
بنام خداوند جان و خرد

Clinical application of FAPI PET/CT Scan in malignancy

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Introduction

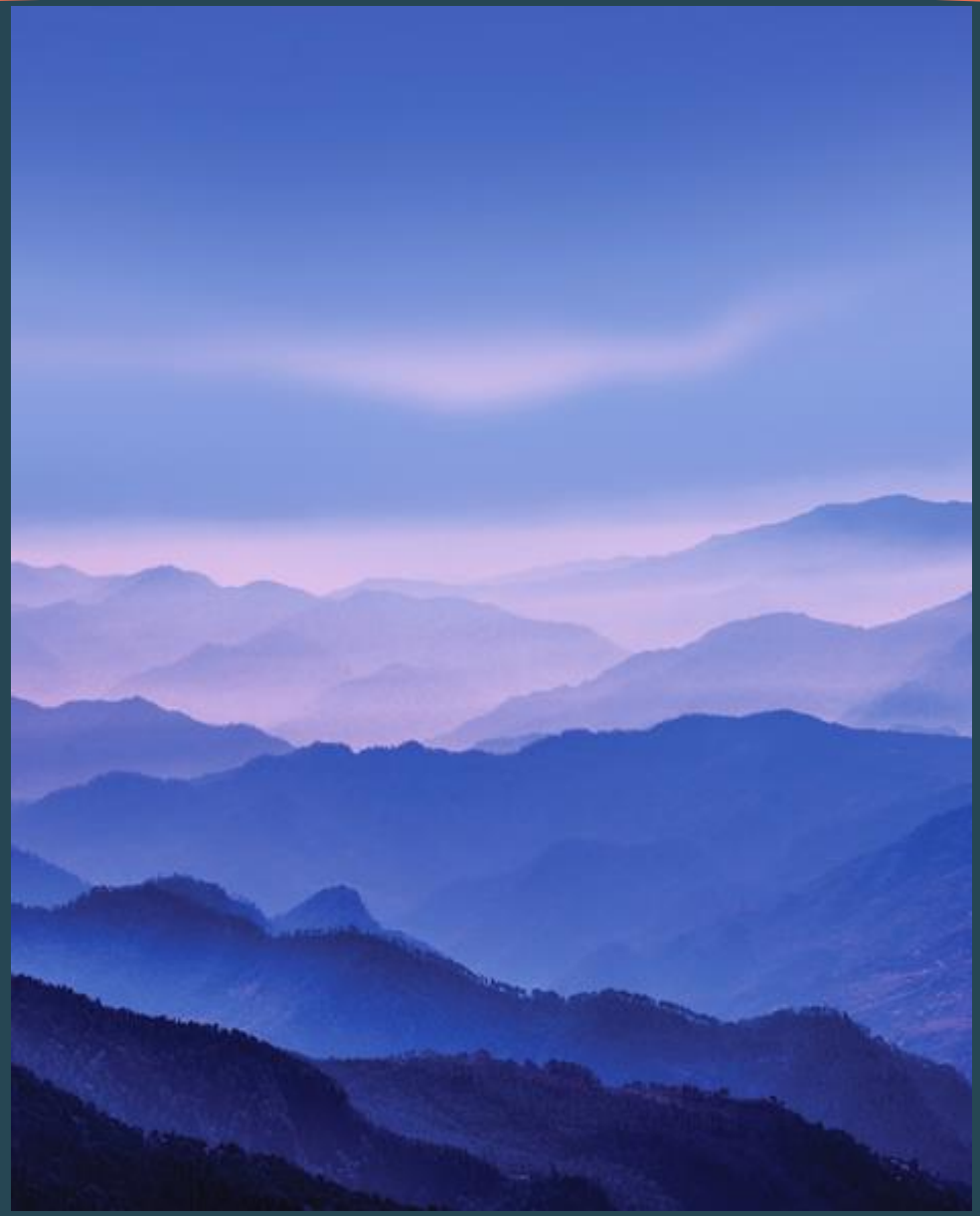
- Currently, 18F-fluorodeoxyglucose (FDG) is the most widely used tracer for oncologic positron emission tomography (PET) imaging; However, nonspecific and physiological 18F-FDG uptake in crucial organs reduces diagnostic accuracy in many cases.

- FAPI imaging has been explored for various purposes in different clinical settings, with promising results.

- Cancer initiation, progression, and metastasis causes a wide spectrum of dynamic alterations in the tumor microenvironment (TME), which is composed of the extracellular matrix (ECM) and a variety of cell types, including cancer-associated fibroblasts (CAFs), immune cells, and vascular endothelial cells.

- CAFs have several biological markers, including α-smooth muscle actin, fibroblast activation protein (FAP), and platelet-derived growth factor receptor-β.

- FAP is a type II integral membrane glycoprotein of the dipeptidyl peptidase 4 family with both dipeptidyl peptidase and endopeptidase activities which is overexpressed in the CAF cell membrane and stroma in approximately 90% of epithelial neoplasms.



