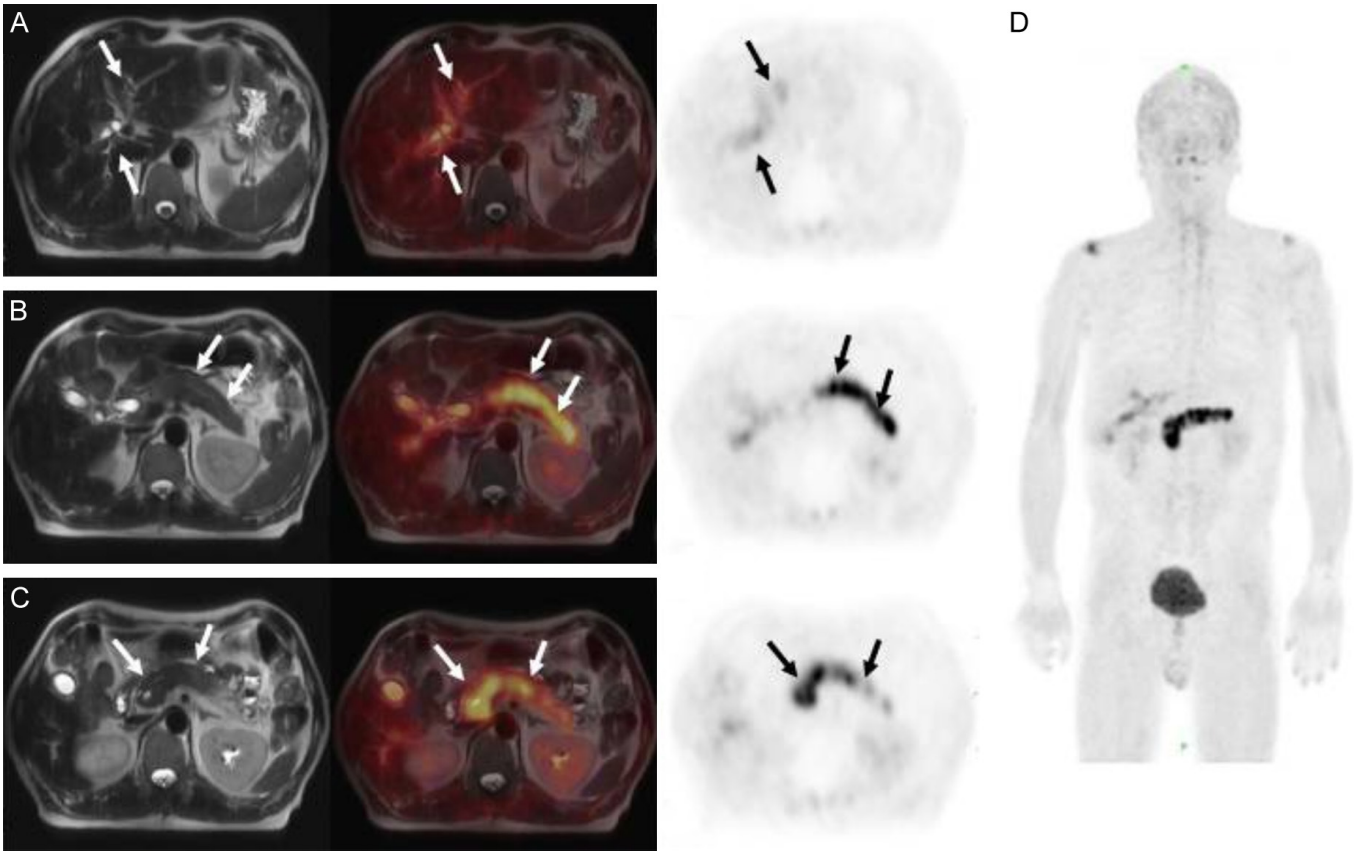

Figure 7. [^{68}Ga]Ga-FAPI PET/MR images of IgG4-RD revealed intensely increased [^{68}Ga]Ga-FAPI uptake throughout the entire pancreas and a dilated bile duct, leading to a definitive diagnosis of IgG4-RD. Adapted without any changes from the European Journal of Hybrid Imaging [55] under the Creative Commons Attribution 4.0 International License (CC BY). https://creativecommons.org/licenses/by/4.0/.

