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İÇİNDEKİLER

FAP BIOLOGY, TUMOR MICROENVIRONMENT, and FAPI RADIOPHARMACEUTICALS

BÖLÜM 0

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1. Introduction

Fibroblast activation protein (FAP) has gained increasing attention as a key molecular target in oncologic imaging and theranostics due to its prominent expression in cancer-associated fibroblasts (CAFs), a major component of the tumor microenvironment (TME). Unlike conventional imaging approaches that primarily reflect tumor cell metabolism, FAP-targeted imaging provides insight into stromal activity, which plays a pivotal role in tumor progression, invasion, and therapeutic resistance.

The development of radiolabeled fibroblast activation protein inhibitors (FAPIs) has enabled non-invasive visualization of stromal remodeling across a wide spectrum of malignancies. This approach represents a conceptual shift from tumor-centric to microenvironment-centric imaging, with potential implications for both diagnosis and treatment planning.

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2. Biology of Fibroblast Activation Protein (FAP)

2.1 Molecular Structure and Function

FAP is a type II transmembrane serine protease belonging to the dipeptidyl peptidase (DPP) family, sharing structural similarities with DPP-4. It possesses both dipeptidyl peptidase and endopeptidase activity, enabling degradation of extracellular matrix (ECM) components such as collagen and gelatin (Puré & Blomberg, 2018; Calais, 2020). FAP is minimally expressed in normal adult tissues but is highly upregulated in pathological conditions involving tissue remodeling, including cancer, fibrosis, and wound healing (Tillmanns et al., 2015; Levy et al., 2002; Rettig et al., 1992).

2.2 Expression in Cancer

FAP is predominantly expressed in CAFs rather than tumor cells themselves. CAFs contribute to tumor progression through:

- ECM remodeling
- Promotion of angiogenesis
- Immunosuppression
- Facilitation of tumor invasion and metastasis

High FAP expression has been reported in a variety of malignancies, including breast, colorectal, pancreatic, and gastric cancers (Scanlan et al., 1994; Dohi et al., 2009). Importantly, FAP expression often correlates with aggressive tumor biology and poor prognosis (Cohen et al., 2008; Coto-Llerena et al., 2020).

Beyond its mere presence, FAP expression reflects an active and dynamic stromal response that evolves throughout tumor progression. CAFs expressing FAP are involved not only in

structural remodeling but also in biochemical signaling networks that influence tumor behavior. These fibroblasts secrete growth factors, cytokines, and extracellular matrix components, thereby creating a permissive microenvironment for tumor proliferation and dissemination. Importantly, the level and spatial distribution of FAP expression may vary within the same tumor, reflecting intratumoral heterogeneity. This heterogeneity may partially explain variable imaging findings and underscores the importance of interpreting FAPI uptake in the context of tumor biology rather than as a uniform marker of disease burden.

3. Tumor Microenvironment and Role of CAFs

3.1 Composition of the Tumor Microenvironment

The tumor microenvironment is a complex and dynamic ecosystem composed of:

- Cancer cells
- Fibroblasts (CAFs)
- Immune cells
- Endothelial cells
- Extracellular matrix

CAFs are one of the most abundant stromal components and play a central role in shaping tumor behavior (Altmann et al., 2021; Meyet et al., 2020; Lindner et al., 2018).

3.2 Functional Role of CAFs

CAFs are not a homogeneous population; they exhibit functional heterogeneity, including:

- Myofibroblastic CAFs (matrix remodeling)

- Inflammatory CAFs (cytokine secretion)
- Immune-modulatory CAFs

FAP-positive CAFs contribute to:

- Tumor growth via paracrine signaling
- Immune evasion through T-cell suppression
- Increased interstitial pressure, limiting drug delivery

In addition to their structural role, CAFs actively modulate the tumor microenvironment through complex bidirectional interactions with tumor and immune cells. Through secretion of cytokines such as TGF-β and IL-6, CAFs contribute to immune suppression and facilitate tumor immune escape. Furthermore, CAF-mediated extracellular matrix deposition increases tissue stiffness and interstitial pressure, which may impair both drug delivery and immune cell infiltration (Whiteside, 2008; Sahai et al., 2020). This multifaceted role positions CAFs not only as passive structural components but as active regulators of tumor progression, thereby strengthening the rationale for targeting FAP in both imaging and therapeutic applications.

3.3 Clinical Implications

From a clinical perspective, the prominence of CAFs in desmoplastic tumors provides a unique opportunity for stromal-targeted imaging. In malignancies such as pancreatic and gastric cancers, where tumor cell density may be relatively low compared to stromal content, FDG uptake can be heterogeneous or even underestimated. In contrast, FAPI PET/CT may offer a more stable and comprehensive representation of tumor extent by visualizing the surrounding stromal reaction. However, this advantage should be interpreted cautiously, as increased stromal activity does not

necessarily correlate with viable tumor burden, particularly in treated or fibrotic lesions.

4. Development of FAPI Radiopharmaceuticals

4.1 Early Development

The development of FAPI radiopharmaceuticals represents a major milestone in the transition toward microenvironment-targeted imaging. Initial efforts focused on identifying small-molecule inhibitors with high affinity and specificity for fibroblast activation protein, while maintaining favorable pharmacokinetic properties suitable for in vivo imaging.

Early preclinical studies demonstrated that FAP-targeted compounds could achieve rapid tumor accumulation with minimal retention in non-target tissues, thereby enabling high-contrast imaging. These promising findings facilitated rapid clinical translation, largely driven by the pioneering work of Uwe Haberkorn and Clemens Kratochwil, who systematically optimized tracer design and evaluated their clinical applicability.

4.2 Key FAPI Compounds

Several FAPI tracers have been developed, including:

- **68Ga-FAPI-02** (first-generation)
- **68Ga-FAPI-04** (improved tumor retention)
- **68Ga-FAPI-46** (enhanced stability and uptake)

Over time, these tracers have undergone progressive structural optimization aimed at improving tumor retention, binding affinity, pharmacokinetic behavior, and suitability for both diagnostic and therapeutic applications. Early-generation compounds such as

^{68}Ga-FAPI-02 demonstrated promising tumor uptake but relatively rapid washout from tumor tissue, thereby limiting their potential utility for radionuclide therapy.

Subsequent modifications led to the development of ^{68}Ga-FAPI-04 and ^{68}Ga-FAPI-46, which demonstrated improved tumor retention and higher tumor-to-background ratios in clinical studies. These improvements contributed significantly to the broader clinical adoption of FAPI PET/CT across multiple tumor types.

More recently, increasing interest has focused on next-generation tracers such as FAPI-74, which can be labeled with both ^{68}Ga and ^{18}F. In particular, ^{18}F-labeled FAPI compounds may provide practical advantages including centralized large-scale production, wider distribution capability, and potentially improved image resolution. These characteristics may facilitate multicenter standardization and broader clinical implementation.

In parallel, theranostic-oriented FAPI derivatives incorporating DOTA chelators have been developed to enable labeling with therapeutic radionuclides such as ^{177}Lu, ^{90}Y, and ^{225}Ac. Consequently, the evolution of FAPI compounds has expanded their role beyond diagnostic imaging toward integrated theranostic applications. Among these tracers, 68Ga-FAPI-04 and 68Ga-FAPI-46 remain the most widely utilized compounds in current clinical studies (Chandekar et al., 2023). Nevertheless, no universal consensus currently exists regarding the optimal FAPI tracer for routine clinical use. Major FAPI tracers and their principal characteristics are summarized in Table 1.

Table 1. Major FAPI Tracers and Their Characteristics

Tracer	Key Feature	Advantages	Potential Limitation
68Ga-FAPI-02	First-generation FAPI tracer	Initial proof of concept	Rapid tumor washout
68Ga-FAPI-04	Improved retention	High tumor uptake and favorable TBR	Limited therapeutic retention
68Ga-FAPI-46	Increased stability	Enhanced tumor retention and broader clinical use	Optimal indications under investigation
FAPI-74	Dual-label capability (68Ga/18F)	Wider distribution potential	Limited long-term experience
DOTA-containing FAPI derivatives	Theranostic design	Therapeutic radionuclide labeling	Dosimetry challenges

4.3 Pharmacokinetics

FAPI tracers exhibit several advantageous properties:

- Rapid tumor uptake (within minutes)
- Fast blood clearance
- Low physiologic uptake in most organs

These features allow for high tumor-to-background ratios even at early imaging time points. FAPI radiotracers exhibit highly

favorable pharmacokinetic characteristics that distinguish them from conventional PET tracers. Following intravenous administration, these agents demonstrate rapid tumor uptake—often within minutes—combined with fast clearance from the bloodstream. This results in low background activity in most normal tissues, including the brain, liver, and oral cavity (Chen et al., 2020).

The rapid kinetics of FAPI tracers allow imaging at flexible time points, often earlier than conventional FDG PET/CT protocols. This not only improves patient convenience but may also enhance clinical workflow efficiency. However, the relatively fast washout from certain tumor types may limit delayed imaging and has implications for therapeutic applications.

5. Imaging Characteristics of FAPI PET/CT

FAPI PET/CT demonstrates:

- High contrast imaging
- Low background uptake in brain and liver
- Reduced dependence on patient preparation

Unlike FDG, FAPI uptake is not significantly influenced by blood glucose levels, making it more practical in certain clinical settings.

Additionally, FAPI imaging may provide superior visualization in:

- Peritoneal carcinomatosis
- Liver metastases
- Fibrotic tumor components

In addition to its favorable tumor-to-background contrast, FAPI PET/CT offers practical advantages in routine clinical workflows.

The rapid pharmacokinetics of FAPI tracers allow imaging at early time points, often within minutes after injection, without compromising image quality. This feature may improve patient throughput and simplify scheduling compared to FDG PET/CT. Nevertheless, interpretation should consider that high contrast does not inherently imply higher specificity, and imaging findings must always be integrated with clinical and anatomical data.

The low physiologic background activity observed with FAPI tracers may be particularly advantageous in anatomically complex regions or organs with inherently high FDG uptake. For example, low background activity in the brain and liver may facilitate improved visualization of intracranial lesions and hepatic metastases. Similarly, reduced bowel uptake may improve the detection of peritoneal carcinomatosis and abdominal lesions.

Physiologic uptake of FAPI tracers has been reported in several normal tissues and organs, reflecting either constitutive fibroblast activity or physiologic tissue remodeling processes. Mild to moderate physiologic uptake may be observed in the pancreas, uterus, salivary glands, oral mucosa, thyroid, and bone marrow (Table 2). Variable uptake has also been described in sites associated with hormonal activity and tissue repair, including the breasts and endometrium. In addition, physiologic activity may occasionally be observed in healing tissues and degenerative musculoskeletal structures. Familiarity with these normal biodistribution patterns is essential to avoid misinterpretation and reduce false-positive findings during image interpretation (Meyer et al., 2020; Chen et al., 2020).

However, although high tumor-to-background contrast is one of the major strengths of FAPI imaging, increased contrast should not automatically be interpreted as increased specificity. Benign

fibroblast activation associated with inflammation, fibrosis, or treatment-related tissue remodeling may still produce significant uptake and potentially mimic malignant disease.

Table 2. Physiologic Biodistribution of FAPI Tracers

Organ/System	Typical Uptake	Clinical Relevance
Brain	Very low	Improves intracranial lesion conspicuity
Liver	Low	Facilitates liver metastasis detection
Pancreas	Mild	Potential source of physiologic uptake
Salivary glands	Mild	Physiologic background activity
Oral mucosa	Mild–moderate	May mimic pathology
Thyroid	Variable	Requires cautious interpretation
Uterus / Endometrium	Variable	Hormonal influence possible
Bone marrow	Mild	Background activity

6. Comparison with FDG: Biological Perspective

While FDG reflects glucose metabolism, FAPI targets stromal activity. These modalities provide complementary biological information. This distinction is particularly relevant in tumors with

dense stromal components, where FAPI imaging may outperform FDG PET/CT in lesion conspicuity and tumor delineation. Rather than representing competing techniques, FDG and FAPI PET/CT should be viewed as biologically complementary modalities. While FDG reflects tumor metabolism and proliferative activity, FAPI imaging provides insight into stromal remodeling and tumor-host interactions. The integration of these two approaches may offer a more comprehensive characterization of tumor biology, particularly in heterogeneous malignancies. Major biological and practical differences between FDG PET/CT and FAPI PET/CT are summarized in Table 3.

Table 3. Biological Comparison Between FDG PET/CT and FAPI PET/CT

Feature	FDG PET/CT	FAPI PET/CT
Biological target	Glucose metabolism	Fibroblast activation/stromal activity
Tumor information	Cellular metabolism	Tumor microenvironment
Brain background	High	Low
Liver background	Moderate	Low
Inflammatory uptake	Acute inflammation	Chronic inflammation/fibrosis
Patient preparation	Fasting required	Minimal preparation
Potential role	Standard oncologic imaging	Complementary biologic imaging

7. Limitations of FAP-Targeted Imaging (Biological Context)

Despite its promise, FAP expression is not tumor-specific. Increased uptake may occur in:

- Fibrotic diseases
- Chronic inflammation
- Post-surgical healing

This overlap represents a key interpretative challenge (Tillmanns et al., 2015; Levy et al., 2002; Rettig et al., 1992).

A key limitation of FAPI imaging lies in its biological non-specificity. Because FAP expression is associated with fibroblast activation rather than malignancy itself, increased uptake may be observed in a wide range of benign conditions. Growing evidence suggests that radiolabeled FAPI compounds are not inherently more tumor-specific than 18F-FDG, as increased uptake may also occur in a variety of benign inflammatory and fibrotic conditions (Sollini et al., 2021). Consequently, FAPI PET/CT should not be interpreted in isolation but rather in conjunction with clinical findings and other imaging modalities.

In contrast to the predominantly metabolic uptake pattern observed with 18F-FDG in acute inflammation, increased FAPI uptake has also been demonstrated in chronic inflammatory and fibrotic processes, likely related to fibroblast activation and tissue remodeling (Sollini et al., 2021). This phenomenon not only represents a potential interpretative pitfall in oncologic imaging but also highlights the broader biological relevance of FAP expression in non-malignant diseases.