- It is expressed on both cancer-associated fibroblasts (CAFs) and normal activated fibroblasts (NAFs) involved in wound healing and tissue repair.
- FAP has long been a target for cancer therapy, but the development of FAP targeted radioligands has led to an increased interest in imaging FAP for assessment of cancer and other diseases.
- Although the FAP PET will play a role in non-oncologic diseases, the primary focus of this presentation is its oncologic applications.

FAPI PET is:

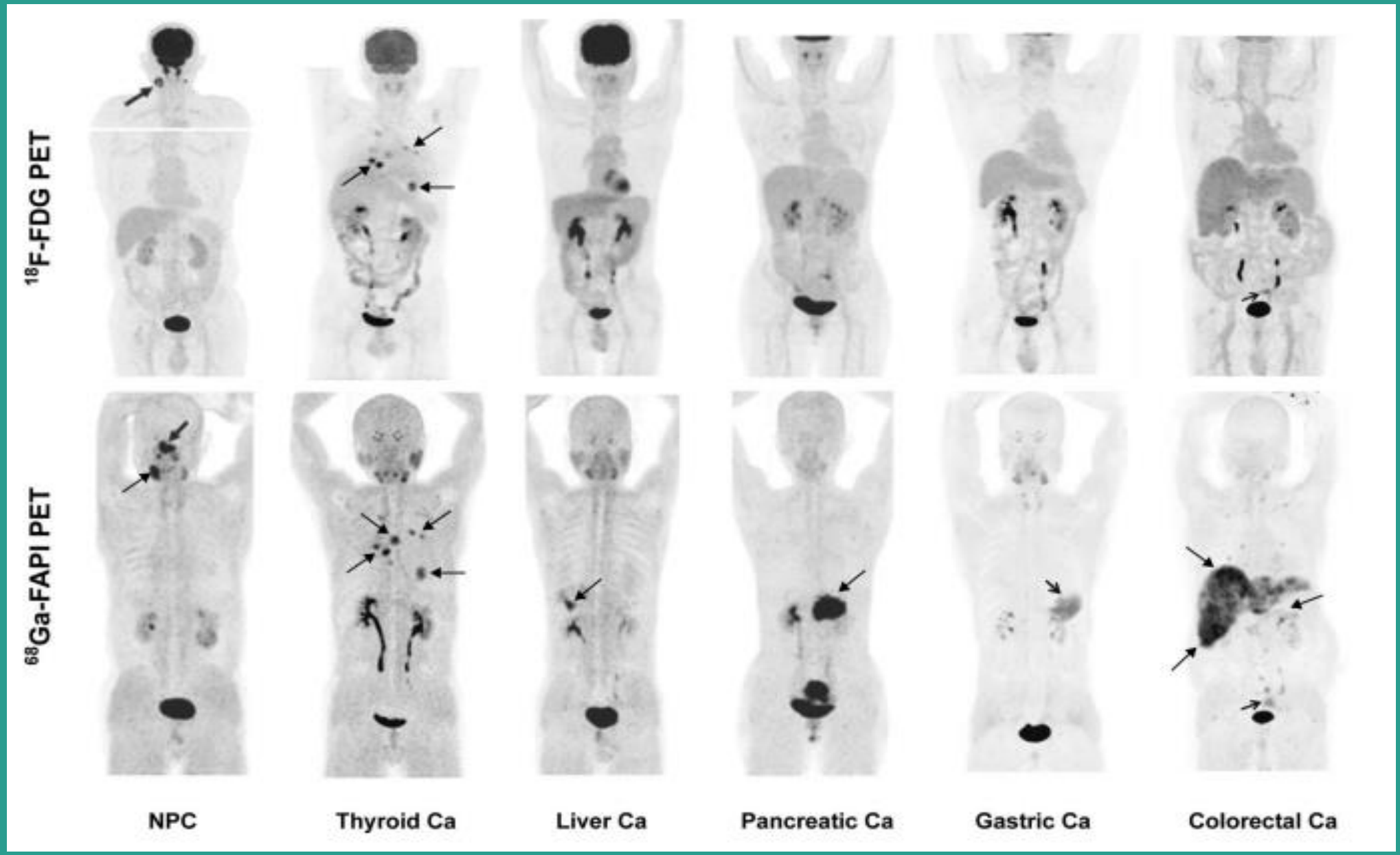
- Independent of glucose metabolism
- Background signals in the brain, liver, nasopharyngeal, oral mucosa, and gastrointestinal tract are low
- FAPI PET can be used without any dietary preparation
- Provides stable tracer uptake from 10 min to 3 h after administration.

➢ Hence, clinical interest in FAPI imaging has considerably increased.

❖ FAPI imaging has been explored for various purposes in different clinical settings, with promising results.