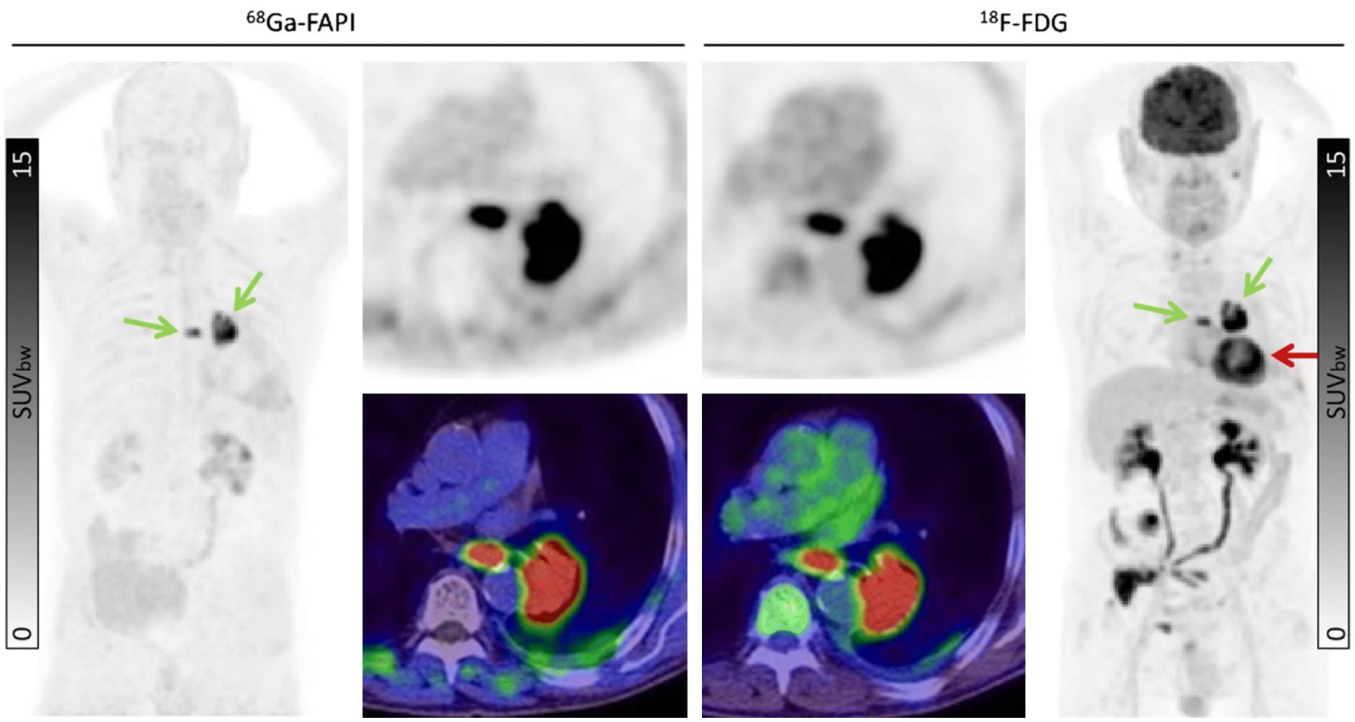

Figure 8. An 80-year-old male patient with lung cancer (indicated by green arrows) was diagnosed using [^{18}F]FDG PET/CT. Subsequent [^{68}Ga]Ga-FAPI PET/CT imaging revealed comparable tracer uptake (SUVmax: 15.99 for [^{18}F]FDG vs. 17.95 for [^{68}Ga]Ga-FAPI). A notable advantage of [^{68}Ga]Ga-FAPI, in this case, was the absence of uptake in the cardiac muscle, which is prominently observed with [^{18}F]FDG (indicated by red arrow). Adapted without any changes from the European Journal of Nuclear Medicine and Molecular Imaging [57] under the Creative Commons Attribution 4.0 International License (CC BY). https://creativecommons.org/licenses/by/4.0/.