Furthermore, because FAP expression may vary according to tumor stage, stromal composition, and temporal changes within the tumor microenvironment, the diagnostic performance of FAPI PET/CT may also vary during different phases of tumor progression. Therefore, it remains premature to conclude that FAPI imaging universally outperforms ^{18}F-FDG PET/CT across all tumor types and disease stages.

At present, FAPI PET/CT should be viewed not as a replacement for 18F-FDG PET/CT, but rather as a biologically complementary imaging modality that may provide additional insight into stromal remodeling and tumor–microenvironment interactions (Sollini et al., 2021).

The principal strengths and current limitations of FAPI PET/CT are summarized in Table 4.

Table 4. Advantages and Limitations of FAPI PET/CT

Advantages	Limitations
High tumor-to-background contrast	Lack of tumor specificity
Rapid tumor uptake	Inflammatory uptake
Low physiologic brain uptake	Fibrosis/wound healing uptake
Flexible imaging timing	Limited histopathologic validation
Reduced dependence on preparation	Lack of standardized protocols
Theranostic potential	Limited long-term data

8. **FAPI Imaging in Radiotherapy Planning**

FAPI-based imaging has emerged as a promising modality for radiotherapy (RT) planning, particularly in tumors where precise delineation of tumor margins is challenging with conventional imaging techniques. Accurate target volume definition is crucial in RT, as it directly affects treatment efficacy while minimizing radiation-induced toxicity to adjacent healthy tissues. Recent studies have demonstrated that FAPI PET/CT may improve tumor visualization by providing high tumor-to-background ratios (TBRs), thereby facilitating more accurate gross tumor volume (GTV) contouring (Syed et al., 2020; Conen et al., 2020). FAPI-targeted imaging may significantly enhance RT planning accuracy and support more individualized radiation treatment strategies. Nevertheless, further prospective studies with larger patient cohorts are necessary to standardize threshold values, optimize imaging protocols, and validate clinical outcomes. In addition to improved lesion visualization, FAPI PET/CT may reduce interobserver variability in target volume delineation by providing clearer tumor boundaries compared with conventional anatomical imaging alone. This may be particularly relevant in tumors with infiltrative growth patterns or poorly defined margins.

Furthermore, FAPI-based imaging may facilitate dose escalation strategies by improving identification of biologically active tumor subregions while minimizing radiation exposure to surrounding healthy tissues. Another potential advantage is the detection of occult disease not clearly visible on conventional imaging, which may alter radiation field design and overall treatment planning.

Despite these promising findings, the integration of FAPI PET/CT into routine radiotherapy planning remains investigational, and

standardized contouring protocols as well as prospective outcome data are still needed.

9. Theranostic Potential

FAP is not only a promising diagnostic imaging target but also a potential therapeutic target within the tumor microenvironment. The incorporation of DOTA chelators into FAPI molecules enables labeling with diagnostic radionuclides such as 68Ga as well as therapeutic radionuclides including 177Lu, 90Y, and 225Ac, thereby creating opportunities for FAPI-based theranostic applications and personalized treatment strategies across various solid tumors (Sharma et al., 2021).

The growing interest in FAPI theranostics is largely related to the biological characteristics of fibroblast activation protein (FAP), which is highly expressed in cancer-associated fibroblasts (CAFs). Because stromal components may constitute a substantial proportion of total tumor mass in many epithelial malignancies, targeting FAP-positive stromal elements has emerged as a novel therapeutic strategy. In addition to directly irradiating stromal fibroblasts, FAPI-targeted radionuclide therapy may exert a "crossfire effect," delivering radiation to adjacent tumor cells within the tumor microenvironment. Furthermore, disruption of the stromal barrier may potentially improve the penetration and effectiveness of chemotherapy, immunotherapy, and other targeted therapies.

Another important aspect of FAPI-based therapy is its potential immunomodulatory role. FAP-expressing CAFs contribute to the formation of an immunosuppressive tumor microenvironment; therefore, combining FAPI-targeted radionuclide therapy with immunotherapeutic agents may produce synergistic antitumor

effects. These observations have generated increasing interest in integrating FAPI theranostics into multimodal oncologic treatment paradigms.

Early clinical experiences have demonstrated favorable biodistribution characteristics, including low physiologic background uptake and high tumor-to-background contrast, which make FAPI compounds attractive candidates for targeted radionuclide therapy (Lindner et al., 2018; Ballal et al., 2022). Preliminary therapeutic applications have produced encouraging clinical observations in selected patients with advanced malignancies.

Preclinical investigations have further expanded interest in this field. Experimental studies using 225Ac-FAPI compounds demonstrated substantial tumor growth suppression in xenograft models (Watabe et al., 2020). In addition, alternative radionuclide pairs such as 64Cu/67Cu and SPECT-compatible isotopes including 99mTc and 188Re have been explored to improve accessibility and broaden therapeutic applications, particularly in centers where PET infrastructure is limited (Hicks et al., 2021; Lindner et al., 2020).

Despite these promising developments, several important challenges remain. One of the major limitations is the relatively rapid washout of some FAPI tracers from tumor tissue, which may reduce therapeutic radiation delivery and limit overall efficacy (Langbein et al., 2019; Xu et al., 2022; Zhang et al., 2022; Lin et al., 2021)

Since current FAPI tracers exhibit relatively rapid tumor clearance compared with established theranostic agents such as PSMA or somatostatin receptor ligands, radionuclides with shorter physical

half-lives may provide a more favorable pharmacokinetic match for therapeutic applications (Lindner et al., 2019; Lindner et al., 2020). Consequently, ongoing research efforts are focused on developing compounds with prolonged tumor retention through molecular modifications such as dimerization and albumin-binding strategies.

Furthermore, optimal patient selection, treatment timing, dosimetric standardization, and long-term safety profiles have yet to be clearly established. The heterogeneity of FAP expression among different tumor types and disease stages may further influence therapeutic response and clinical applicability (Busek et al., 2018). In addition, most currently available evidence is derived from small retrospective series and early-phase studies, underscoring the need for prospective clinical validation.

Nevertheless, the currently available data suggest that FAPI-targeted radionuclide therapy may become an important component of future theranostic strategies, particularly in tumors with prominent stromal burden. Further prospective studies are required to better define its therapeutic efficacy, safety profile, and long-term clinical impact.

10. Future Perspectives

The rapidly evolving field of FAPI imaging continues to expand beyond early proof-of-concept studies toward broader translational and clinical applications (Sollini et al., 2021). Future developments will likely focus not only on improving diagnostic performance but also on optimizing theranostic strategies, quantitative imaging approaches, and integration into precision oncology frameworks.

One of the major areas of ongoing research is the development of novel FAPI radiopharmaceuticals with improved pharmacokinetic

properties. Molecular modifications aimed at prolonging tumor retention, enhancing tumor uptake, and improving therapeutic efficacy are actively being investigated. In particular, dimerization strategies, albumin-binding approaches, and alternative chelator designs may improve both imaging performance and radionuclide therapy applications.

In addition, increasing interest has emerged regarding ^{18}F-labeled FAPI tracers, including FAPI-74, which may provide several practical advantages compared with ^{68}Ga-based compounds. The longer half-life of ^{18}F enables centralized production and broader distribution, potentially facilitating multicenter studies and wider clinical implementation. Improved image resolution and higher production capacity may further enhance clinical applicability in high-volume imaging centers.

Another important future direction involves the integration of FAPI PET/CT into precision oncology. Because FAPI imaging reflects stromal activation and tumor microenvironment remodeling rather than solely tumor metabolism, it may provide complementary biological information that could influence individualized treatment strategies. Potential applications include patient selection for stromal-targeted therapies, treatment response assessment, and evaluation of tumor heterogeneity.

Because FAP expression may vary during different stages of tumor progression, the role of FAPI imaging may also evolve according to tumor biology and temporal stromal remodeling (Henry et al., 2007). This dynamic behavior may partially explain variability in imaging findings across different tumor stages and clinical settings, while also highlighting the potential value of longitudinal FAPI imaging approaches.

In the future, combined evaluation of metabolic, stromal, and molecular imaging data may allow a more comprehensive characterization of tumor biology than any single imaging modality alone.

Artificial intelligence and radiomics-based approaches may also significantly expand the clinical utility of FAPI imaging. Advanced quantitative analysis may enable extraction of high-dimensional imaging features that are not visually appreciable, potentially improving lesion characterization, prognostic stratification, and prediction of therapeutic response. However, these technologies require robust external validation and standardized imaging protocols before routine clinical implementation.

Future prospective multicenter studies, including head-to-head comparisons with 18F-FDG PET/CT and histopathological validation, will be essential to define the precise clinical role of FAPI imaging across different tumor types and disease stages (Sollini et al., 2021). Standardization of acquisition protocols, interpretation criteria, quantitative parameters, and reporting systems will likely become increasingly important as clinical utilization expands.

Ultimately, the long-term success of FAPI imaging will depend not only on diagnostic performance but also on its ability to provide clinically actionable information beyond existing imaging modalities while maintaining reproducibility, accessibility, and cost-effectiveness.

11. Conclusion

FAP-targeted imaging represents a paradigm shift from tumor-centered imaging toward microenvironment-focused oncology. By visualizing stromal activity and fibroblast activation, FAPI PET/CT provides biological information that complements conventional metabolic imaging with ^{18}F-FDG PET/CT. This distinction may be particularly relevant in tumors characterized by dense stromal architecture, heterogeneous metabolic activity, or complex treatment-related changes.

Beyond diagnostic imaging, the emergence of FAPI-based theranostic approaches further highlights the translational potential of targeting the tumor microenvironment. Early experiences with FAPI-directed radionuclide therapy have demonstrated encouraging feasibility and safety profiles, although important challenges regarding tumor retention, dosimetry, and patient selection remain unresolved.

Despite its considerable promise, several limitations continue to restrict widespread clinical implementation. Lack of tumor specificity, variability in FAP expression, limited histopathological validation, and the absence of standardized imaging protocols underscore the need for cautious interpretation and further prospective validation. As understanding of the tumor microenvironment continues to evolve, FAPI-based imaging and theranostics may play an increasingly important role in the future landscape of precision oncology.

Current evidence remains encouraging but still preliminary, underscoring the need for cautious interpretation and robust prospective validation before widespread routine implementation (Sollini et al., 2021) .

Future integration of FAPI imaging with quantitative imaging biomarkers, radiomics, artificial intelligence, and multimodal treatment strategies may further expand its clinical relevance within precision oncology. Nevertheless, the ultimate role of FAPI PET/CT will depend on its ability to provide clinically actionable information beyond existing imaging approaches while maintaining reproducibility, accessibility, and cost-effectiveness.

At present, FAPI PET/CT should be viewed not as a replacement for established imaging modalities, but rather as a biologically complementary technique and a supplement to 18F-FDG PET/CT (Sollini et al., 2021).

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BÖLÜM 6

FAPI PET/CT IN HEADAND NECK MALIGNANCIES AND THORACIC MALIGNANCIES

Buket EREN SARIBAŞ[1]

Introduction

Fibroblast activation protein (FAP) is a cell membrane-bound serine peptidase that is highly expressed in cancer-associated fibroblasts within the stroma of various cancer types (Sharma et al., 2021). The preclinical and clinical results of recently developed quinoline-based PET tracers that function as fibroblast activation protein inhibitors (FAPI) are promising (Kratochwil et al., 2019). These novel FAP-targeted tracers, labeled with Ga-68, have demonstrated tumor-to-background contrast ratios that are comparable to or higher than those obtained with 18F-FDG PET/CT (Giesel et al., 2019). This tracer has increasingly been utilized in the management of cancer patients for whom conventional imaging modalities are insufficient.

Key Advantages of Ga-68 FAPI PET/CT Imaging

- Low physiological uptake (particularly in the brain and liver)
- High tumor-to-background ratio (TBR) (Chen et al., 2020)
- Rapid kinetics, allowing early image acquisition (Ballal et al., 2021)
- No requirement for fasting

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- Lower dependence on inflammatory activity compared with conventional metabolic imaging modalities

Head and neck cancers and thoracic malignancies are ideal targets for FAPI imaging due to their prominent desmoplastic reaction. In this chapter, the role of FAPI PET/CT in head and neck and thoracic malignancies is discussed in light of the current literature.

1. Ga-68 FAPI PET/CT in Head and Neck Cancers

Head and neck cancers (HNCs) encompass a group of tumors originating from the oral cavity, including cancers of the lip, tongue, buccal region, palate, salivary glands, pharynx, larynx, and thyroid. Squamous cell carcinoma constitutes the predominant histological subtype among malignancies arising in the head and neck region. Although squamous cell carcinoma accounts for the majority of head and neck malignancies, less common histological subtypes include adenocarcinomas, adenoid cystic carcinomas, thyroid carcinomas, and sarcomas (Chow, 2020). Globally, head and neck cancers represent the seventh most common malignancy. Their development is closely linked to tobacco and alcohol exposure, as well as infection with oncogenic viruses, particularly HPV and EBV (Mody et al., 2021).

Head and neck cancers are malignancies that are relatively difficult to evaluate due to their localization within a small anatomical region and their close proximity to other adjacent structures. In addition, physiological areas of FDG uptake in the head and neck region (e.g., brain, salivary glands, etc.), as well as infectious/inflammatory FDG uptake and post-surgical or post-radiotherapy FDG uptake, may lead to false-positive findings and adversely affect the diagnostic sensitivity of FDG PET/CT in head

and neck cancers (Purohit et al., 2014). Owing to its high tumor-to-background ratio (TBR) and enhanced image contrast, Ga-68 FAPI PET/CT facilitates lesion visualization in anatomically intricate regions such as the head and neck and may provide advantages over FDG PET/CT. A meta-analysis by Chandekar and colleagues reported that Ga-68 FAPI PET/CT exhibits greater sensitivity than FDG PET/CT for detecting both primary tumors and recurrent disease in patients with head and neck cancers (Chandekar et al., 2023).