❖ Tumors that have a high content of FAP-expressing CAFs, include:

- Gastro-intestinal adenocarcinoma
- Pancreatic ductal adenocarcinoma (PDAC)
- Cholangiocarcinoma
- Esophageal
- Head and neck cancer
- Thyroid cancer
- Unknown primary (CUP),
- Lung
- Bladder
- Ovarian
- Breast cancers
- Metastatic brain tumors


^{18}F-FDG PET
^{68}Ga-FAPI PET
NPC
Thyroid Ca
Liver Ca
Pancreatic Ca
Gastric Ca
Colorectal Ca

- On the other hand, several cancer types do not induce a strong and/or consistent FAP uptake such as:

- Lymphoma
- Myeloma
- Prostate adenocarcinoma
- Renal cell carcinoma
- Melanoma
- Seminoma

PROCEDURE/SPECIFICATIONS OF THE EXAMINATION

1. Request:

- Medical condition of the patient, including relevant medical history and one or more specific clinical questions that the PET should address
- Previous medical procedures that can promote fibroblast activity (e.g. surgery, biopsy, radiation therapy) should be mentioned
- Lesions outside of the classical field-of-view (FOV) of a whole-body PET (e.g. vertex, arms, lower limbs) should be mentioned.
- Information relevant for the hybrid partner examination (CT or MRI) needs to be provided, including claustrophobia as well as recent renal function (glomerular filtration rate) and history of hypersensitivity reactions to iodinated or gadolinium containing contrast media for contrast-enhanced CT or MRI, respectively.
- Confirmation that the patient is not pregnant and ongoing lactation should be mentioned, as well.
- Currently there are no known drug interactions for FAP ligands.
- It is useful to mention if a patient is taking fibroblast-targeting drugs such as nintedanib or pirfenidone

2. Patient Preparation and Precautions

- ✓ Well hydrated to promote clearance of urinary excreted tracer
- ✓ No caloric fasting nor adaption of anti-diabetic drugs is necessary
- ✓ Avoiding strenuous exercise in the preceding 24 hours is not required
- ✓ General radiopharmaceutical administration procedures to handle potential pregnancy and lactation should be applied; In case of documented pregnancy, alternative imaging procedures should be strongly considered.
- ➢ Precautions for lactating women depend on radionuclide and injected activity; an interruption of 4 to 24 hours of lactation can be requested, depending on radionuclide and institutional policy.
- ✓ FAP PET can be considered in pediatric patients, although experience in children is limited. No adverse events have been reported in these rare cases.
- ➢ Proper procedures for immobilization, adapted to the age of the child and their anticipated compliance, should be available, ranging from restraining devices to sedation to general anesthesia, similar to other PET imaging procedures

3. Administered Activity

The injected activity depends on the radiopharmaceutical used and…

- Most studies using gallium-68 based radiopharmaceuticals use administered activities ranging from 120-300 MBq, with average values around 150 MBq, resulting in roughly 2.0 MBq/kg

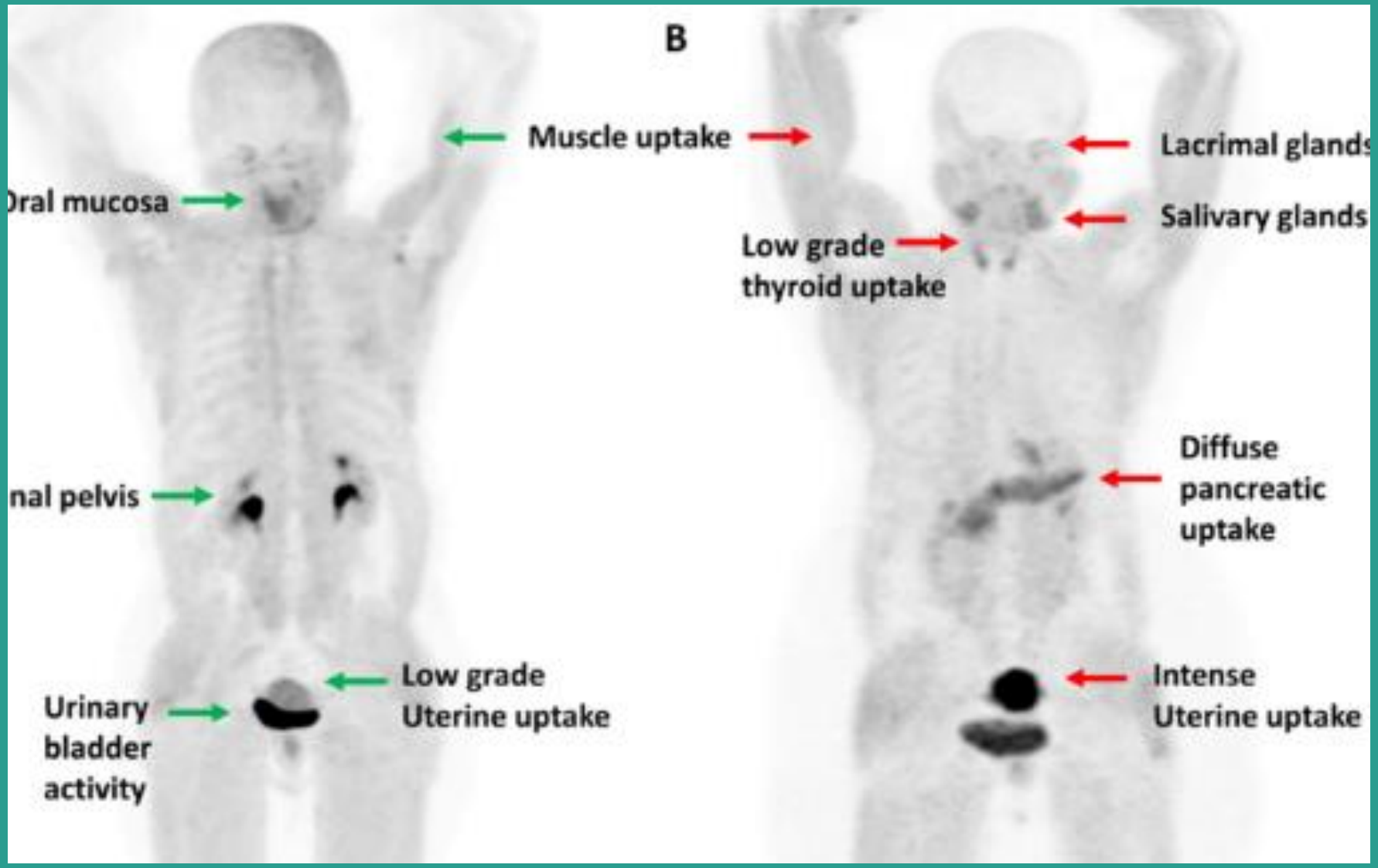
- For fluorine-18 based radiopharmaceuticals, which can typically be produced in higher amounts, the administered activity tends to be higher, with ranges from 185-300 MBq, with average values around 230 MBq, resulting in roughly 4.4 MBq/kg. Based on this experience, an administrated activity of 175-275 MBq or 3-4 MBq/kg is recommended.