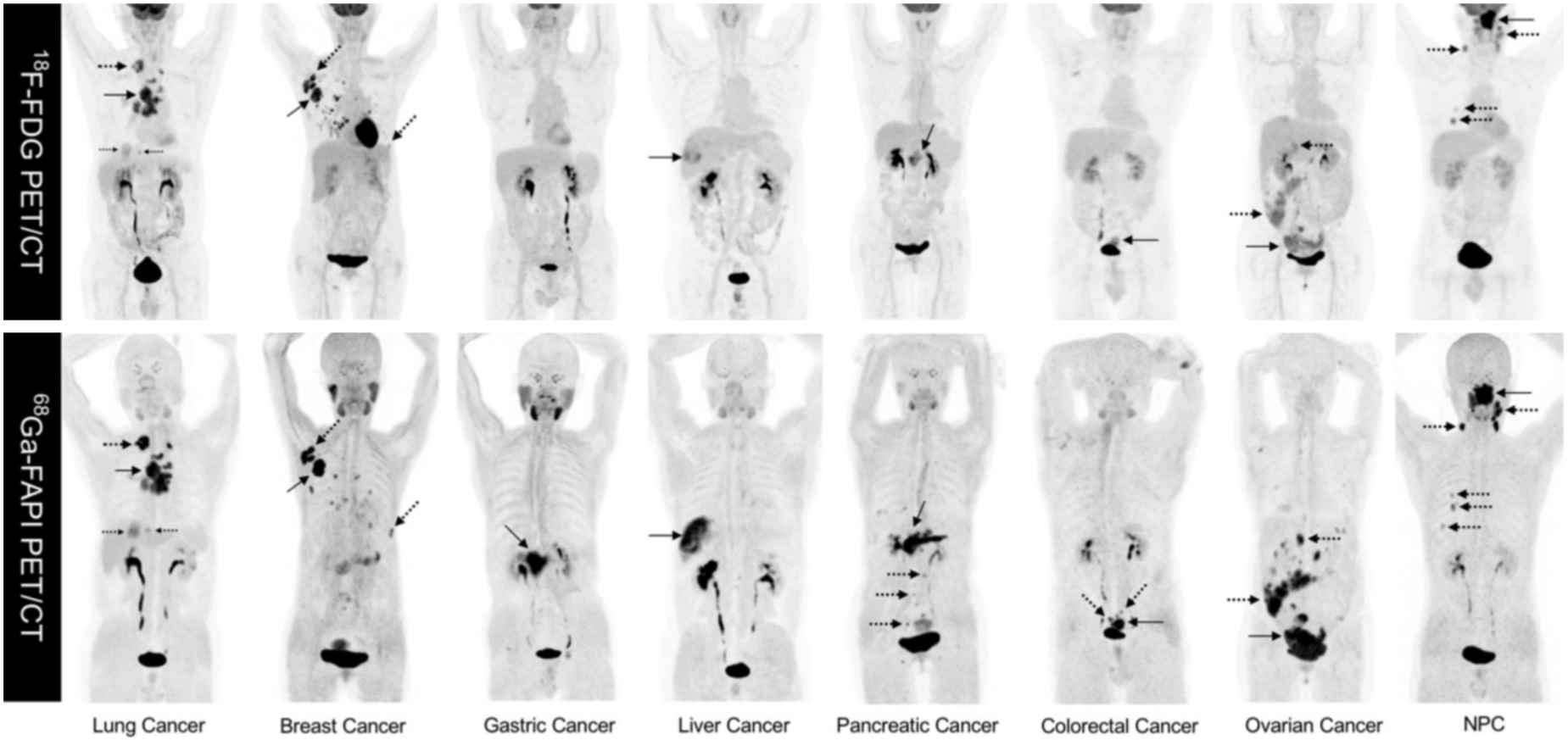

Figure 9. Representative comparison of eight patients with different tumor entities undergoing [^{18}F]FDG PET and [^{68}Ga]Ga-FAPI-04 PET imaging within less than one week. Solid arrows indicate a primary tumor, while dotted arrows indicate metastatic lesions. NPC: nasopharyngeal carcinoma. Adapted without any changes from Theranostics [58] under the Creative Commons Attribution 4.0 International License (CC BY). https://creativecommons.org/licenses/by/4.0/.

potential to identify primary tumors in cases where other diagnostic modalities cannot do so, even for small tumors with low glucose metabolic activity.

For example, one study compared [^{68}Ga]Ga-FAPI-04 and [^{18}F]FDG for gastric tumors [24]. Only five out of ten tumors were initially detected using [^{18}F]FDG. However, significantly higher TBRs with FAPI detected all ten primary gastric tumors [24]. In another case study, a 68-year-old female with a right hepatic lobe mass, elevated α-fetoprotein (>54,000 ng/mL), and neuroendocrine carcinoma (Ki-67 proliferation index of 80%) exhibited a higher [^{68}Ga]Ga-DOTA-FAPI-04 uptake than [^{18}F]FDG uptake [59]. The potential influence of physiologic FAP expression by pancreatic Langerhans islet alpha cells on FAPI PET was examined by a retrospective study, which included pancreatic tissues from a cohort of 40 patients, comprising 24 males and 16 females, with a median age of 68 years (range: 14-84 years) [60]. Among these patients, 20 had NETs, and 20 had pancreatic ductal adenocarcinoma. The immunohistochemistry analysis consistently revealed FAP expression with a score of 2 in the alpha cells of the pancreatic Langerhans islets in all 40 patients, regardless of cancer type. Notably, 8 out of the 20 patients with pancreatic adenocarcinoma had received neoadjuvant chemotherapy, but there were no observed differences in FAP expression based on chemotherapy status. This suggests that FAP expression in the pancreas is unlikely to impact the diagnostic accuracy of FAP-targeting radiotracers. The diagnostic utility of FAPI was supported by another study, which showed that [^{68}Ga]Ga-FAPI-04 successfully detected primary gastric cancer in four cases of gastric adenocarcinoma and three cases of signet ring cell carcinoma, which had been previously missed by [^{18}F]FDG [23].

There was a case in which [^{68}Ga]Ga-FAPI-04 was used to delineate primary and metastatic lesions of signet-ring cell carcinoma following [^{18}F]FDG PET/CT [61]. By using [^{68}Ga]Ga-FAPI-04, the lesions were more clearly defined, and additional lesions were detected compared to [^{18}F]FDG PET/CT [61]. Syed et al. also demonstrated a high uptake of [^{68}Ga]Ga-FAPI in head and neck cancers with low background uptake in healthy tissues (like salivary glands) in head and neck regions [61]. Similarly, in a study examining the added value of [^{68}Ga]Ga-FAPI PET/CT in 18 patients with head and neck cancer for whom [^{18}F]FDG PET/CT could not localize the primary site, [^{68}Ga]Ga-FAPI PET/CT detected primary tumors in 7 out of 18 (38.89%) patients [62]. Moreover, within this cohort, [^{68}Ga]Ga-FAPI PET/CT had a greater detection rate for adenocarcinoma (2/2, 100%) than squamous cell carcinoma (SCC) (5/16, 31.25%). Among the head and neck carcinomas from unknown primary (HNCUP) patients with negative [^{18}F]FDG findings, the primary tumor sites were the nasopharynx (n = 1), palatine tonsil (n = 2), submandibular gland (n = 2), and hypopharynx (n = 2). The authors suggest that given that the false-negative [^{18}F]FDG findings for three of those seven primary tumors may be due to small size. Hence, due to the low tumor glucose metabolic activity, [^{68}Ga]Ga-FAPI-04 is promising for detecting primary cancers early, with even small tumors showing evidence of moderate FAP expression [62].