1.1. Primary Tumor Imaging

1.1.1. Head and Neck Squamous Cell Carcinomas

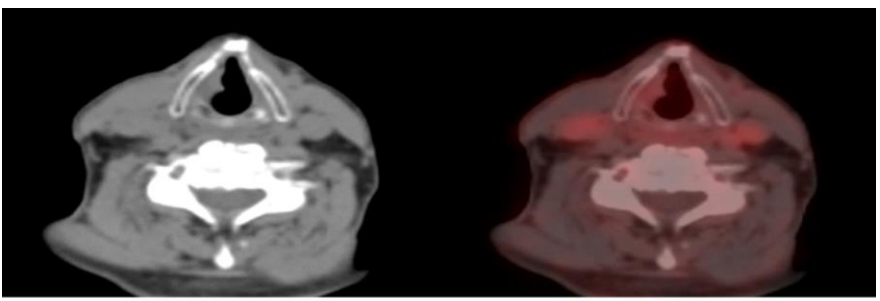
Head and neck squamous cell carcinomas(HNSCC), which constitute the largest subgroup of head and neck cancers (HNCs), are tumors arising from the squamous epithelium lining the oral cavity and typically present with a primary tumor accompanied by nodal metastases (Solomon et al., 2018). The most common site of distant metastasis from HNSCC is the lung. Bone and liver metastases follow in frequency (de Bree et al., 2023). Treatment of HNSCC consists of surgery, anticancer drug therapy, and radiotherapy (Kitamura et al., 2020).

FDG PET/CT has long been used as a successful imaging modality in the staging, treatment response assessment, and follow-up of HNSCC. However, in recent years, the role and advantages of Ga-68 FAPI PET imaging in HNSCC have been increasingly investigated.

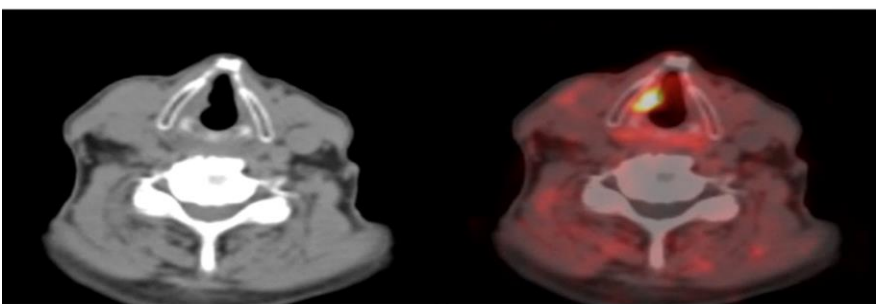
A study by Kalender et al, demonstrated that Ga-68 FAPI PET/CT exhibits marked uptake in both primary tumors and regional lymph nodes in patients with laryngeal squamous cell

carcinoma (LSCC), suggesting its potential to enhance diagnostic sensitivity in staging laryngeal cancer when compared with FDG PET/CT (Kalender et al., 2026). Kuyumcu et al, emphasized the effectiveness of FAPI PET in detecting primary tumors in HNSCC and also demonstrated that FAPI PET shows high sensitivity in identifying metastatic lymph nodes, with markedly higher specificity compared with FDG PET (Kuyumcu et al., 2025). In the study by Jiang et al, it was shown that Ga-68 FAPI PET demonstrates high sensitivity in the detection of primary lesions in HNSCC and has higher specificity and accuracy compared with FDG PET in nodal staging (Jiang et al., 2023). In addition, it wasfound to be more successful than FDG PET in the detection of distant metastases, and it also has potential for use in treatment response assessment.

Figure 1. A 69-year-old male patient was diagnosed with glotticlaryngeal squamous cell carcinoma. While the primary lesion in the rightglottic region demonstrated low 18 F-FDG uptake (SUVmax: 2.2), it exhibitedsignificantly



^{18}F-FDG PET/CT (axial CT and fusion images)



^{68}Ga-FAPI PET/CT (axial CT and fusion images)

increased uptake of 68 Ga-FAPI (SUVmax: 13.9), which is ofparticular note.

1.1.2. Adenocarcinomas and Adenoid Cystic Carcinomas

Head and neck adenocarcinomas are malignant tumors originating from the glandular epithelium in the head and neck region. These tumors most frequently develop in the salivary glands, sinonasal cavity, and mucosal glands. They include subtypes such as adenoid cystic carcinoma (ACC), mucoepidermoid carcinoma, salivary duct carcinoma and sinonasal adenocarcinoma.

In head and neck adenocarcinomas -particularly adenoid cystic carcinoma- Ga-68 FAPI PET/CT has emerged as an important imaging modality due to the dense stromal component and the FAP-rich cancer-associated fibroblast (CAF) microenvironment. Studies in the literature have reported high and specific FAPI uptake in both primary and metastatic adenoid cystic carcinomas, with improved lesion delineation owing to a high TBR (Röhrich et al., 2021).

In addition, case reports in patients with ACC and hidradenocarcinoma have demonstrated significantly higher FAPI uptake in both primary tumors and metastatic lesions compared with FDG, suggesting that FAPI PET/CT may provide superior tumor-to-background contrast relative to FDG PET/CT, particularly in the evaluation of small lesions (Civan et al., 2023; Ding et al., 2024).

1.1.3. Thyroid Cancers

The majority of thyroid cancers originate from thyroid follicular cells, while a smaller proportion arises from parafollicular cells. Treatment is generally surgical, followed by

radioactive iodine ablation. Differentiated thyroid cancers typically show high radioiodine uptake and low FDG uptake; therefore, staging and follow-up are not usually performed with FDG PET/CT. However, when thyroid cancer undergoes dedifferentiation, radioiodine uptake decreases and FDG uptake increases. For this reason, FDG PET/CT is used to detect tumor recurrence and metastases in dedifferentiated thyroid cancers. Nevertheless, the sensitivity of FDG PET/CT ranges between 68.8% and 82%. This limitation is mainly attributed to the complex anatomy of the head and neck region, as well as non-malignant uptake related to physiological, infectious, and inflammatory processes. Fu et al, compared FAPI PET/CT and FDG PET/CT in patients with metastatic differentiated thyroid cancer (DTC) of various histologies and found that FAPI uptake was higher than FDG uptake in most metastatic DTC lesions (Fu et al., 2022). Sayıner et al, in a cohort of patients with recurrent papillary thyroid carcinoma (PTC), demonstrated that FAPI PET/CT detected more metastatic foci than FDG PET/CT (86.2% vs. 72.4%) and that when both imaging modalities were used together, the detection rate increased to 93.1% (Sayıner et al., 2023). Similar studies and case reports are also available in the literature (Guglielmo et al., 2024).

1.1.4. Head and Neck Cancers of Unknown Primary

Head and neck cancers of unknown primary (HNCUP) refer to metastatic involvement of lymph nodes in the head and neck area in cases where the primary tumor cannot be identified (Grau et al., 2000). Although FDG PET/CT is currently used for the detection of the primary lesion, it may miss small lesions due to physiological and non-malignant uptake as well as partial volume effects. Therefore, FAPI, which targets cancer-associated

fibroblasts (CAFs) within the tumor stroma, has been investigated for primary tumor detection in HNCUP.

In a prospective study by Gu et al, including 91 patients with HNCUP, FAPI demonstrated a higher detection rate for the primary site compared with FDG, as well as higher sensitivity, positive predictive value, and accuracy (Gu et al., 2024). In another study conducted by Gu et al, involving 18 patients with negative FDG PET results, moderate-to-intense FAPI uptake was observed at the primary lesion, along with a high tumor-to-contralateral ratio (Gu et al., 2022).

1.2. Nodal and Distant Metastases

Accurate nodal and distant metastasis staging in head and neck malignancies is of fundamental importance for determining treatment strategies and predicting prognosis. In particular, cervical lymph node metastases indicate locoregional disease spread, whereas the presence of distant metastases is generally associated with advanced-stage disease and leads to changes in therapeutic management. Although FDG PET/CT is widely used in the staging of head and neck cancers, false-positive findings related to inflammation and physiological glucose metabolism may create diagnostic challenges, particularly within the complex anatomical structures of the head and neck region. Therefore, PET imaging studies using FAPI have gained increasing attention in recent years. In particular, its low physiological uptake in the brain, muscles, salivary glands, and inflammatory tissues provides a significant advantage by improving lesion contrast in the head and neck region and enhancing the assessment of metastatic disease.

Studies in the literature indicate that FAPI PET/CT yields highly promising results in the detection of cervical lymph node metastases. It has been reported that, particularly in cases where

inflammatory lymph nodes may lead to false-positive findings on FDG PET/CT, FAPI PET may provide higher specificity (Kuyumcu et al., 2025). In a study comparing the staging potential of FAPI PET/CT with FDG PET/CT in patients with oral SCC, FAPI PET demonstrated a performance comparable to FDG PET in the detection of primary lesions, while showing significantly higher specificity for lymph node metastasis detection (Chen et al., 2022). In addition, there are studies demonstrating that delayed imaging with FAPI PET/CT increases sensitivity in the detection of cervical lymph node metastases (Jiang et al., 2025). However, some studies have also reported that FAPI PET/CT and FDG PET/CT have comparable sensitivity and specificity (Promteangtrong et al., 2022).

In addition to nodal staging, FAPI PET/CT also yields remarkable findings in the evaluation of distant metastases. Its ability to provide high-contrast imaging in bone metastases is considered a significant advantage, and it has been reported that FAPI PET/CT is superior to FDG PET/CT in the detection of bone metastases (Zheng et al., 2022). There are studies demonstrating that FAPI PET/CT performs better than FDG PET/CT in identifying distant metastatic lesions, particularly in the bones and lungs (Zheng et al., 2022; Jiang et al., 2023). Meta-analyses have emphasized that FAPI PET/CT can achieve diagnostic performance comparable to, or in some cases superior to, FDG PET/CT in detecting both nodal and distant metastatic lesions, and that it may reduce false-positive rates due to its low inflammatory background uptake.

In conclusion, FAPI PET/CT emerges as a promising molecular imaging modality for the evaluation of both nodal and distant metastases in head and neck cancers. Due to its low physiological background activity, high tumor contrast, and

relatively reduced susceptibility to inflammatory changes, it may provide significant advantages, particularly in the assessment of cervical lymph node metastases and bone metastases. However, most of the existing studies are retrospective in design and include limited patient cohorts. Therefore, larger-scale, prospective, and multicenter studies are needed to establish the true clinical value of FAPI PET/CT in nodal and distant metastatic staging of head and neck malignancies. In clinical practice, the most rational approach appears to be the adoption of a hybrid strategy, particularly in equivocal cases, in which findings identified on FDG PET/CT are confirmed using FAPI PET/CT.

1.3. Radiotherapy Planning

In head and neck cancers, accurate delineation of tumor boundaries in radiotherapy planning is of critical importance due to the complex anatomy of the region and the close proximity of critical organs. FAP-targeted FAPI PET/CT (particularly Ga-68 and experimental Ga-86 derivatives) enables imaging of the tumor stroma and provideslow background activity along with a high TBR; thus, it may contribute to more precise delineation of the gross tumor volume (GTV) and reduce potential geographic misses (de Rigger et al., 2025; Shagera et al., 2026). Studies have shown that FAPI PET/CT can improve target volume definition in radiotherapy planning and, in some cases, may lead to modifications in the radiotherapy plan (Shagera et al., 2026). However, larger and prospective studies are needed to confirm the clinical utility of Ga-labeled FAPI PET/CT.

1.4. Future Perspectives

In head and neck malignancies, FAPI PET/CT has the potential to play an important role in both diagnostic imaging and

theranostic applications in the future, owing to its innovative approach targeting the tumor stroma. Studies published in the current literature suggest that FAPI PET, due to its low physiological background activity and high tumor-to-background contrast, may provide additional advantages over FDG PET/CT, particularly in the detection of primary tumor extension, recurrences and distant metastases. Furthermore, FAPI-based imaging has been reported to contribute to more accurate delineation of radiotherapy target volumes, adaptive radiotherapy strategies, and the assessment of treatment response. Recent theranostic-focused studies have demonstrated that FAPI-targeted radioligand therapies may represent a promising therapeutic option for advanced-stage or treatment-resistant head and neck tumors. For instance, Ballal et al, conducted a treatment study using ^{177}Lu-DOTAGA.(SA.FAPI)$_2$, a compound structurally similar to FAP ligands, in 15 patients with differentiated thyroid cancer who were refractory to radioactive iodine therapy and had progressed under sorafenib/lenvatinib treatment (Ballal et al., 2022A). The authors reported a significant reduction in serum thyroglobulin (Tg) levels in these patients. Although no complete molecular response was observed, partial responses and stable disease were achieved. In addition, this radiopharmaceutical demonstrated a meaningful improvement in quality of life in a patient with medullary thyroid carcinoma (Ballal et al., 2022B). In the literature, studies and case reports involving agents such as ^{177}Lu-EB-FAPI and ^{177}Lu-FAPI-46 have also been reported, generally resulting in partial responses or stable disease rather than complete remission (Fu et al., 2023; Fu et al., 2022; Assadi et al., 2021; Fu et al., 2022). Collectively, these studies and case reports increase the promise that FAPI-targeted radioligand therapy may become a potent treatment option in therapy-refractory head and neck tumors in the future. However,

since most available data are based on small patient cohorts and early-phase studies, larger-scale, prospective, and multicenter trials are required to define its definitive role in routine clinical practice.

2. Ga-68 FAPI PET/CT in Thoracic Malignancies

Thoracic malignancies comprise a heterogeneous group of tumors originating from the lungs, pleura, mediastinum, and chest wall within the thoracic cavity. The most common entities within this group include lung cancers, pleural malignant mesothelioma, mediastinal tumors (e.g., thymic epithelial tumors, germ cell tumors, and lymphoproliferative disorders), esophageal cancer, and primary sarcomas arising from the chest wall (Buchalet&Durdux, 2023). In the diagnostic workup, thoracic computed tomography (CT) is generally used as the first-line imaging modality, while PET/CT provides significant additional value for the assessment of metabolic activity and the detection of distant metastases (Detterbeck et al., 2013). However, the diagnostic utility of FDG PET/CT may be limited by physiological and non-malignant tracer uptake, as well as by high background activity. In recent years, fibroblast activation protein inhibitor (FAPI)-based imaging modalities have demonstrated remarkable diagnostic potential in thoracic malignancies.