4. Uptake Time

- The uptake time usually ranges between 30 and 60 minutes after administration of 68Ga-FAPI compounds
- Early scan acquisitions, e.g., 10 or 20 minutes after injection, have been reported, and lesion uptake is relatively stable between 20 and 120 minutes
- Late time points 1 h and 3 h after injection have been also proposed. These result in improved discrimination between malignant and chronic inflammatory or fibrotic 68GaFAPI avid lesions

- For 18F-FAPI-74, the recommended uptake time is 60 minutes, resulting in optimal tumor to background ratios with limited background noise

- Overall, we recommend an uptake time of 20 to 60 minutes for gallium-68 labeled compounds and 30 to 90 minutes for fluorine-18 labeled compounds.


B
Muscle uptake
Oral mucosa
nal pelvis
Low grade
Uterine uptake
Urinary
bladder
activity
Lacrimal glands
Salivary glands
Low grade
thyroid uptake
Diffuse
pancreatic
uptake
Intense
Uterine uptake

- FAP PET imaging can be used for initial staging, re-staging, therapy response evaluation and whole-body target expression assessment for therapy selection.

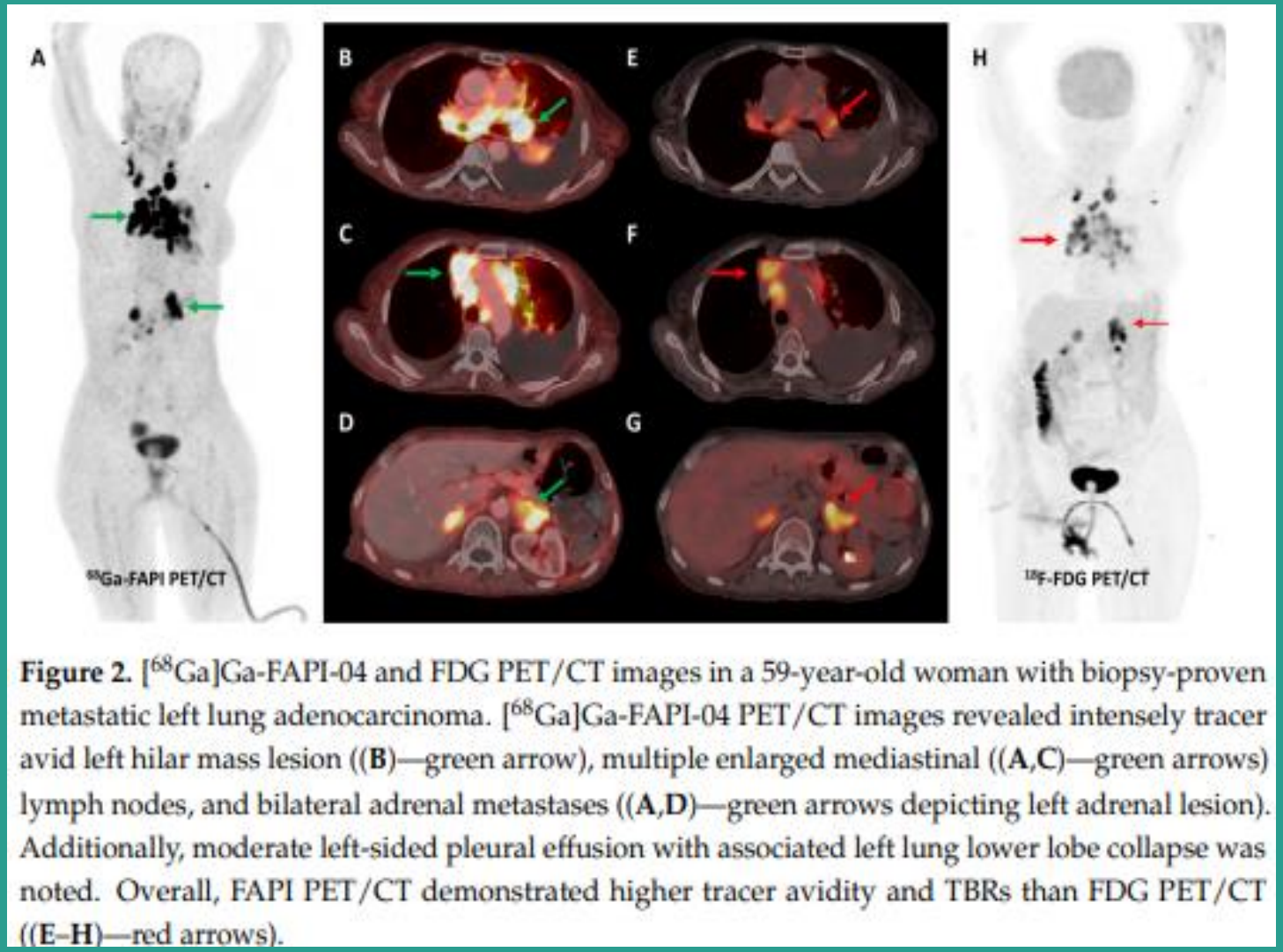


Figure 2. [^{68}Ga]Ga-FAPI-04 and FDG PET/CT images in a 59-year-old woman with biopsy-proven metastatic left lung adenocarcinoma. [^{68}Ga]Ga-FAPI-04 PET/CT images revealed intensely tracer avid left hilar mass lesion ((**B**)—green arrow), multiple enlarged mediastinal ((**A**,**C**)—green arrows) lymph nodes, and bilateral adrenal metastases ((**A**,**D**)—green arrows depicting left adrenal lesion). Additionally, moderate left-sided pleural effusion with associated left lung lower lobe collapse was noted. Overall, FAPI PET/CT demonstrated higher tracer avidity and TBRs than FDG PET/CT ((**E**–**H**)—red arrows).