There is also growing evidence that [^{68}Ga]Ga-FAPI can be utilized for imaging solitary fibrous tumors (SFTs), a rare fibroblastic mesenchymal neoplasm. In a case report, primary SFTs that were barely perceptible on [^{18}F]FDG PET/CT had a substantial uptake of [^{68}Ga]Ga-FAPI [63]. Furthermore, the authors noted that two lesions in the lumbar vertebrae that did not exhibit [^{18}F]FDG uptake were also detected by [^{68}Ga]Ga-FAPI PET/CT. One possible explanation for this may be that SFT is rich in cancer-associated fibroblasts (CAF), which overexpress FAP and are a crucial part of the tumor microenvironment. Hence, [^{68}Ga]Ga-FAPI may perform better than [^{18}F]FDG in identifying SFT foci, further suggesting that [^{68}Ga]Ga-FAPI could be a useful potential tracer in identifying fibroblastic tumors.

Potential detection of metastatic tumors with FAPI

FAPI PET/CT demonstrates potential for detecting metastatic tumors across various cancer types, including prostate cancer, neuroendocrine tumors, nasopharyngeal carcinoma, gastrointestinal cancers, and breast cancer. [^{68}Ga]Ga-FAPI PET/CT outperforms [^{18}F]FDG PET/CT in detecting metastatic lesions, particularly in lymph nodes, and shows promise as a prognostic marker and in assessing tumor aggressiveness. FAPI PET/CT may provide additional value to the current standard in staging various cancers, which relies on accurate detection of nodal and visceral metastases.

Prostate cancer

In a case of mixed large-cell neuroendocrine carcinoma-acinar adenocarcinoma of the prostate, [^{68}Ga]Ga-FAPI PET/CT showed promising results in detecting the inter-metastatic heterogeneity present in metastatic neuroendocrine prostate cancer [64]. Another case report supports further investigation of FAPI PET/CT as a prognostic marker for prostate cancer [40]. After exhausting standard therapy, a 77-year-old man underwent [^{177}Lu]Lu-PSMA radioligand therapy twice; despite this, there was a progression. At restaging, modest lymph node and bone metastase uptake was seen on [^{68}Ga]Ga-PSMA-11 PET/CT. However, additional [^{18}F]FDG-avid lesions were discovered, which did not demonstrate significant PSMA expression, resulting in a mismatch pattern. Hence, [^{68}Ga]Ga-FAPI-04 PET/CT was performed to determine candidacy for FAP-based treatment. [^{68}Ga]Ga-FAPI-04 PET/CT showed very strong tracer uptake in both lymph nodes and bone metastases, and all [^{18}F]FDG and PSMA-positive lesions were also positive for expression of FAP, suggesting a role for FAPI-based theranostics in patients with dedifferentiated prostate cancer.

Neuroendocrine tumors

Additionally, in a case, a patient with pulmonary nodules and a nonspecific hepatic lesion underwent a series of [^{18}F]FDG PET/CT and [^{11}C]-acetate PET/CT imaging studies, which did not elucidate the underlying disease [65]. However, the images acquired by [^{68}Ga]Ga-FAPI-04 PET/CT displayed strong uptake at the tail of the pancreas and effectively delineated a lesion in the liver with elevated uptake. The patient underwent surgical treatment and was confirmed to have pancreatic NET. As mentioned earlier, in a patient with multiple metastases from primary pancreatic NET, abnormal hepatic and pancreatic uptake was visualized by [^{18}F]FDG, [^{68}Ga]Ga-FAPI, and [^{68}Ga]Ga-DOTATATE PET/CT [66]. Notably, [^{68}Ga]Ga-FAPI PET/CT exhibited the highest tumor-to-liver ratios. Another case involving a 56-year-old patient with multiple liver masses was confirmed as having grade 2 well-differentiated NET [67]. Compared to [^{68}Ga]Ga-DOTATATE PET/CT, [^{68}Ga]Ga-FAPI PET/CT had superior lesion differentiation and selection due to lower background activity. To evaluate the correlation between [^{68}Ga]Ga-DATA5m.SA.FAPi PET/CT and Ki-67 as a marker of tumor aggressiveness in patients with liver metastases from NET, 13 patients were included in a retrospective analysis [68]. While [^{18}F]FDG SUVmax and [^{68}Ga]Ga-DOTATOC SUVmax showed moderate correlations with Ki-67, FAPI SUVmax exhibited no significant correlation. However, FAPI-positive tumor fraction was strongly correlated with Ki-67, suggesting that FAPI PET/CT may serve as a parameter for assessing dedifferentiation and aggressiveness of liver metastases in NET [68].

Nasopharyngeal carcinoma

A study of 15 patients with nasopharyngeal carcinoma compared the diagnostic performance of [^{68}Ga]Ga-DOTA-FAPI-04 PET/MR to [^{18}F]FDG PET/MR [34]. Although [^{68}Ga]Ga-FAPI and [^{18}F]FDG PET/MR both achieved a 100% success rate in detecting the primary tumor, [^{68}Ga]Ga-FAPI PET/MR outperformed [^{18}F]FDG PET/MR in delineating the primary tumor, evaluating the skull base, and detecting intracranial invasion by suspected distant metastases. The study found that [^{68}Ga]Ga-FAPI PET/MR can be used as a single-step staging modality for nasopharyngeal carcinoma. However, further investigation was recommended to determine the value of [^{68}Ga]Ga-FAPI PET/MR in evaluating lymph nodes and distant metastases [34].