2.1. Primary Tumor Imaging

2.1.1. Lung Cancer

Lung cancer (LC) ranks among the primary causes of cancer-associated deaths globally, affecting both male and female populations. Around 85% of all lung cancer cases are categorized as non-small cell lung cancer (NSCLC), whereas small cell lung carcinoma (SCLC) accounts for approximately 15% of cases. Less

common types include neuroendocrine tumors (NETs) and other histological subtypes.

The principal histological subtypes of NSCLC are adenocarcinoma, squamous cell carcinoma and large cell carcinoma. Adenocarcinoma is the most common subtype of NSCLC, exhibits a weaker association with smoking than squamous cell carcinoma and is more frequently observed in women. Primary lesions are predominantly located in the peripheral regions of the lungs. Squamous cell carcinoma, in contrast, is strongly associated with tobacco use and is typically centrally located. Large cell carcinomas are poorly differentiated malignant epithelial tumors and generally demonstrate aggressive clinical behavior. Small cell lung carcinoma (SCLC) is a highly aggressive tumor characterized by a high proliferation rate and a marked tendency for early metastatic spread.

Although FDG PET/CT is widely used in staging and treatment monitoring of lung cancer, FDG affinity varies according to histological subtypes. It is well recognized that FDG uptake is not significantly high in certain histological subtypes, particularly adenocarcinoma and neuroendocrine tumors (Novruzov et al., 2022; Ambrosini et al., 2012). In these subtypes with relatively low FDG affinity, false-negative results may occur. Table 1 presents the FDG affinities of histological subtypes of lung cancer; the data in the table have been summarized based on generally accepted FDG metabolic patterns in the oncology, nuclear medicine and PET/CT literature, as well as our own clinical experience.

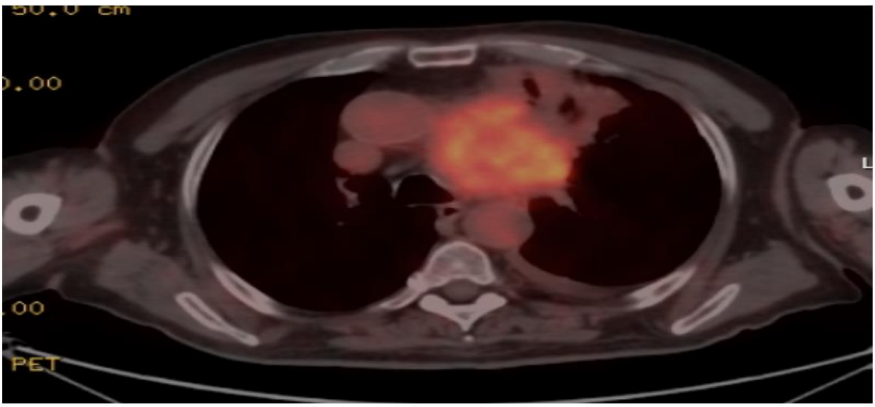
Table 1. FDG Affinities of Histological Subtypes of Lung Cancer		
Histological subtype	**FDG affinity**	**Note**
Adenocarcinoma	Moderate to high	Variable according to subtype
Squamous Cell Carcinoma (SCC)	High	Generally demonstrates more intense FDG uptake than adenocarcinoma
Large Cell Carcinoma	High	Marked uptake due to aggressive biology
Small Cell Lung Cancer (SCLC)	Very high	Rapid proliferation, high metabolic activity
Pulmonary Neuroendocrine Tumors	Moderate to low	Lower uptake in low-grade neuroendocrine tumors

As can be seen from the table, the variable FDG uptake observed particularly in adenocarcinomas and neuroendocrine tumors may create challenges in disease staging and in monitoring treatment response using FDG PET in patients with these diagnoses. Therefore, FAPI PET/CT imaging is being increasingly investigated, especially in patients with NSCLC, including those with adenocarcinoma and neuroendocrine tumors.

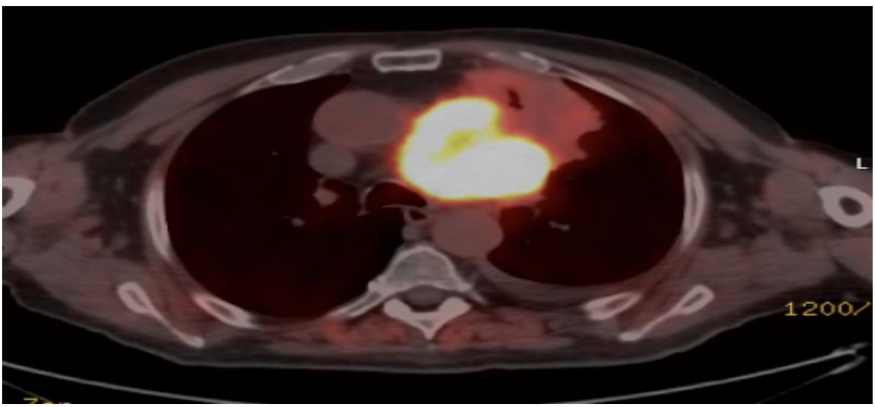
In a study including 68 patients with pathologically confirmed lung cancer in which FAPI PET/CT was compared with FDG PET/CT, FAPI PET/CT demonstrated higher sensitivity, specificity, accuracy, and negative predictive value. No significant difference was observed between the two imaging modalities in terms of positive predictive value. As a result of this study, Wei et al concluded that FAPI PET/CT may be superior to FDG PET/CT for lesion detection in patients with lung cancer (Wei et al., 2023). Zanoni et al, in a study including 50 patients, reported that in patients with lung cancer, FAPI PET/CT demonstrated similar or higher sensitivity compared to FDG PET/CT for primary tumor

detection (T staging) and a higher accuracy (92% vs. 80%) (Zanoni et al., 2024). However, they ultimately emphasized that rather than a marked difference between the two imaging modalities in T staging, there was only a slight superiority of FAPI. Zhou et al, conducted another study in patients with NSCLC and compared the diagnostic performance of FAPI PET/CT in clinical staging with FDG PET/CT (Zhou et al., 2022). They demonstrated that FAPI PET/CT provided higher tumor-to-background contrast, particularly in delineating the primary tumor (T stage), thereby improving staging accuracy. In addition to these findings, there are also several studies suggesting that FAPI PET/CT does not show a clear superiority over FDG PET/CT in primary tumor imaging. Wu et al,reported that FAPI uptake in normal lung tissue was similarly low to FDG, and that there was no significant difference between the two radiopharmaceuticals in terms of SUVmax and TBR values (Wu et al., 2022). In this context, it may be stated that neither imaging modality demonstrates a clear superiority over the other in detecting lung lesions. Similarly, Can et al showed that there was no significant difference in SUVmax and TBR values in primary lesions of patients with NSCLC (Can et al., 2022). In conclusion, considering that there are studies demonstrating both the superiority of FAPI PET/CT over FDG PET/CT in detecting primary lung lesions and studies showing comparable results between the two modalities, FAPI PET/CT may be used in certain cases to improve diagnostic accuracy and sensitivity; however, it has not replaced FDG PET/CT.

Figure 2. A 66-year-old male patient diagnosed with lung adenocarcinoma. In the primary lesion located in the left lung paramediastinal region, markedly higher uptake is observed on Ga-68 FAPI (SUVmax: 33.8) compared to F-18 FDG (SUVmax: 12.5).



F-18 FDG PET/CT (axial fusion images)



Ga-68 FAPI PET/CT (axial fusion images)

2.1.2. Malignant Mesothelioma

Malignant pleural mesothelioma (MPM) is an aggressive thoracic malignancy arising from mesothelial cells, characterized by a strong tendency for local invasion and a poor prognosis. In the tumor biology of this disease, a prominent desmoplastic stromal

reaction and the significant role of cancer-associated fibroblasts are well recognized. The high expression of FAP due to the dense stromal composition of mesothelioma has rendered the use of FAPI-based imaging agents biologically meaningful in this tumor. Considering the limitations of conventional imaging methods in mesothelioma due to its diffuse pleural involvement pattern and complex anatomical spread, Ga-68 FAPI PET/CT is thought to provide additional value. Although the current literature on the use of FAPI PET/CT in mesothelioma is limited, the early published data are promising.Güzel et al,included 21 patients with malignant mesothelioma, 17 of whom had pleural mesothelioma, and reported that FAPI PET/CT demonstrated significantly higher SUVmax, TBR, and volumetric parameters in primary tumors and metastatic lesions compared to FDG PET/CT (Güzel et al., 2023). Kessler et al,showed that in patients with malignant mesothelioma, FAPI PET/CT and FDG PET/CT had approximately comparable sensitivity; however, FAPI PET/CT demonstrated significantly higher specificity and positive predictive value compared to FDG PET/CT (Kessler et al., 2024). In addition, another study reported that metabolic tumor volume (MTV) assessed by FAPI PET/CT in patients with malignant pleural mesothelioma was an independent risk factor, suggesting that FAPI PET/CT may provide not only diagnostic but also prognostic information (Kessler at al., 2026). When the current literature is evaluated, Ga-68 FAPI PET/CT appears to be a promising imaging modality in malignant pleural mesothelioma, capable of providing high tumor contrast, depicting tumor spread in detail, and laying the groundwork for potential theranostic applications. However, the current level of evidence is limited, and prospective and comparative studies in larger patient cohorts are needed to clearly demonstrate the superiority of this method over FDG PET/CT.

2.1.3. Thymic Epithelial Tumors

Thymic epithelial tumors comprise a heterogeneous group of neoplasms that include thymomas and thymic carcinomas. Compared to thymomas, thymic carcinomas exhibit more aggressive biological behavior, with pronounced invasive characteristics and a higher metastatic potential. Histopathologically, a dense stromal component, desmoplastic reaction, and fibroblast activation within the tumor microenvironment play important roles in the biology of both thymomas and thymic carcinomas. For this reason, FAP-targeted molecular imaging approaches have attracted attention as a novel diagnostic strategy in thymic epithelial tumors. In particular, given the physiological FDG uptake in the mediastinal region due to the heart, great vessels, and thymic tissue, FAPI PET/CT is considered to have potential advantages in the evaluation of anterior mediastinal tumors. However, the literature on these malignancies remains very limited. In a prospective study conducted by Shen et al., it was reported that FAPI PET/CT demonstrated superior performance compared to FDG PET/CT in thymic epithelial tumors with regard to histological classification, staging and assessment of metastatic spread. In particular, the high FAPI uptake observed in thymic carcinomas suggests that this method is a promising molecular imaging modality capable of reflecting tumor stroma and biological aggressiveness (Shen et al.,2023). There are several case reports describing intense FAPI uptake in primary lesions in patients with thymic carcinoma and thymoma, and indicating that FAPI PET/CT shows higher TBR compared to FDG PET/CT (Yang et al., 2021; Dahlke at al., 2025). In addition, a case report has also described lower uptake on FAPI PET/CT compared to FDG PET/CT in a patient with thymoma (Kepenek et al., 2023). As can be understood, the current literature is limited to a small number of studies and prospective studies in larger patient cohorts are needed.

2.1.4. Other Thoracic Malignancies

Although the current literature regarding the diagnostic and prognostic role of Ga-68 FAPI PET/CT in other thoracic malignancies is limited, promising findings have been reported, particularly in esophageal malignancies and rare thoracic tumors. Liu et al., in their study investigating the clinical value of FAPI PET/CT in the initial staging of patients with esophageal cancer, reported that all primary lesions in the 44 included patients demonstrated increased Ga-68 FAPI uptake, and that lymph node metastases were successfully detected (Liu et al., 2023). In another study, it was demonstrated that semi-quantitative parameters derived from Ga-68 FAPI PET/CT may have prognostic value in patients with esophageal squamous cell carcinoma who had received chemoradiotherapy (Zhao et al., 2023).

In the literature, there are also case reports involving various hematological and mesenchymal thoracic malignancies. In a case report of a patient with a mass in the anterior mediastinum diagnosed as diffuse large B-cell lymphoma (DLBCL), it was reported that the mediastinal mass demonstrated prominent Ga-68 FAPI uptake (Yang et al., 2022). Similarly, in another case report of a patient with primary pulmonary mucosa-associated lymphoid tissue (MALT) lymphoma, it was reported that FAPI PET/CT showed higher uptake in the pulmonary lesion compared to FDG PET/CT (wang et al., 2025). On the other hand, in a patient with pleural spindle cell sarcoma, it was reported that Ga-68 FAPI and FDG uptake in the pleural lesions were at similar levels (Cui et al., 2024).

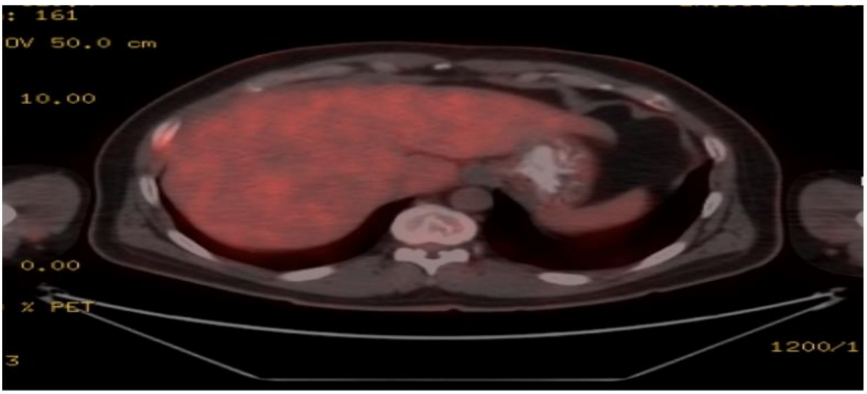
Taken together, these data suggest that Ga-68 FAPI PET/CT may provide potential diagnostic and prognostic contributions across various thoracic malignancies; however, the

current literature is largely composed of case reports and limited patient series. Therefore, larger-scale prospective studies are needed to further define the clinical utility of this imaging modality.