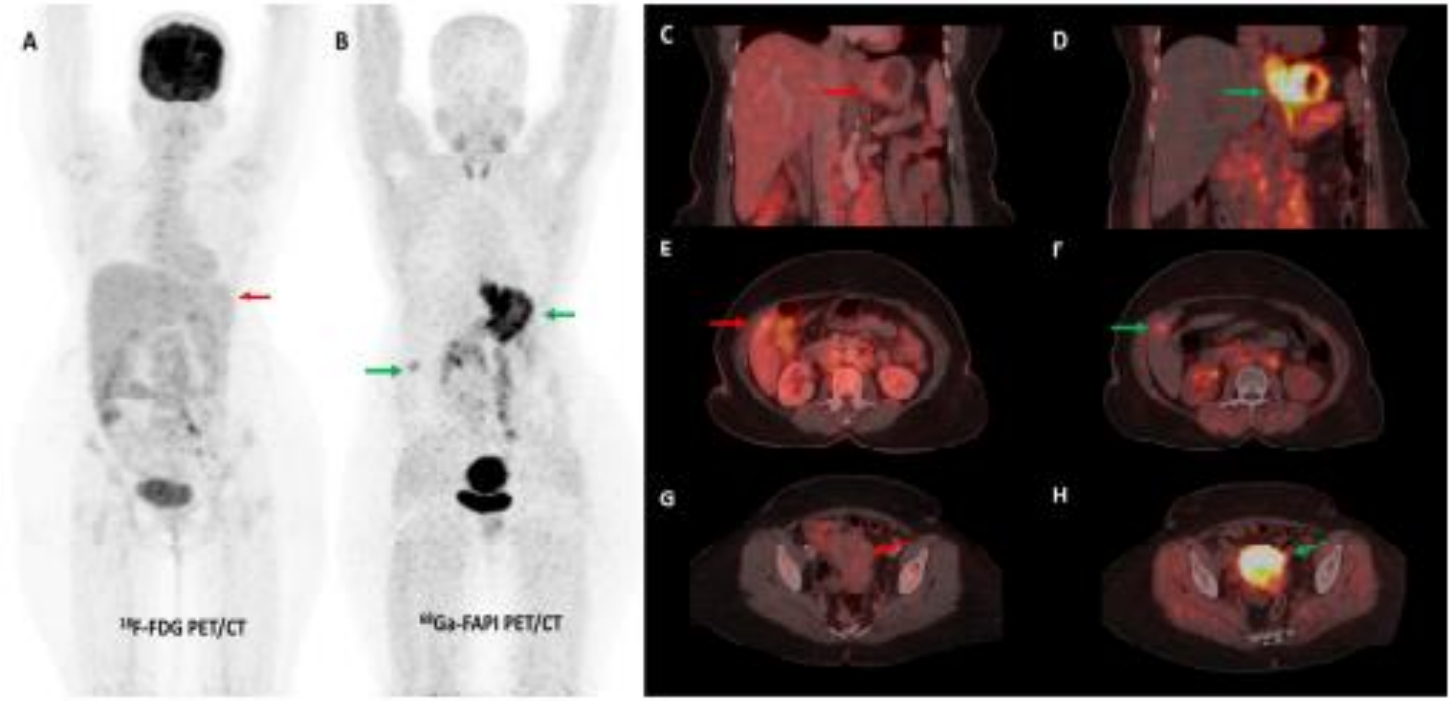


Figure 3. FDG and [^{68}Ga]Ga-FAPI-04 PET/CT images in a 42-year-old woman with biopsy-proven gastric adenocarcinoma. The primary lesion in the stomach showed no abnormal FDG uptake ((**A**,**C**)—red arrows) with intense [^{68}Ga]Ga-FAPI-04 tracer avidity ((**B**,**D**)—green arrows). FAPI PET/CT revealed a tracer avid hypodense lesion in segment V of the liver ((**B**,**F**)—green arrows), which was not picked up on FDG PET/CT ((**E**)—red arrow), leading to upstaging of disease. Additionally, the uterus showed no abnormal FDG uptake ((**G**)—red arrow) but had diffuse intense FAPI uptake ((**H**)—green arrow), which was interpreted as physiologic/benign uptake.