Gastrointestinal cancers

[^{68}Ga]Ga-FAPI-04 was furthermore found to be superior to [^{18}F]FDG in detecting tumor recurrence and nodal metastasis in a prospective study by Liu et al., which included 41 patients with gastric, duodenal, and colorectal cancer [46]. Specifically, [^{68}Ga]Ga-FAPI-04 was superior to [^{18}F]FDG in the detection of nodal metastasis but not distal metastasis [46]. The superior diagnostic performance of [^{68}Ga]Ga-FAPI-04 over [^{18}F]FDG was similarly supported in another study evaluating 10 patients with gastric cancer who had regional lymph nodes and distant metastases [23]. This study determined that the sensitivities of [^{68}Ga]Ga-FAPI-04 PET and [^{18}F]FDG PET for detecting metastatic lesions were 60% and 50%, respectively. Qin et al. compared the efficacy of [^{68}Ga]Ga-DOTA-FAPI-04 PET/MR with [^{18}F]FDG PET/CT in diagnosing metastatic gastric cancer lesions [69]. [^{68}Ga]Ga-DOTA-FAPI-04 PET/MR was able to detect gastric cancer metastases to the peritoneum, abdominal lymph nodes, liver, and bones at a higher rate than [^{18}F]FDG PET/CT. Although this did not hold for ovarian metastases, the study found that, when combined with hybrid MRI, [^{68}Ga]Ga-DOTA-FAPI-04 PET/MR could help avoid misdiagnosis. Similarly, a case report on appendiceal mucinous adenocarcinoma with lymph node metastases and extensive peritoneal carcinomatosis found that [^{68}Ga]Ga-FAPI was able to identify several primary and metastatic lesions in the ileocecal intestinal wall, peritoneum, mesentery, the omentum, and a nearby enlarged mesenteric lymph node, all of which were previously undetected by [^{18}F]FDG [70]. This may have been due to the low level of glucose transporter protein type 1 expressed in this subtype of adenocarcinoma.

Breast cancer

Lastly, the importance of FAPI PET in staging newly diagnosed breast cancer was evaluated in a prospective study of 34 patients who underwent [^{68}Ga]Ga-FAPI and [^{18}F]FDG PET/CT within one week of diagnosis [47]. In their analysis, the authors noted that [^{68}Ga]Ga-FAPI PET/CT was found to have superior accuracy compared to [^{18}F]FDG PET/CT in excluding the presence of axillary nodal metastases. Therefore, staging, which depends critically on detecting nodal and visceral metastases, may represent an area where FAPI PET can provide additional value to the current standard, with potential applications spanning a wide breadth of oncologic imaging.

Other benefits of FAPI

Greater convenience

Both [^{68}Ga]Ga-FAPI and [^{18}F]-FAPI differ from [^{18}F]FDG in terms of patient preparation for imaging. Unlike [^{18}F]FDG, FAPI imaging does not require fasting, other dietary preparations, or resting time [14]. Likewise, FAPI PET/CT can be performed even on patients with high serum glucose levels, such as people with diabetes [6]. The lack of patient preparation required for FAPI utilization suggests that image acquisition could begin much earlier than that for [^{18}F]FDG imaging [71].

[^{68}Ga]Ga-DOTA-FAPI-04 as a promising tool for differentiating ovarian physiological uptake

Abnormal [^{18}F]FDG uptake can occur in both functioning and malignant ovarian lesions. A study assessed the fea-