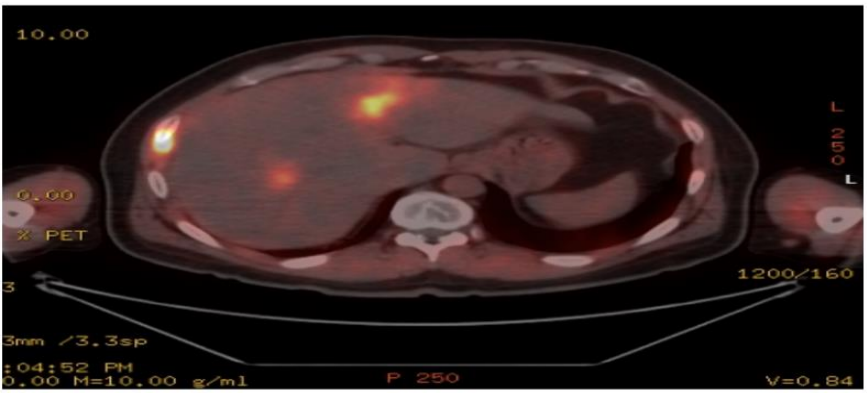
2.2. Nodal and Distant Metastases

In thoracic malignancies, Ga-68 FAPI PET/CT has been reported to yield promising results in the evaluation of nodal and distant metastases. In particular, in mediastinal lymph node staging, FAPI tracers have been shown to provide higher tumor-to-background contrast due to low physiological background activity and lower non-specific uptake in inflammatory processes compared to FDG. In a prospective pilot study conducted in patients with NSCLC, Kang et al. reported that FAPI PET/CT demonstrated high diagnostic accuracy in the detection of mediastinal nodal metastases and provided significantly superior discriminative performance compared to FDG PET/CT (Kang et al., 2024). It was also emphasized that FAPI PET/CT has a lower rate of false positivity in inflammatory or reactive lymph nodes. Similarly, in a study by Demmert et al., FAPI PET/CT was shown to have a higher accuracy rate than FDG PET/CT in identifying true nodal involvement (94% vs. 55%) and many lymph nodes that appeared false-positive on FDG PET/CT were found to be negative on FAPI PET/CT imaging (Demmert et al., 2023). These findings suggest that FAPI PET/CT may provide clinical benefits in nodal staging, particularly in populations with a high prevalence of granulomatous diseases. In general, considering the results of the studies available in the literature, it can be stated that FAPI PET/CT demonstrates a high success rate in the detection of nodal metastases and also exhibits a high positive predictive value. Similarly, it has been reported that FAPI PET/CT offers significant advantages in the

evaluation of distant metastases due to its high lesion contrast. Zannan et al. reported that the accuracy of FAPI PET/CT was significantly higher than that of FDG PET/CT in the detection and assessment of nodal and distant metastases of primary extrapulmonary thoracic tumors (Zhang et al., 2024). Yang et al. demonstrated that the sensitivity of FAPI PET/CT for the detection of nodal and distant metastases in lung cancer was superior to that of FDG PET/CT (99% vs. 77%) (Yang et al., 2024). In a case report, markedly higher FAPI uptake compared to FDG uptake was reported in bone metastases of esophageal cancer (Miao et al., 2025). In a recently published meta-analysis, it was reported that FAPI PET/CT is superior to FDG PET/CT in the detection of lymph node metastases and demonstrates at least comparable performance in bone metastases (Wu et al., 2024). In particular, due to its high tumor-to-background ratio in bone metastases, small osteolytic lesions can be visualized more clearly, and it has been suggested that FAPI PET/CT may provide additional value in the assessment of metastatic foci in organs such as the brain and liver, where FDG shows physiologically high uptake. Therefore, the current data suggest that Ga-68 FAPI PET/CT may represent a powerful complementary imaging modality for the assessment of both nodal and distant metastatic disease burden in thoracic malignancies.



F-18 FDG PET/CT (axial fusion images)



Ga-68 FAPI PET/CT (axial fusion images)

Figure 3. A 44-year-old male patient diagnosed with SCLC. While low 18F-FDG uptake is observed in distant metastases in the right seventh rib and segment III of the liver (rib SUVmax: 2.1; liver SUVmax: 6.3), markedly increased uptake is noted on 68Ga-FAPI PET/CT (rib SUVmax: 14.8; liver SUVmax: 10.0).

2.3. Radiotherapy Planning

Ga-68 FAPI PET/CT has recently emerged as a novel molecular imaging modality that has attracted attention in target volume delineation and radiotherapy planning, particularly in

thoracic malignancies. Studies in lung cancer have demonstrated that FAPI PET/CT can provide clearer tumor boundaries in gross tumor volume (GTV) delineation compared to FDG PET/CT (Qin et al., 2026). It has been reported that FAPI PET/CT imaging may have higher specificity, particularly in the evaluation of mediastinal lymph nodes and in the differentiation of inflammatory tissue from tumor tissue. As a result, changes in radiotherapy target volumes may occur, with target volumes decreasing in some patients while additional tumor foci are identified in others. In addition, it has been suggested that FAPI PET/CT-based planning may reduce the radiation dose to the heart, esophagus, and healthy lung tissue. In some studies conducted in esophageal cancer, FAPI PET/CT has been shown to delineate primary tumor borders more clearly and to be useful in the detection of mediastinal lymph node metastases(Kröger et al., 2025; Ristau et al., 2020). In this way, it is thought that radiotherapy fields can be defined more accurately and the risk of geographic miss can be reduced. Some studies have also reported that FAPI PET/CT can reveal additional lesions that are not detected by conventional imaging methods.

However, most of the available studies have retrospective designs and include limited patient numbers. Therefore, FAPI PET/CT is not yet accepted as a standard radiotherapy planning method in thoracic malignancies. Nevertheless, early results appear promising, particularly with regard to target volume delineation and normal tissue sparing. Large-scale prospective studies to be conducted in the future are expected to more clearly define the clinical role of FAPI PET/CT.

2.4. Future Perspectives

Ga-68 FAPI PET/CT is a candidate to become an important component of oncologic imaging in the future, owing to its high

TBR and its unique imaging approach targeting tumor stroma in thoracic malignancies. Particularly in tumors with prominent stromal activity, such as lung cancer and malignant mesothelioma, the role of FAPI imaging in diagnosis, staging, and treatment response assessment is expected to progressively increase. One of the most important areas of future development is theranostic applications. By labeling FAPI ligands with therapeutic radionuclides such as Lu-177, Y-90, or Ac-225, both imaging and targeted therapy can be achieved. It is thought that FAPI-based radioligand therapies may yield promising results, especially in advanced-stage or treatment-refractory thoracic malignancies. In addition, the use of FAPI PET/CT in radiotherapy planning is also expected to increase. Owing to its high TBR, it may contribute to more precise tumor boundary delineation, particularly in complex anatomical regions such as mediastinal invasion or pleural spread, thereby facilitating target volume definition. The integration of artificial intelligence and radiomic analyses with FAPI imaging will also be an important area of research in the future. Correlating quantitative imaging data with prognostic biomarkers may contribute to treatment response prediction and the development of personalized therapeutic strategies. In order for all this potential to be fully translated into clinical practice, large-scale prospective studies, standardization of imaging protocols, and comparative evaluations of different FAPI agents are required. With data to be obtained in the coming years, the true clinical value of Ga-68 FAPI PET/CT in thoracic oncology is expected to be more clearly defined.

3. Limitations

Although Ga-68 FAPI PET/CT has attracted attention due to its high tumor-to-background contrast and promising diagnostic performance in head and neck cancers and thoracic malignancies, it

currently has several limitations that restrict its routine clinical use. The major limitation is that fibroblast activation protein (FAP) is not specific to malignant tissues. Although high levels of FAP expression are observed in cancer-associated fibroblasts (CAFs), increased FAPI uptake can also be seen in benign and inflammatory processes. In particular, false-positive uptake may occur in pulmonary fibrosis, organizing pneumonia, granulomatous diseases, post-surgical fibrotic changes, radiation-induced tissue injury, and areas of active inflammation. This situation leads to reduced specificity, especially in cases where chronic inflammatory lung diseases are common.Another important limitation is the heterogeneous distribution of FAP expression both among different thoracic malignancies and within the same tumor type. Although high FAPI uptake has been reported in certain histological subtypes of lung cancer, malignant mesothelioma, and some metastatic lesions, more limited uptake may be observed in tumors with low stromal activity. In addition, intratumoral heterogeneity may complicate quantitative assessment and lesion characterization. A substantial proportion of the current literature on Ga-68 FAPI PET/CT is based on retrospective and single-center studies with small patient cohorts. Due to the heterogeneity of study populations and differences in imaging protocols, the generalizability of the reported results is limited. Compared to the extensive body of evidence available for FDG PET/CT, there is still a need for large-scale prospective and multicenter studies in FAPI imaging. Furthermore, there is no full consensus regarding optimal imaging timing, standardized acquisition protocols, interpretation criteria, and SUV threshold values. From a practical standpoint, the production and availability of FAPI tracers also represent an important limitation. Currently, these agents can be produced only in a limited number of centers and have not yet been incorporated into routine clinical practice in many countries.

Despite all these limitations, Ga-68 FAPI PET/CT is considered a highly promising imaging modality in head and neck and thoracic oncologic imaging. However, in order for this method to be fully integrated into routine clinical practice, standardization must be achieved, large-scale prospective studies must be conducted, and long-term clinical outcomes need to be established.

4. Pitfalls

Although Ga-68 FAPI PET/CT is a promising imaging modality in head and neck and thoracic malignancies due to its high contrast resolution and low physiological background activity, there are several pitfalls in clinical interpretation. These situations mainly arise from the fact that FAP expression is not specific to malignancy and can also be increased in a variety of benign processes outside the tumor microenvironment.

Inflammatory and infectious processes represent one of the most important pitfalls. Acute and chronic inflammation, granulomatous diseases, pulmonary infections, organizing pneumonia, and dental infections in the head and neck region may demonstrate prominent FAPI uptake, leading to false-positive interpretations. In the head and neck region, particularly post-surgical changes and radiation-induced inflammatory responses may be mistaken for residual tumor. Fibrosis, granulation tissue, and wound healing processes developing after radiotherapy and surgery may also increase FAP expression, resulting in intense uptake on FAPI PET/CT. This situation particularly reduces specificity in the evaluation of recurrence and necessitates correlation with anatomical imaging modalities. In addition, physiological and benign tissue uptake should be considered in terms of false positivity. In the head and neck region, salivary glands, muscle tissue, and certain glandular structures; and in the

thoracic region, pleural reactive areas and some vascular structures may show variable degrees of FAPI uptake. Since FAPI PET/CT primarily targets tumor stroma and fibroblast activity rather than tumor cell proliferation, low uptake may be observed in tumors with low stromal content, necrotic lesions, or hypocellular tumors. These situations and other potential pitfalls are summarized in Table 2.

Table 2. Major Diagnostic Pitfalls in Ga-68 FAPI PET/CT

Condition	**Potential Effect**	**Clinical Consequence**
Inflammation and infections	Increased FAPI uptake	False positivity
Granulomatous diseases	Reactive stromal activity	False positivity
Post-surgical / post-radiotherapy changes	Fibrosis and wound healing	Confusion with residual / recurrent tumor
Physiological tissue uptake	Benign FAPI activity	False positivity
Pleural reactive changes	Reactive fibroblast activation	Confusion with metastasis
Necrotic / hypocellular tumors	Low FAP expression	False negativity
Tumors with low stromal component	Reduced FAPI uptake	Underestimation of tumor extent

Overall, although Ga-68 FAPI PET/CT is a highly effective imaging modality in head and neck and thoracic malignancies, failure to consider the aforementioned pitfalls may result in misinterpretation. Therefore, clinical expertise, radiological experience, and integration with other imaging modalities are essential for achieving accurate diagnostic performance.

5. Conclusion

FAPI PET/CT stands out as a promising molecular imaging modality in head and neck and thoracic malignancies, owing to its innovative approach targeting cancer-associated fibroblasts within the tumor microenvironment. Due to its low physiological background activity and high tumor-to-background contrast, it can provide significant advantages in the evaluation of primary tumors, lymph node metastases, and distant metastatic lesions.

Current studies suggest that FAPI PET/CT may provide additional diagnostic value compared to FDG PET/CT in certain clinical settings. However, due to the presence of FAPI uptake in benign fibrotic and inflammatory processes, and the fact that the available data are largely based on small patient series, there is a need for clearer definition of its clinical indications.

In conclusion, FAPI PET/CT is an innovative imaging modality with the potential to improve diagnostic accuracy and contribute to patient management in head and neck and thoracic malignancies. Future large-scale studies and advances in FAPI-based theranostic applications are expected to further clarify its role in oncologic imaging and therapy.

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BREAST CANCER: 68Ga-FAPI PET/CT

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Introduction: The Evolving Landscape of Molecular Imaging in Breast Cancer

The clinical management of breast cancer (BC) is increasingly incorporating stromal imaging approaches that complement, and in selected scenarios may overcome the limitations of, conventional glucose metabolism–based imaging. For decades, 18F-fluorodeoxyglucose (FDG) Positron Emission Tomography/Computed Tomography (PET/CT) has become an important tool in selected BC settings, particularly for staging advanced disease and detecting recurrence. However, its reliance on glucose metabolism often limits its sensitivity in certain BC histotypes and small lesions. Of note, invasive lobular carcinoma (ILC) represents a clinically relevant example of this limitation; approximately 15% of ILC primary tumors lack FDG uptake entirely, and mean maximum standardized uptake value (SUVmax) values are significantly lower than those of invasive ductal carcinoma (IDC), potentially leading to understaging in this histological subtype (Metser et al., 2026).

The emergence of radiopharmaceuticals targeting the Fibroblast Activation Protein (FAP), collectively referred to as Fibroblast Activation Protein Inhibitors (FAPI), represents a paradigm shift. By focusing on the essential supporting structures of a tumor rather than just the malignant cells, FAPI PET/CT addresses the clinical necessity for high-contrast imaging, particularly in cases where low metabolic activity or high physiological background noise hinders conventional scans (Loktev et al., 2018).

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Achieving a high Tumor-to-Background Ratio (TBR) is vital for accurate staging and the subsequent selection of therapy. Throughout this evaluation, we utilize specific quantitative metrics, including the SUV, to assess tracer concentration and distribution. This move toward FAPI-based imaging is predicated on the profound biological advantages offered by targeting the tumor stroma, a driver of malignancy that often precedes and surrounds the metabolic footprint of cancer cells.