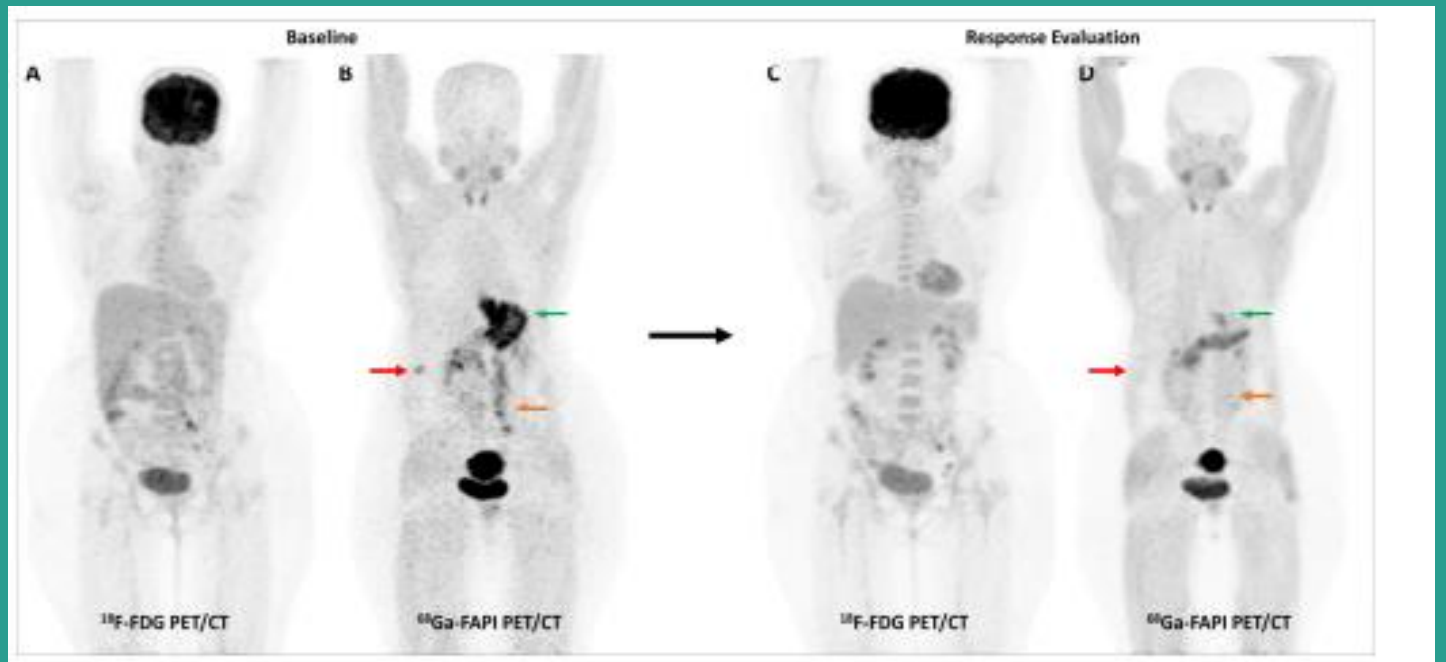


Figure 4. Incremental role of [^{68}Ga]Ga-FAPI-04 PET/CT over FDG PET/CT in a 42-year-old woman with metastatic gastric adenocarcinoma for post-chemotherapy response assessment. Baseline (**A**) and follow-up (**C**) FDG PET/CT scans did not reveal significant abnormal tracer uptake in the primary and metastatic lesions. Baseline [^{68}Ga]Ga-FAPI-04 PET/CT (**B**) showed tracer avid gastric primary (green arrow), abdominal lymph nodes (orange arrow), and solitary liver metastasis (red arrow). Post-chemotherapy [^{68}Ga]Ga-FAPI-04 PET/CT (**D**) demonstrated minimal tracer avidity in the gastric primary (green arrow) with resolution of tracer avidity in the abdominal lymph nodes (orange arrow) and liver lesion (red arrow), suggesting a favorable response to treatment.