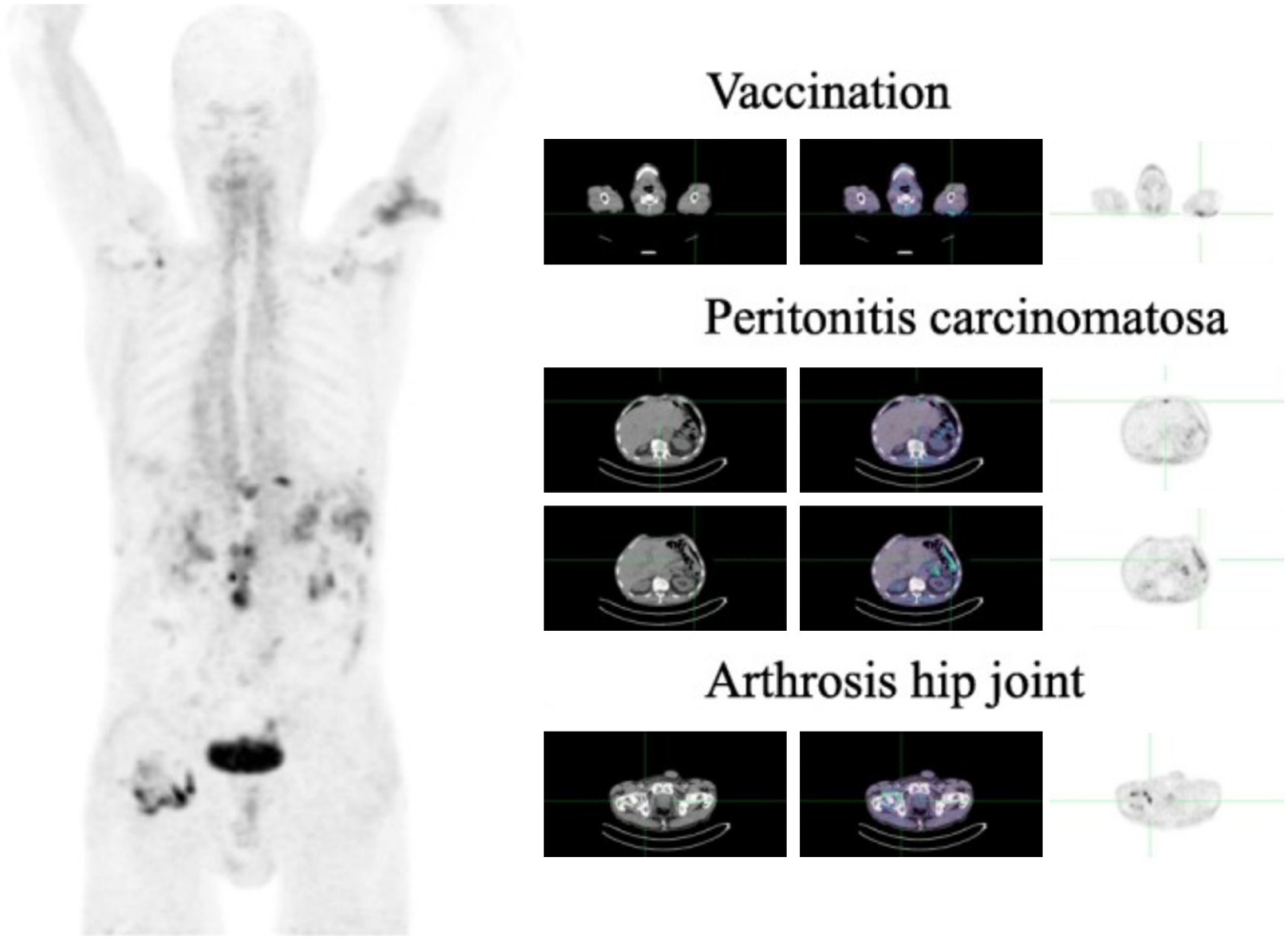

Figure 10. MIP and transaxial slices (CT, fused PET/CT, and PET) of a patient with gastric cancer and peritonitis carcinomatosa show tracer uptake in the left shoulder, abdomen, and right hip joint. The left shoulder accumulation is due to a chronic inflammation from a six-month-long peptide vaccination. The right hip joint uptake corresponds to activated arthritis, while the multiple abdominal lesions are caused by peritonitis carcinomatosa. Adapted without any changes from EJNMMI Radiopharmacy and Chemistry [16] under the Creative Commons Attribution 4.0 International License (CC BY). https://creativecommons.org/licenses/by/4.0/.

sibility of early diagnosis of primary ovarian disease with [^{68}Ga]Ga-DOTA-FAPI-04 PET/CT [71]. It was found that both ovarian functional and pathological changes can be [^{18}F]FDG avid, but [^{68}Ga]Ga-DOTA-FAPI-04 has no physiological accumulation in the ovary and is not affected by the menstrual cycle [71]. Hence, [^{68}Ga]Ga-DOTA-FAPI-04 may have the potential to accurately diagnose ovarian disorders and discriminate between normal and pathological ovarian lesions in the early stages [71].

Limitations of FAPI

Non-specific uptake

Some common pitfalls of FAPI include its non-tumor-specific uptake (**Figures 10** and **11**) [16].

FAPI can accumulate in degenerative lesions (for example, benign lesions of bones and joints), scar tissue, muscle, head and neck, mammary glands, and the uterus, which might be reported as false positives [39, 72]. Similar to [^{18}F]FDG, which is known to accumulate in acute inflammation, recent studies have demonstrated that there is also increased uptake of radiolabeled FAPI in chronic inflammation [73, 74]. This could be due to FAP activation in chronic inflammation, which may lead to a fibrotic reaction [73, 74]. This limitation of FAPI is especially concerning for cancer patients, who have often undergone previous rounds of radiation therapy. The chronic inflammation from past radiation therapy may be misinterpreted as tumor recurrence, increasing the possibility of false-positive cancer diagnosis.

Variations with age and menopause status

The uptake of FAPI in the normal endometrium and breast appears to be correlated with menopausal status [75]. FAPI uptake in healthy hormone-responsive organs significantly differed between premenopausal and postmenopausal females [75]. A study consisting of 12 premenopausal (<35 years) and 68 postmenopausal (>65 years) patients showed significantly higher mean SUVmax