Biological Rationale of FAPI Imaging: Targeting the Tumor Stroma

The tumor microenvironment (TME) is increasingly recognized as an active driver of tumor progression and therapeutic resistance. Among its key components, cancer-associated fibroblasts (CAFs) promote extracellular matrix remodeling, angiogenesis, and immune modulation. Fibroblast activation protein (FAP), a type II transmembrane serine protease, is highly expressed by CAFs in many epithelial tumors, including BC, while showing limited expression in normal adult tissues. This makes FAP an attractive target for high-contrast stromal imaging, allowing FAPI PET/CT to visualize desmoplastic tumor activity beyond glucose metabolism–based imaging (Giorello et al., 2021; Hawsawi et al., 2008; Pabst et al., 2025).

Technical Parameters and Tracers

Tracer selection has expanded to include several high-affinity FAP-targeted ligands. While 68Ga-FAPI-04 and 68Ga-FAPI-46 remain the most extensively evaluated tracers in BC, other agents such as 68Ga-FAPI-02, 68Ga-FAPI-74, 68Ga-DOTA.SA.FAPI, and 18F-FAPI-04 have also been investigated (Chopra et al., 2024; Glatting et al., 2022). The development of 18F-labeled FAPI tracers may offer additional logistical advantages because of the longer physical half-life of 18F and its suitability for centralized production and wider distribution. Another practical advantage of FAPI imaging is its rapid tracer kinetics. Although many protocols still acquire images at approximately 60 minutes after injection, emerging data suggest that early imaging, including

10–30-minute post-injection acquisitions, may provide sufficient diagnostic information in BC. In a prospective dual-phase study, early 18F-FAPI-04 PET/CT imaging at approximately 10 minutes showed diagnostic performance comparable to 60-minute delayed imaging (Li et al., 2025).

Imaging Advantages of FAPI PET/CT Compared with FDG PET/CT

Unlike 18F-FDG PET/CT, FAPI PET/CT does not require fasting or blood glucose regulation, as tracer uptake is not primarily driven by glucose metabolism or insulin-dependent pathways. This has practical relevance in diabetic patients and in patients receiving corticosteroids, in whom FDG image quality may be compromised by hyperglycemia or altered insulin dynamics (Hope et al., 2025). Additionally, the rapid tracer kinetics of FAPI agents allow earlier image acquisition, further streamlining patient workflow, reducing preparation-related delays, and providing greater scheduling flexibility in high-volume PET centers. FAPI PET/CT generally demonstrates a favorable biodistribution profile for whole-body oncologic imaging, characterized by relatively low physiological background activity in several organs that commonly limit 18F-FDG PET/CT interpretation.

Brain and calvarium: The absence of prominent physiological FAPI uptake in the brain provides favorable lesion-to-background contrast for detecting cerebral and leptomeningeal metastases, while also facilitating the visualization of adjacent calvarial or skull-base metastatic lesions that may be obscured by intense cortical glucose metabolism on 18F-FDG PET/CT.

Liver: Improving the visibility of subcentimetric hepatic lesions.

Gastrointestinal Tract: Reducing interpretive difficulties related to physiological bowel activity and metformin-associated FDG uptake. This is particularly relevant in ILC, which exhibits a known predilection for GI tract metastases; the low background activity of FAPI in the bowel may improve detection of peritoneal

and hollow viscera involvement that is frequently missed on 18F-FDG PET/CT.

Bone Marrow: Reducing background noise in osseous structures, which is clinically meaningful given that bone is among the most common metastatic sites in BC, including ILC.

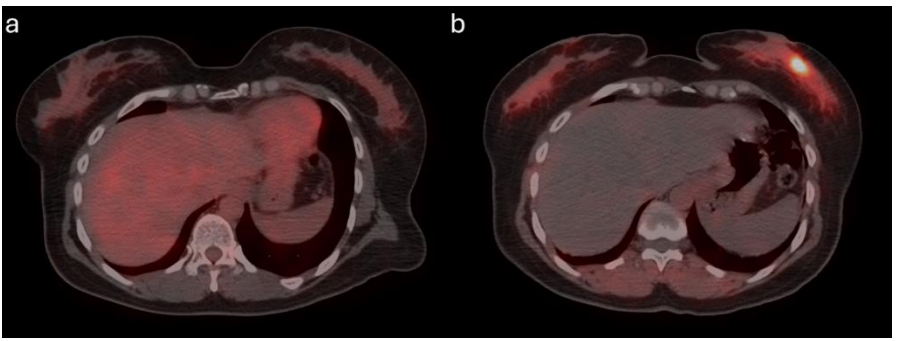
This favorable biodistribution profile may translates directly into higher TBR, which is the principal quantitative advantage of FAPI over FDG in BC imaging.

68Ga-FAPI PET/CT in Primary Breast Cancer

68Ga-FAPI PET/CT demonstrates consistently high tracer uptake across both invasive IDC and ILC, regardless of histological subtype. Backhaus et al. (2022) reported no statistically significant difference in SUVmax between IDC and ILC (14.5 ± 5.8 vs. 10.6 ± 2.8; P = .20). This subtype-independent accumulation is particularly relevant for ILC, which is known to exhibit low FDG avidity due to its low cellular density, single-file growth pattern, and minimal desmoplastic response. In a dedicated ILC cohort (n = 23), Sahin et al. (2024) demonstrated markedly higher FAPI uptake compared to FDG across all lesion sites (mean SUVmax 13.22 ± 8.1 vs. 3.43 ± 2.12; P < 0.001), with 68Ga-FAPI PET/CT identifying additional lesions — including multicentric foci, lymph node metastases, and liver metastases — in 78.2% of patients.

Figure 1.

A 45-year-old woman with biopsy-proven hormone receptor–positive invasive ductal carcinoma of the left breast, Ki-67 index of 5%, and HER2-ultralow expression. (A) Axial 18F-FDG PET/CT shows no significant uptake in the primary lesion. (B) Axial 68Ga-FAPI-04 PET/CT shows prominent uptake in the primary tumor.



Source: Author's own figure.

Receptor Status

FAP expression in BC stroma appears largely independent of hormone receptor (HR) and human epidermal growth factor receptor 2 (HER2) status. Backhaus et al. (2022) found no significant differences in SUVmax among HR-positive/HER2-negative, HER2-positive, and triple-negative subtypes in primary tumors or lymph node metastases. Similarly, Elboga et al. (2021) reported comparable FDG-to-FAPI SUVmax uptake ratios across luminal A, luminal B HER2-negative, luminal B HER2-positive, HER2-enriched, and triple-negative groups ($P = 0.58$). However, the same group noted numerically higher mean FAPI SUVmax values in HER2-expressing subtypes (luminal B HER2-positive: 21.2 ± 8.3; HER2-enriched: 17.9 ± 6.0) compared to luminal A (10.1 ± 5.6), reaching statistical significance ($P = 0.009$). This finding was not replicated in subsequent studies and warrants further investigation. Evangelista et al. (2023) similarly concluded

that FAPI uptake shows no correlation with immunohistochemical profile across the reviewed literature.

Grade and Ki-67 Index

The relationship between FAPI uptake and tumor grade is inconsistent across studies. Backhaus et al. (2022) found no significant grade-dependent differences in SUVmax (grade 1: 18.2 ± 8.4; grade 2: 12.5 ± 2.8; grade 3: 14.7 ± 8.2), and Elboga et al. (2021) reported similar uptake ratios between grade 2 and grade 3 tumors ($P = 0.83$), with no correlation between Ki-67 and FAPI SUVmax ($r = 0.017$; $P = 0.92$). In contrast, Zheng et al. (2023) demonstrated a statistically significant positive correlation between FAPI SUVmax and pathological grade (grade 1: 3.02 ± 1.44; grade 2: 8.18 ± 5.0; grade 3: 11.39 ± 5.35; $P < 0.05$ for all pairwise comparisons), as well as with final clinical stage ($P = 0.004$). This discrepancy may reflect differences in study design, patient selection, and sample size. Collectively, the data suggest that while FAPI uptake is broadly grade-independent — a key advantage over FDG — a subset of studies indicates a potential trend toward higher FAP expression in higher-grade tumors, likely reflecting more pronounced stromal activation.

Nodal Evaluation

68Ga-FAPI PET/CT demonstrates significant advantages over 18F-FDG PET/CT in lymph node staging of BC. Backhaus et al. (2022) reported strong axillary tracer accumulation in all 13 patients with preoperatively verified lymph node metastases, and showed that in 7 patients with known axillary level I metastases, 68Ga-FAPI PET/CT established or supported involvement of axillary levels II-III or internal mammary lymph nodes, ultimately influencing therapy decisions in 3 patients. These findings are further supported by a dedicated histopathology-confirmed cohort study in which 68Ga-FAPI PET/CT detected axillary nodal

metastases in 39 of 42 patients, compared with only 26 of 42 for 18F-FDG PET/CT, yielding sensitivities of 92.9% and 61.9%, respectively. Metastatic lymph nodes also demonstrated significantly higher SUVmax values with FAPI than with FDG (10.3 ± 5.8 vs. 7.0 ± 4.3; $P = 0.015$), underscoring the superior lesion conspicuity of stromal-targeted imaging in the axillary region (Kalender et al., 2026).

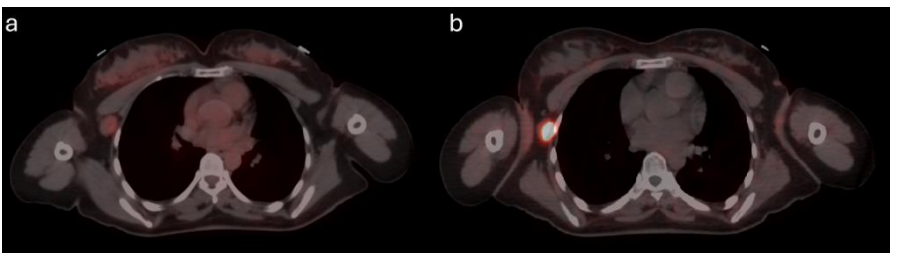
On patient-based analysis across a prospective cohort, Zheng et al. (2023) reported that 68Ga-FAPI PET/CT correctly classified lymph node involvement in 31 of 34 cases (2 false-positive, 1 false-negative), whereas 18F-FDG PET/CT correctly identified only 25 cases (8 false-positive, 1 false-negative). On nodule-based analysis, the specificity and accuracy of 68Ga-FAPI PET/CT were significantly superior (97.7% vs. 54.8% and 95.8% vs. 69.4%, respectively; $P < 0.001$), with overall N staging accuracy reaching 91.2% versus 73.5% — a difference that was particularly pronounced in the determination of N0 axillary status (85.7% vs. 42.9%; $P = 0.013$). In a study focused exclusively on ILC, Sahin et al. reported that while axillary lymph node metastasis was detected in only 1 patient on 18F-FDG PET/CT, this number increased to 8 on 68Ga-FAPI PET/CT. Notably, 89.5% of lymph nodes with a short axis diameter of 8 mm or less showed no 18F-FDG uptake, yet a substantial proportion demonstrated 68Ga-FAPI accumulation, with the weak correlation between 68Ga-FAPI uptake and lymph node size suggesting a size-independent uptake mechanism with relative resistance to the partial volume effect (Sahin et al., 2024). Taken together, these findings indicate that 68Ga-FAPI PET/CT may provide meaningful added value in nodal staging, particularly in the detection of subcentimeter or metabolically low-active lymph node metastases where 18F-FDG PET/CT falls short.

FAPI Positron Emission Tomography / Magnetic Resonance Imaging (PET/MRI) has also demonstrated added value in extra-axillary nodal mapping, including internal mammary lymph node assessment, establishing or supporting involvement in seven of nineteen patients and directly influencing treatment

decisions — including surgical and radiotherapy planning — in three (Backhaus et al., 2022). In metastatic or FDG-low ILC, limited pilot data also suggest that 68Ga-FAPI PET/CT may reveal internal mammary nodal involvement not apparent on diagnostic CT (Eshet et al., 2023). Although these observations indicate a potential role for FAPI PET/CT in detecting clinically relevant extra-axillary nodal disease and may influence regional nodal staging or radiotherapy field design, the evidence remains limited and should be interpreted cautiously.

In a prospective bi-center study, FAP-targeted PET/CT altered TNM staging in 22% of patients and led to treatment modifications in 15% compared with 18F-FDG PET/CT, with even greater impact versus standard-of-care imaging alone (staging change 24%, management change 19%) (Guo et al., 2025).

Figure 2.
A 34-year-old woman with a 9-cm right breast invasive ductal carcinoma (ER 40%, PR 60%, HER2 +++, Ki-67 30%). (A) Axial 18F-FDG PET/CT shows low uptake in the right axillary metastatic nodal lesion. (B) Corresponding axial 68Ga-FAPI-04 PET/CT shows markedly increased uptake.



Source: Author's own figure.

Distant Metastatic Sites

Bone is one of the most clinically relevant metastatic sites in BC, and accurate skeletal staging is essential for treatment

planning. Emerging evidence suggests that FAPI PET/CT may improve the detection of bone metastases compared with 18F-FDG PET/CT, particularly by targeting stromal activation within the bone metastatic microenvironment rather than relying solely on tumor glucose metabolism (Guo et al., 2025; He & Tan, 2026). In a recent study including patients with different malignancies, 68Ga-DOTA-FAPI-04 PET/CT detected more bone metastatic lesions than 18F-FDG PET/CT and showed a particular advantage for osteoblastic metastases, a pattern in which FDG uptake may be limited (Guo et al., 2025). A subsequent systematic review and meta-analysis also reported higher pooled detection rates for 68GaFAPI-04 PET/CT than 18F-FDG PET/CT in both patient-based analyses (0.99 vs. 0.79) and lesion-based analyses (1.00 vs. 0.71) (He & Tan, 2026). These findings support the potential role of FAPI PET/CT as a sensitive complementary tool for skeletal staging in BC. However, increased FAPI uptake may also occur in benign skeletal conditions such as fractures, degenerative changes, arthritis, Schmorl nodes, fibrous dysplasia, and other inflammatory or reparative processes; therefore, CT morphology and clinical correlation remain essential to avoid false-positive interpretation (Guo et al., 2025; He & Tan, 2026).