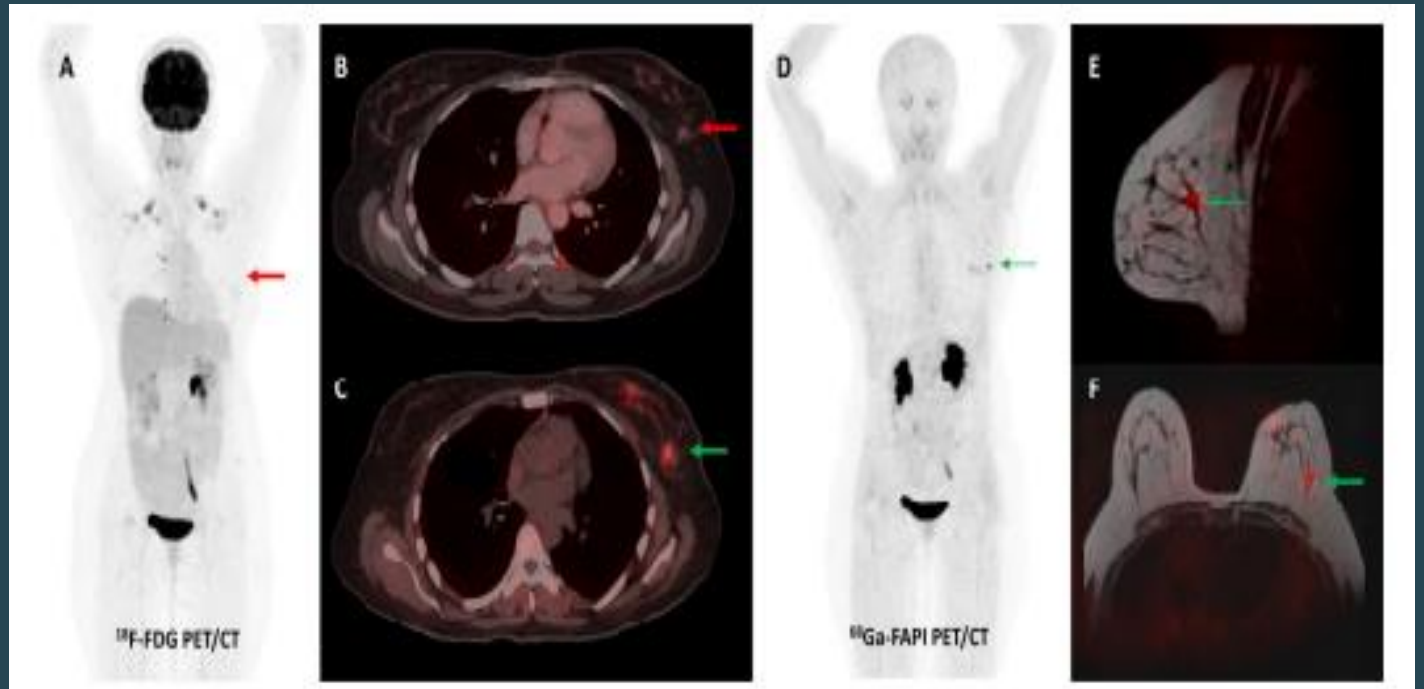


Figure 7. Forty-four-year-old woman, a known case of epithelial ovarian carcinoma post hysterectomy and bilateral salpingo-oophorectomy, underwent FDG and [^{68}Ga]Ga-FAPI-04 PET/CT for restaging. FAPI tracer avid ((**C**,**D**)—green arrows) and non-FDG avid ((**A**,**B**)—red arrows) ill-defined soft tissue density nodule (~1 × 0.8 cm) was noted in the upper outer quadrant of the left breast, which was corroborated on the fused PET-MR mammogram images ((**E**,**F**)—green arrows). Subsequently, an ultrasound-guided left breast biopsy was performed which showed invasive lobular carcinoma with ER/PR positive and HER2 negative receptor status.