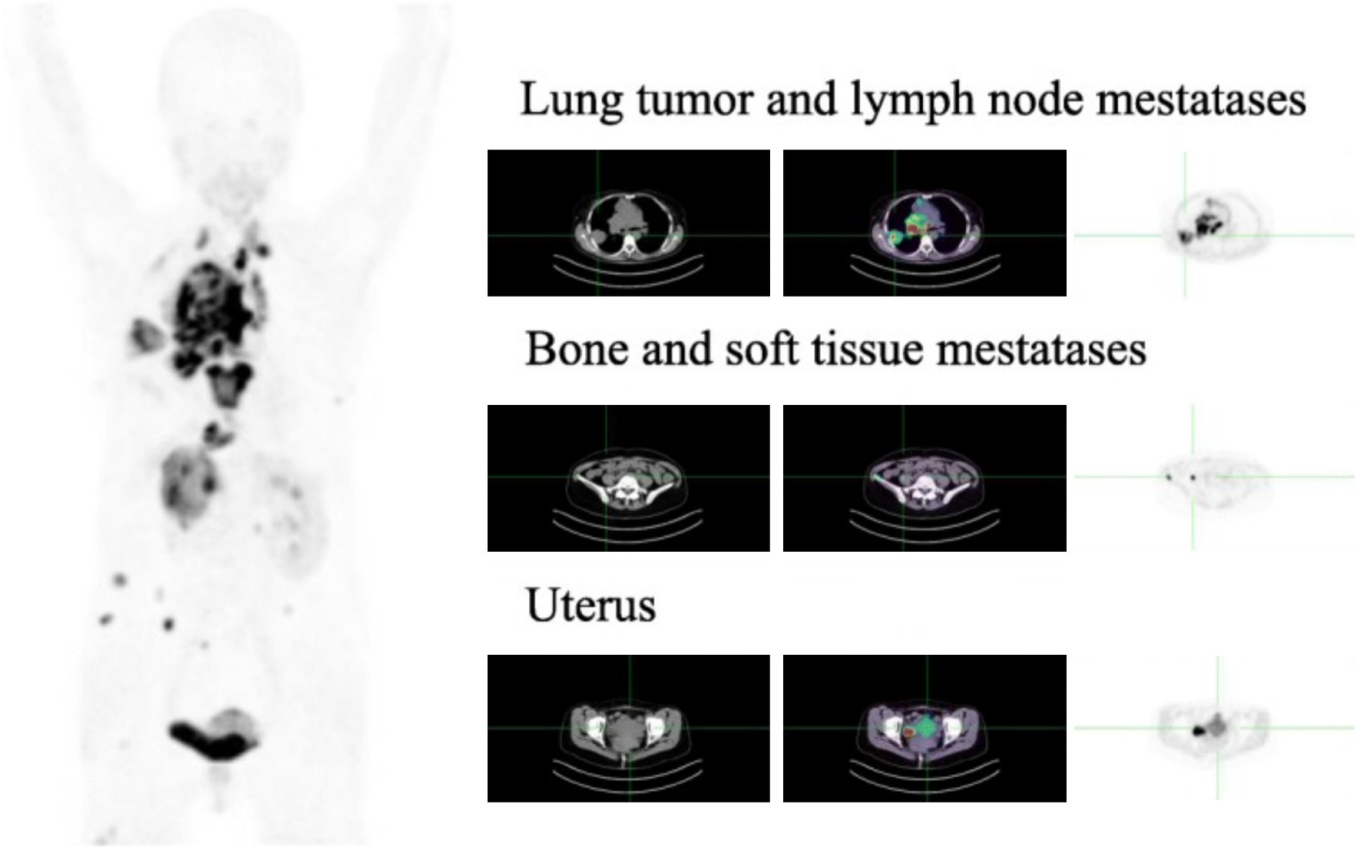

Figure 11. MIP and transaxial slices (CT, fusion image, and PET) from a patient diagnosed with non-small cell lung cancer reveal tracer uptake in the primary tumor, mediastinal lymph node metastases, bone metastases, and soft tissue metastasis. Additionally, physiological uptake is observed in the uterus. Adapted without any changes from EJNMMI Radiopharmacy and Chemistry [16] under the Creative Commons Attribution 4.0 International License (CC BY). https://creativecommons.org/licenses/by/4.0/.

among premenopausal compared to postmenopausal women in the endometrium (11.7 vs. 3.0; P<0.001) and breast (1.8 vs. 1.0; P = 0.004) [75].

Since female patients have avid [^{68}Ga]Ga-FAPI uterine uptake, studies have investigated the physiological uptake of [^{68}Ga]Ga-FAPI by the uterus in women of different ages. One retrospective study found that [^{68}Ga]Ga-FAPI uptake was higher in females of reproductive and perimenopausal age compared to postmenopausal females [76]. [^{68}Ga]Ga-FAPI uptake was also higher in patients who had uterine fibroids or had undergone previous invasive gynecologic surgeries (cesarean operation, induced abortion, intrauterine device implantation, and myomectomy). Moreover, [^{68}Ga]Ga-FAPI uptake was associated with uterine volume and age [76]. MRI and CT images demonstrated an age-related decrease in uterine volume. The uterus of reproductive and perimenopausal patients had higher [^{68}Ga]Ga-FAPI-04 uptake than that of postmenopausal patients. Images demonstrated that the uterus with the oldest age and the smallest size had the lowest uptake of [^{68}Ga]Ga-FAPI-04. Thus, [^{68}Ga]Ga-FAPI-04 uptake was positively correlated with uterine volume and negatively with age. Interestingly, there was no correlation between [^{18}F]FDG and [^{68}Ga]Ga-FAPI uptake in the uterus [76]. Nonetheless, [^{68}Ga]Ga-FAPI still has utility in evaluating patients with malignant uterine lesions [75, 76].