FAP-targeted PET/CT also demonstrated notable superiority over FDG in detecting abdominal lymph node metastases (28 vs. 3 lesions) and liver metastases (28 vs. 11 lesions), sites where low physiological background activity provides favorable lesion conspicuity in one prospective study (Guo et al., 2025).

Post-Treatment Assessment

Although the role of FAPI PET/CT in BC treatment monitoring remains under investigation, emerging data suggest potential value in response assessment. Preliminary studies further indicate that FAPI imaging may detect early recurrence after chemotherapy and may help predict pathological response after

neoadjuvant therapy (Chen et al., 2023; Elboga et al., 2021). PET/MRI data also showed lower FAPI tumor-to-background ratios in patients with pathological complete response, supporting FAPI uptake as a potential biomarker of residual disease (Backhaus et al., 2023). In the post-neoadjuvant treatment response assessment setting, reported sensitivity and specificity ranges of FAPI PET were 73–100% and 71–100%, respectively, further supporting its potential utility for treatment monitoring (Duijx et al., 2026). However, because current evidence is limited by small cohorts and incomplete histopathological validation, FAPI PET/CT should be regarded as a promising complementary approach rather than a validated standard for response monitoring (McGale et al., 2025).

Current Limitations and Diagnostic Pitfalls

Despite its promising diagnostic performance, FAPI PET/CT is not without limitations, and awareness of its pitfalls is essential for accurate image interpretation.

False-Positive Findings

A critical limitation of FAPI imaging is its lack of tumor specificity, as FAP is expressed not only by cancer-associated fibroblasts but also by activated fibroblasts in a variety of benign conditions. Increased FAPI uptake has been documented in inflammatory and post-surgical processes, degenerative joint disease, fracture sites, granulomatous diseases such as tuberculosis, and fibrotic conditions (Bentestuen et al., 2026). Within the breast itself, false-positive foci can arise from post-biopsy inflammatory changes, radiation-induced fibrosis, and scarring, all of which may mimic malignant lesions and complicate interpretation, particularly during follow-up after local treatment (Chen et al., 2021; Kömek et al., 2021).

A specific interpretative pitfall in breast FAPI PET/CT is hormone-related physiological uptake in normal fibroglandular

breast tissue. Because breast density and stromal composition may vary under endogenous or exogenous hormonal stimulation, increased estrogen levels may upregulate FAP expression and increase physiological FAPI uptake in the breast. This effect appears particularly relevant during estrogen-dominant phases of the menstrual cycle, such as the peri-ovulatory period, and may reduce lesion conspicuity by increasing background breast activity. Therefore, when feasible, scheduling FAPI PET/CT outside the ovulatory phase may help reduce physiological interference in hormone-sensitive organs such as the breast and uterus (Dendl et al., 2021; Heller et al., 2018; Sonni et al., 2021; Wang et al., 2021).

In addition to menstrual-cycle–related variation, lactational status may represent another source of physiological or hormonally mediated FAPI uptake in breast tissue. Increased bilateral breast FAPI uptake has been observed in lactating patients, suggesting that lactation should also be recognized as a potential interpretative pitfall when evaluating breast FAPI PET/CT (Yerdeş & Elboğa, 2026).

False-Negative Findings

Despite the promising role of 68Ga-FAPI PET/CT in BC imaging, false-negative results remain an important pitfall that should not be overlooked. Civan et al. (2023) reported a case in which multiple lymph node metastases demonstrating intense ^{18}F-FDG uptake showed no significant FAPI accumulation on 68Ga-FAPI-04 PET/CT, with histopathological confirmation ultimately revealing ER^+ BC metastasis. Similarly, Zheng et al. (2021) described a case where early osteogenic bone metastasis was missed by both 68Ga-FAPI and 18F-FDG PET/CT, attributing this to low FAP expression in early bone metastases. These cases collectively underscore that additional verification should always be considered when clinical suspicion remains high despite negative FAPI findings. The exact mechanisms underlying false-negative 68Ga-FAPI PET/CT results in BC remain unclear, but several theoretical explanations may be considered. Intratumoral heterogeneity in FAP expression, reduced cancer-associated

fibroblast (CAF) density — particularly in luminal/ER^{+} subtypes with less pronounced stromal desmoplasia — and low FAP expression at early metastatic sites may collectively contribute to insufficient tracer uptake below detectable thresholds. Subcentimeter lesions below the spatial resolution of the PET system are susceptible to partial volume effects, leading to underestimation of true tracer uptake.

Methodological and Study-Level Limitations

At the level of published evidence, the current body of literature on FAPI PET in BC is characterized by small sample sizes, heterogeneous patient populations including both untreated and pre-treated patients across variable disease stages, and a lack of standardized acquisition and reporting protocols. Most comparative studies have used retrospective designs, and histological verification of individual lesions has often been clinically driven rather than systematic, introducing confirmation bias. The use of different FAPI ligands across studies further limits direct comparisons, though available data suggest broadly comparable diagnostic performance among FAP-targeting agents.

Table 1. Comprehensive Comparison of FAPI PET/CT and FDG PET/CT Parameters

Feature / Parameter	18F-FDG PET/CT	68Ga-FAPI PET/CT
Biological Target	Glucose metabolism	FAP on cancer-associated fibroblasts
Patient Preparation	Requires strict fasting and blood glucose regulation	No fasting or blood glucose regulation required
Tracer production	Cyclotron-based 18F production.	Mainly 68Ga generator-based labeling
Tracer Kinetics	Slower kinetics; imaging typically at 60 minutes.	Rapid kinetics; early imaging (10–30 min) is feasible
Common False-Positive Pitfalls	Infections, physiological muscle uptake, acute inflammation.	Post-biopsy changes, scarring, radiation-induced fibrosis, arthritis

Source: Prepared by the author based on the cited literature.

Future Perspectives and Theranostic Applications

Beyond currently investigated FAPI tracers, newer FAP-targeted agents may further expand the role of stromal imaging in BC. In a prospective study of patients with suspected recurrent or metastatic BC, 68Ga-FAP-2286 PET/CT detected more lesions than 18F-FDG PET/CT, with the greatest incremental value observed for hepatic and bone metastases. This advantage was partly attributed to lower physiological liver background activity and improved lesion conspicuity, particularly for metastatic disease. Early experience with 177Lu-FAP-2286 also suggests a

potential theranostic role in selected patients with advanced FAP-positive BC, although the available therapeutic data remain preliminary and limited to very small patient cohorts (Liu et al., 2026).

More recently, α-emitting FAP-targeted radiopharmaceuticals have further expanded the theranostic landscape in BC. Preliminary clinical experience with 225Ac-3BP-3940, administered either as monotherapy or in a TANDEM approach combining α- and β-emitting nuclides (177Lu or 90Y]), demonstrated a favorable safety profile and encouraging survival outcomes in heavily pretreated patients with metastatic BC across diverse tumor subtypes (Perrone et al., 2025). These findings suggest that α-emitting FAP-directed radiopharmaceutical therapy (FRT) may offer an additional therapeutic option in cases refractory to standard systemic therapies, although the available data remain limited to small retrospective cohorts. Larger prospective trials are warranted to define optimal patient selection criteria, dosimetry protocols, and potential combination strategies with existing systemic agents.

Conclusion

FAPI PET/CT has emerged as a stromal-targeted molecular imaging approach in BC, addressing several limitations of glucose metabolism–based imaging. Unlike 18F-FDG PET/CT, which may be falsely negative in low-grade, luminal, and ILC, FAPI imaging targets FAP-expressing CAF within the TME. By visualizing stromal activation rather than tumor glycolysis alone, FAPI PET/CT may provide higher lesion-to-background contrast and improved lesion conspicuity, particularly for small lesions, nodal disease, non-FDG-avid bone metastases, and selected metastatic sites.

Current evidence suggests that FAPI PET/CT can detect additional disease foci in patients initially characterized as limited-stage by 18F-FDG PET/CT, potentially leading to upstaging and

changes in therapeutic decision-making. However, the available BC data remain limited by small sample sizes, mostly retrospective designs, and incomplete histopathological validation. Moreover, false-positive uptake may occur in inflammatory conditions, post-surgical or reparative fibrosis, hormonal breast tissue activation, and wound-healing contexts, requiring careful interpretation with CT morphology and clinical correlation.

Therefore, FAPI PET/CT should currently be presented as a promising complementary modality rather than a validated replacement for 18F-FDG PET/CT. Its potential utility in initial staging, restaging, and treatment response assessment, together with the emerging theranostic perspective of FAP-targeted radionuclide therapy, positions FAPI-based imaging as an important candidate for future personalized oncology in BC.

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Tumor Microenvironment-Targeted Imaging: FAPI PET/CT in Gastrointestinal Malignancies

BÖLÜM 6

Edanur EKİNCİ YILDIRIM[1], Ömer YILDIRIM[2]

Introduction

Gastrointestinal (GI) cancers represent a major global health burden and remain among the leading causes of cancer-related morbidity and mortality. Accurate tumor detection and staging are essential for optimizing therapeutic strategies and improving patient outcomes. In current clinical practice, ^{18}F-FDG PET/CT is widely employed for the assessment of GI malignancies because it provides information regarding tumor glucose metabolism. Nevertheless, its diagnostic accuracy may be compromised by physiological tracer accumulation within the gastrointestinal tract and by the relatively low FDG uptake observed in certain histological variants, particularly mucinous and diffuse-type tumors [1, 2].

To address these shortcomings, increasing attention has been directed toward imaging strategies that target the tumor microenvironment (TME) rather than tumor cells alone. The TME consists of a complex network of extracellular matrix components, immune cells, and cancer-associated fibroblasts (CAFs), which collectively contribute to tumor growth, invasion, and metastatic spread. Fibroblast activation protein (FAP), a membrane-bound serine protease highly expressed on CAFs but largely absent from

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normal tissues, has emerged as a promising molecular target for diagnostic imaging [3].

Radiopharmaceuticals targeting fibroblast activation protein, commonly known as FAPI compounds, offer exceptional imaging benefits such as minimal background interference and elevated tumor-to-background contrast. These attributes allow for a more precise visualization of malignancies and can significantly boost detection rates in various gastrointestinal (GI) cancers compared to traditional FDG PET/CT. Current meta-analytical data suggests that ^{68}Ga-FAPI PET/CT delivers superior sensitivity when identifying primary tumors, involved regional lymph nodes, and distant metastases [2, 4]. Supporting this, Zhao et al. observed that ^{68}Ga-FAPI PET/CT was notably more effective than FDG PET/CT at detecting primary GI malignancies [5].

The utility of FAPI-based imaging transcends simple tumor identification. Research indicates that FAPI PET/CT matches or exceeds the diagnostic accuracy of conventional methods for assessing nodal involvement, which is a vital component of staging and therapeutic strategy [6]. Furthermore, retrospective data has highlighted intense tracer accumulation in ^{68}Ga-FAPI-04 PET/CT for specific pathologies that usually show low FDG uptake, such as signet ring cell gastric adenocarcinoma. This underscores the clinical importance of FAPI imaging in addressing complex diagnostic challenges [7].

Another important limitation of FDG PET/CT is the presence of physiological bowel uptake, which may obscure lesions and complicate image interpretation. Owing to its generally lower physiological gastrointestinal activity, FAPI PET/CT can provide clearer tumor delineation and improved lesion conspicuity, as demonstrated in multiple clinical investigations [4]. Collectively, these findings suggest that imaging directed at the tumor

microenvironment may offer meaningful diagnostic advantages and could contribute to more accurate staging, treatment planning, and therapeutic response evaluation in GI malignancies.

This chapter aims to review the biological basis of FAPI PET/CT, summarize its diagnostic performance relative to FDG PET/CT, and discuss its emerging clinical applications in gastrointestinal cancers based on the currently available evidence.

Esophageal Cancer

Esophageal cancer is a common and highly lethal malignancy that continues to constitute a significant global health problem. Histologically, the disease is primarily categorized into squamous cell carcinoma and adenocarcinoma. Squamous cell carcinoma most frequently develops in the upper and middle segments of the esophagus, whereas adenocarcinoma predominantly originates in the distal esophagus or at the gastroesophageal junction. Despite their distinct epidemiological and anatomical characteristics, both histological subtypes exhibit a prominent desmoplastic stromal response accompanied by extensive infiltration of cancer-associated fibroblasts (CAFs). The abundance of CAFs results in elevated fibroblast activation protein (FAP) expression within the tumor microenvironment, supporting the use of FAP-targeted imaging strategies in esophageal malignancies [9,10].

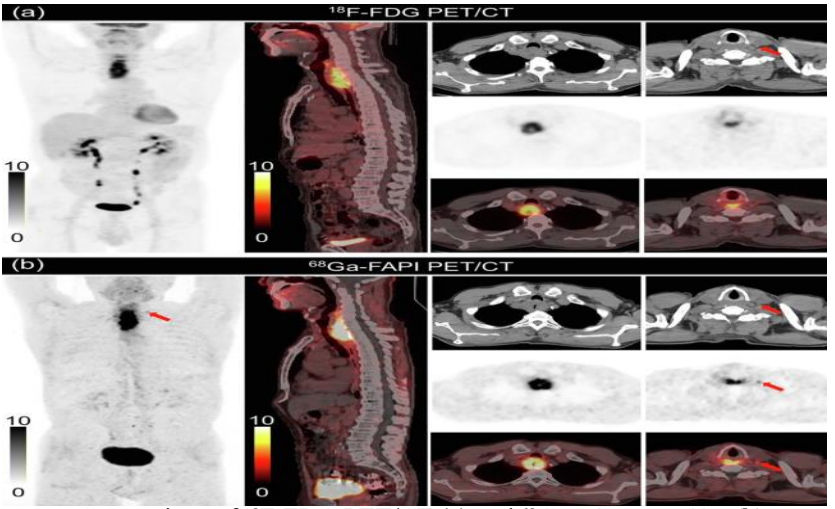
^{18}F-FDG PET/CT currently plays an important role in the staging and therapeutic evaluation of esophageal cancer. Because FDG uptake reflects enhanced glycolytic activity, this modality is effective for detecting primary tumors as well as distant metastatic lesions. However, FDG accumulation is not specific to malignant tissue and may also occur in inflammatory conditions, infectious processes, post-treatment changes, or granulation tissue formation. Consequently, interpretation can be challenging, particularly in

mediastinal lymph nodes where inflammatory uptake may reduce diagnostic specificity and adversely affect staging accuracy [11].