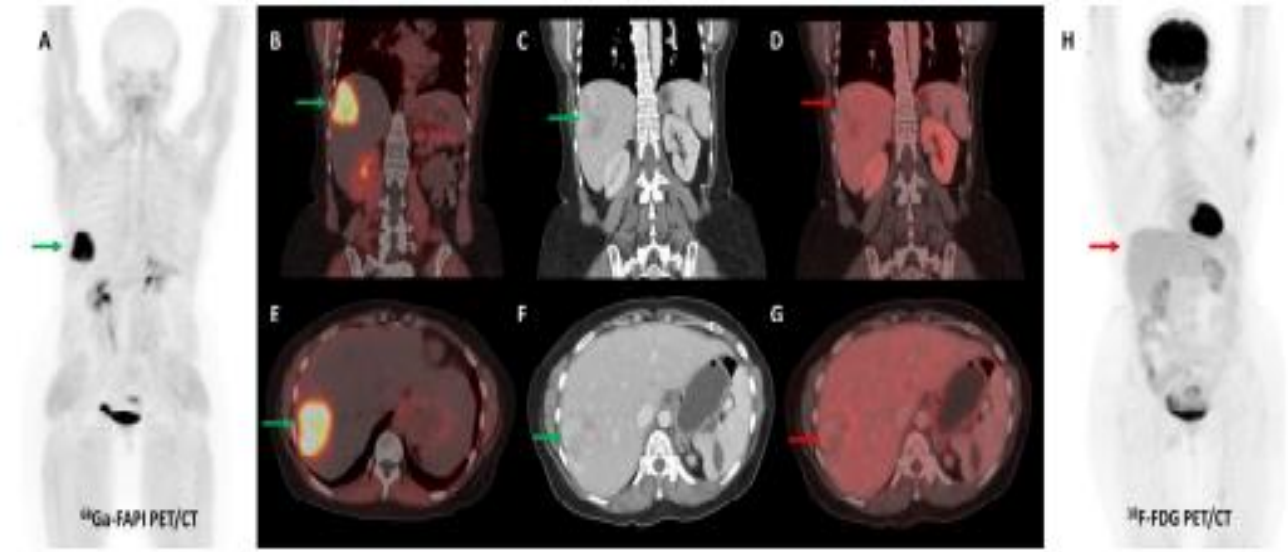


Figure 8. Forty-seven-year-old woman, a known case of ovarian carcinoma (clear cell type) post-surgery and adjuvant platin-based chemotherapy had rising serum CA-125 levels. She underwent [^{68}Ga]Ga-FAPI-04 and FDG PET/CT for restaging, which revealed a heterogeneously enhancing lesion (~5.1 × 3.5 cm) in segment VII of the liver ((**C**,**F**)—green arrows) with intense FAPI uptake ((**A**,**B**,**E**)—green arrows) and no significant FDG uptake ((**D**,**G**,**H**)—red arrows) suggestive of liver metastasis.

➢Pitfalls:

1. wound healing, tissue remodeling, fibrosis, degenerative, arthritic processes, and atherosclerosis
2. Variable physiological uterine tracer uptake
3. Other reported sites of non-tumor-specific uptake include muscles, caring/wounds, oral/nasal mucosa, salivary glands, teeth, and mammary glands
4. Several case reports have highlighted FAPI uptake in benign tumors such as cutaneous fibroma, schwannoma, renal angiomyolipoma, pulmonary solitary fibrous tumor
5. inflammatory conditions such as myocarditis, pneumonitis, pleuritis, appendicitis, colitis, and sclerosing cholangitis
6. Post-chemotherapy, RT, and surgery induced inflammation and fibrotic changes

Heavily reliant on the familiarity of reporting physicians with the above-mentioned pitfalls.

TABLE 1
Non-oncologic and Common Pitfalls Seen with FAP PET

Benign lesions
Focal nodular hyperplasia
Hemorrhoids
Splenic hemangioma
Thyroid adenoma
Fibrotic processes
Cardiac fibrosis
Hepatic fibrosis
Pulmonary fibrosis
Myelofibrosis
Wound healing
Inflammatory
Atherosclerosis/arteritis
Esophagitis
IgG4-related processes
Inflammatory bowel disease
Pancreatitis
Periodontitis
Pneumonia
Tuberculosis
Musculoskeletal lesions
Avascular necrosis
Degenerative changes
Enthesopathy
Exostosis
Fracture
Schmorl's nodes
Arthritis
Physiologic organ uptake
Mammary tissue
Pancreatic
Uterine
Ovaries
Gall bladder

Conclusions and Future Directions

- Preliminary data on FAPI PET/CT remains encouraging, demonstrating utility for a diverse range of oncological and non-oncological indications.
- Nuclear medicine physicians across the globe must shoulder the responsibility to conduct well-structured and focused clinical trials that will help us identify appropriate indications and clinical scenarios for the use of FAP-targeted imaging.
- The goal is not to replace the current standard FDG PET/CT but to understand how the complementary information provided by FAPI PET/CT can be utilized to potentially impact clinical decision-making and management protocols.
- Additionally, the realm of FAP-targeted nuclear theranostics is intriguing and warrants further exploration as it can open up a new avenue for patients who have progressed despite conventional treatment modalities.

Thank for your attention

Questions & answers