Controversies in lymph node metastasis

In abdominal malignancies, [^{68}Ga]Ga-FAPI has been found to be superior to [^{18}F]FDG in detecting both primary tumors and nodal and distant metastases [19]. However, the ability of [^{68}Ga]Ga-FAPI to perform nodal staging has not been as impressive as its ability to identify primary tumors [19]. Some studies have found that [^{18}F]FDG is a better agent than [^{68}Ga]Ga-FAPI for lymph node staging [19, 34]. One meta-analysis showed that when analyzing only nodal metastases, high heterogeneity was detected in the pooled sensitivity/specificity of [^{68}Ga]Ga-FAPI (I^2 = 89.18% and I^2 = 95.74%, respectively) [19]. Given that lymph nodes typically comprise a network of fibroblast reticular cells, the considerable diversity of ^{68}Ga-FAPI performance in nodal staging assessment (sensitivity of 59-100 percent) is perhaps unexpected [19].

Controversies in bone metastasis

Initial evidence noted that bone metastases have an increased [^{68}Ga]Ga-FAPI uptake [77-80], suggesting the potential for [^{68}Ga]Ga-FAPI for diagnosing bone metasta-

ses. Several studies have found that [^{68}Ga]Ga-FAPI PET detects a greater number of bone metastases and has a higher SUVmax than [^{18}F]FDG PET [78, 81, 82]. However, one retrospective study found that bone metastases and benign osteoarticular lesions can have increased [^{68}Ga]Ga-FAPI uptake [81]. They discovered that 68.1% of the foci in the bones and joints with high uptake were, in fact, benign disease entities [81]. More consideration should be given to the positive results of FAPI-PET to prevent misdiagnosis, as benign bone and joint conditions frequently coexist with malignant diseases [81].

Tumor and CAF co-evolution

Another issue is the co-evolution of tumors and cancer-associated fibroblasts (CAF) during tumorigenesis and their progression. This phenomenon may impact the stroma and, therefore, the expression of FAP - this could potentially complicate the interpretation of FAPI PET/CT images over time. For instance, colorectal carcinogenesis and heterogeneity are driven by the diverse interactions between cancer cells and CAFs of the tumor microenvironment (TME) [83]. Reactive oxygen species (ROS) and other "metabolic" and "mutagenic" factors stimulate the co-evolution of the tumor and its stroma, DNA damage, and aneuploidy in malignant cells, all of which contribute to the growth of a more aggressive tumor [84]. ROS produced by cancer cells can also encourage fibroblasts to transdifferentiate into myofibroblasts, enhancing tumor growth and spread [85]. This vicious cycle, which results in ongoing variation in FAP, raises the question of whether FAPI is a uniform and reliable tool for cancer diagnosis and surveillance.

Concerns with manufacturing and commercialization

Limited manufacturing and commercialization resources pose a challenge to the widespread utilization of FAPI. Moreover, FAPI radiotracers are mostly labeled with ^{68}Ga produced via a ^{68}Ge/^{68}Ga generator. Due to the radionuclide's short half-life, the ^{68}Ga activity obtained from a generator may be limited [6]. This may hinder both the manufacturing and delivery of the radionuclide. The cost of ^{68}Ge/^{68}Ga generators is also an important limitation to their widespread acceptance [6].

Small sample size and lack of long-term follow-up

Most of the current literature on FAPI uses a relatively small sample size. It lacks long-term follow-up, limiting our knowledge of this imaging tool's full potential and limitations. The study designs used in these studies vary considerably, further impacting the dependability of the results. Furthermore, most studies on FAPI do not have histopathological confirmation of the metastatic lesions [20, 21]. Hence, immunohistochemistry confirmation may be required to correlate tumor tracer uptake with FAP expression [20, 21].

Conclusion

FAPI has several advantages over [^{18}F]FDG for detecting and delineating primary and metastatic tumors due to its increased uptake and TBR. Compared to [^{18}F]FDG, FAPI demonstrated a greater ability to identify both primary and metastatic lesions in several malignancies, particularly those small in size and with low [^{18}F]FDG avidity. FAPI had a higher tumor detection rate for gastrointestinal tumors, liver tumors, breast cancer, and nasopharyngeal carcinoma in comparison to [^{18}F]FDG. In contrast, studies have found that [^{18}F]FDG performs better than FAPI for hematological malignancies like lymphoma and multiple myeloma. While research has posited that FAPI may be more specific to tumors, especially stromal tumors, and have higher tumor-to-background ratios than radiolabeled [^{18}F]FDG, this still needs to be confirmed histologically. FAPI still has several limitations. From its non-specific uptake and variation with age and menopause status to concerns with manufacturing and commercialization, many obstacles still stand in the way of the widespread entry of FAPI into clinical settings. Much of the current research on the efficacy of FAPI has small sample sizes, lacks long-term follow-up, and has not conducted histological verification of FAPI tracer uptake and expression. Moreover, controversies still exist about the ability of FAPI to detect metastases to lymph nodes and bones. Thus, although FAPI has shown promise for diagnosing tumors, it cannot yet replace using [^{18}F]FDG.

Disclosure of conflict of interest

None.

Abbreviations

FAPI, Fibroblast activation protein inhibitor; [^{18}F]FDG, [^{18}F]-fluorodeoxyglucose; TBR, tumor to background ratio; N/A, Not applicable; PET, Positron Emission Tomography.

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