Growing clinical evidence suggests that FAPI PET/CT may overcome some of these limitations. By targeting FAP-expressing CAFs within the tumor stroma, FAPI tracers provide intense uptake in many esophageal tumors while maintaining low background activity in surrounding tissues. This characteristic contributes to high sensitivity for primary lesion detection and favorable tumor-to-background ratios, especially in mediastinal nodal assessment [9,10]. Furthermore, the minimal physiological uptake observed in the mediastinum facilitates visualization of small metastatic lymph nodes and subcentimeter lesions that may be difficult to characterize with conventional imaging. Improved lesion conspicuity may therefore enhance preoperative evaluation and support more accurate radiotherapy target volume delineation.

Despite these advantages, FAPI uptake should not be considered entirely specific for malignant disease. Elevated tracer accumulation has also been reported in benign conditions associated with fibroblast activation and tissue remodeling, including active esophagitis, radiation-related fibrosis, and wound healing reactions [11]. For this reason, PET findings should always be interpreted within the broader clinical context and correlated with endoscopic findings, histopathological data, and other imaging studies to ensure accurate diagnosis and staging.

Figure-1 Representative Case of Upper Oesophageal Cancer Showing Superior Primary Tumour Visualization and Occult Lymph Node Metastasis Detection with ^{68}Ga-FAPI



Comparison of ^{18}F-FDG PET/CT (a) and ^{68}Ga-FAPI PET/CT (b) in a 72-year-old female patient with upper esophageal cancer. The primary lesion demonstrated higher uptake on ^{68}Ga-FAPI PET/CT than on ^{18}F-FDG PET/CT (SUVmax: 18,25 vs. 11,47). In addition, a metastatic left supraclavicular lymph node (arrow, 0,7 cm) was visualized only on ^{68}Ga-FAPI PET/CT and was not detected on the corresponding ^{18}F-FDG PET/CT images. Reproduced from Zhao et al., [5] licensed under CC BY-NC-ND 4.0.

Gastric Cancer

Gastric cancer continues to impose a considerable global disease burden and remains a leading cause of cancer-associated death, particularly in East Asia and other regions with developing healthcare systems [6]. Histopathologically, the most widely used classification system is the Lauren classification, which categorizes tumors into intestinal and diffuse types [7]. The intestinal type is typically characterized by gland-forming structures, a more defined mass-like growth pattern, and development on a background of

chronic atrophic gastritis and intestinal metaplasia [7]. In contrast, the diffuse type is marked by impaired cell adhesion, frequent signet ring cell morphology, and extensive stromal infiltration [7]. In particular, the linitis plastica form demonstrates a pronounced desmoplastic reaction involving the entire gastric wall, accompanied by a dense stromal component [7].

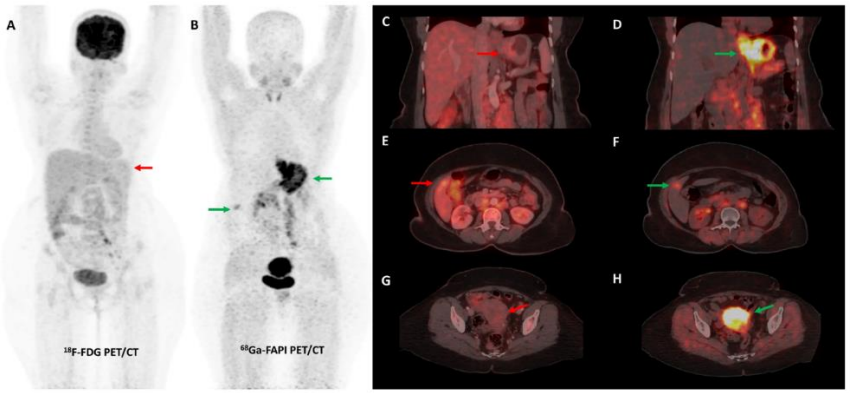
In diffuse-type gastric cancer, FDG PET/CT may show limited uptake due to lower cellular density and relatively reduced glucose metabolism [7]. This limitation can decrease the sensitivity of FDG PET/CT, especially in detecting the primary tumor and peritoneal dissemination [7]. In contrast, the presence of prominent fibroblast activation and stromal proliferation within the tumor microenvironment leads to increased FAP expression, thereby providing a biological advantage for FAPI-based imaging [6, 7].

Several studies have demonstrated the superiority of FAPI PET/CT in this subtype. High SUVmax values and increased tumor-to-background contrast have been reported in primary tumors, with significantly improved lesion detection rates, particularly in diffuse-type and FDG-negative cases [6, 7]. Moreover, peritoneal carcinomatosis lesions can be more clearly visualized with FAPI PET/CT, as the low physiological abdominal background activity facilitates the detection of small peritoneal implants [6, 7]. Importantly, FAPI has been shown to reveal lesions in FDG-negative gastric cancer cases, potentially leading to changes in disease staging [7].

Nevertheless, the specificity of FAPI PET/CT is not absolute. Increased uptake may also be observed in conditions associated with stromal activation, such as gastritis, peptic ulcer disease, postoperative healing tissue, and other inflammatory processes, potentially resulting in false-positive findings [8]. Therefore, interpretation of FAPI findings should be performed in

conjunction with endoscopic evaluation, histopathological confirmation, and clinical data [8].

Figure-2 ^{68}Ga-FAPI-04 PET/CT Detects FDG-Negative Primary Gastric Tumour and Occult Liver Metastasis in Gastric Adenocarcinoma.



Comparison of FDG PET/CT and [^{68}Ga]Ga-FAPI-04 PET/CT in a 42-year-old female patient with gastric adenocarcinoma. The primary gastric tumor was not visualized on FDG PET/CT ((A, C); red arrows) but demonstrated intense uptake on [^{68}Ga]Ga-FAPI-04 PET/CT ((B, D); green arrows). FAPI PET/CT also detected a metastatic lesion in segment V of the liver ((B, F); green arrows) that was occult on FDG PET/CT ((E); red arrow), leading to upstaging of the disease. Diffuse uterine FAPI uptake ((H); green arrow) was considered physiological, whereas no corresponding FDG uptake was present ((G); red arrow). Reproduced from Chandekar et al. [6], licensed under CC BY 4.0.

Colorectal Cancer

Colorectal cancer (CRC) is among the most frequently diagnosed cancers worldwide and continues to be a major contributor to cancer-related mortality. Clinical outcomes are closely linked to disease stage at diagnosis, with metastatic spread being a critical prognostic factor. In particular, hepatic metastases are of considerable importance because the liver is the most

common site of distant involvement through portal venous drainage. The presence of liver metastasis is associated with reduced survival and has a substantial influence on treatment selection and overall disease management [7].

Histopathologically, colorectal cancer is characterized by a prominent tumor microenvironment with abundant stromal components. The density of cancer-associated fibroblasts (CAFs) is particularly increased at the invasive tumor front, where fibroblast activation protein (FAP) expression is also markedly elevated. This biological feature provides a strong rationale for FAPI-based molecular imaging. In particular, the high stromal activity at the invasive margin may facilitate improved visualization of tumor spread and microscopic infiltration [7].

^{18}F-FDG PET/CT is widely used in colorectal cancer, especially for the evaluation of liver metastases and the detection of recurrence. However, physiological FDG uptake within the hepatic parenchyma may reduce lesion contrast and limit the tumor-to-background ratio, particularly in small metastatic foci. This limitation may be especially relevant in subcentimeter lesions and in the assessment of residual disease following chemotherapy.

In contrast, FAPI PET/CT provides a higher tumor-to-background ratio (TBR) due to its low physiological hepatic uptake, thereby enabling improved visualization of liver metastases. Studies have demonstrated that FAPI increases lesion conspicuity, particularly in small metastatic deposits, and may provide better lesion delineation compared with FDG in certain cases. Furthermore, in the evaluation of peritoneal metastases, FAPI PET/CT has been reported to offer superior lesion contrast relative to FDG, with low abdominal background activity facilitating the detection of peritoneal implants [7]. These advantages may have important clinical implications for

cytoreductive surgery planning and for the assessment of treatment response.

Nevertheless, FAPI PET/CT is not entirely tumor-specific. Increased tracer uptake may also be observed in conditions associated with elevated stromal activity, such as active colitis, exacerbations of inflammatory bowel disease, surgical scar tissue, and wound healing processes, potentially leading to false-positive findings. Therefore, imaging findings should be interpreted in conjunction with clinical, endoscopic, and histopathological data [8].

Peritoneal Carcinomatosis

Peritoneal carcinomatosis represents an advanced stage of malignancy resulting from the dissemination of intraperitoneal tumor cells and is associated with a significantly impaired prognosis. It is most commonly observed in ovarian, gastric, and colorectal cancers [7, 8]. In ovarian cancer, the disease frequently spreads via transcoelomic dissemination along peritoneal surfaces, whereas in gastric and colorectal cancers, peritoneal implants typically develop following serosal invasion. Because peritoneal dissemination heavily influences patient outcomes, precise clinical staging is crucial for therapeutic decision-making, particularly when evaluating candidates for cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) [8].

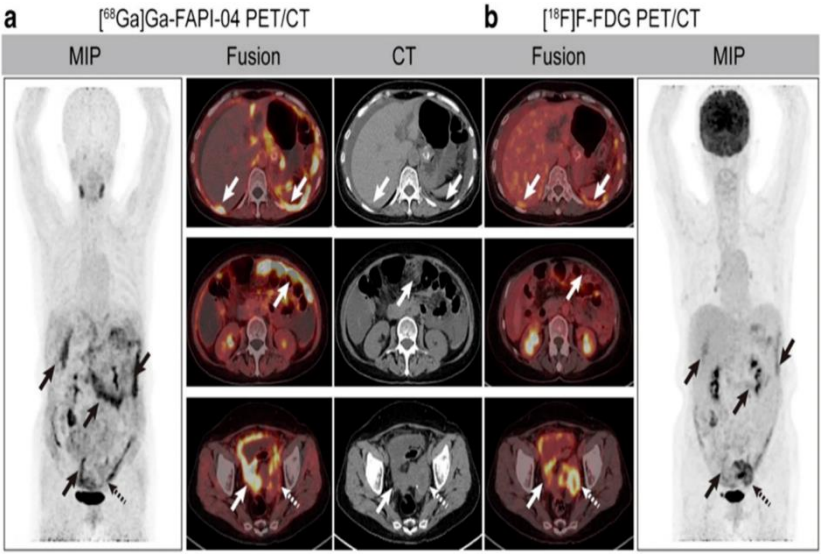
Although ^{18}F-FDG PET/CT is widely used for the evaluation of systemic metastases, it has certain limitations in detecting peritoneal carcinomatosis. Physiological FDG uptake within the gastrointestinal tract and variable activity related to bowel peristalsis may obscure small peritoneal implants. In addition, reduced metabolic activity in certain histological subtypes, such as mucinous adenocarcinoma and diffuse-type gastric cancer, may further decrease FDG sensitivity [9]. These

limitations are particularly relevant for the detection of millimetric and superficial peritoneal lesions.

In contrast, FAPI PET/CT, by targeting cancer-associated fibroblasts within the tumor microenvironment, demonstrates prominent uptake in stroma-rich peritoneal implants. A recent review evaluating clinical applications has reported that FAPI PET provides higher sensitivity and improved tumor-to-background ratios compared with FDG in the detection of peritoneal carcinomatosis. Owing to its low physiological abdominal background activity, FAPI PET/CT enables clearer visualization of small implants and mesenteric involvement [10].

Nevertheless, it should be noted that FAPI uptake is not specific to malignancy. Increased tracer accumulation may also be observed in conditions associated with stromal activation, including peritonitis, postoperative healing tissue, inflammatory adhesions, and fibrotic processes [11]. Therefore, imaging findings should be interpreted in conjunction with clinical and histopathological data.

Figure-3 ^{68}Ga-FAPI-04 PET/CT Demonstrates Higher Peritoneal Metastatic Tumor Burden than ^{18}F-FDG PET/CT in Advanced Ovarian Cancer



Representative comparison of ^{68}Ga-FAPI-04 PET/CT (a) and ^{18}F-FDG PET/CT (b). Mild uptake was observed in the primary left-sided tumor on FAPI PET/CT (SUVmax: 4.5; dotted arrowhead), whereas extensive peritoneal metastases demonstrated intense tracer accumulation (SUVmax: 9.7; solid arrowhead). In contrast, FDG PET/CT showed intense uptake in the ovarian tumor (SUVmax: 8.8; dotted arrowhead) but only limited diffuse activity within the peritoneal metastatic lesions (SUVmax: 2.5; solid arrowhead). FAPI PET/CT identified a larger burden of peritoneal metastatic disease compared with FDG PET/CT. Reproduced from Mori et al. [10], licensed under CC BY 4.0.

Pancreatic Ductal Adenocarcinoma

Pancreatic ductal adenocarcinoma (PDAC) is one of the most aggressive solid malignancies, with the majority of patients presenting at an advanced or metastatic stage at the time of diagnosis, resulting in a poor overall prognosis.

Histopathologically, PDAC is characterized by a pronounced desmoplastic reaction, with a substantial proportion of the tumor mass composed of stromal elements rather than neoplastic cells. Cancer-associated fibroblasts (CAFs) are abundant, and fibroblast activation protein (FAP) expression is particularly elevated in invasive tumor regions. This marked stromal predominance provides a strong biological rationale for FAPI-based imaging approaches [12, 13].

Although ^{18}F-FDG PET/CT is useful for demonstrating metabolic activity in pancreatic cancer, its sensitivity may be limited, particularly in small lesions and in the detection of peritoneal dissemination. In contrast, FAPI PET/CT, through its stromal targeting properties, has been reported to provide a high tumor-to-background ratio in PDAC, along with high SUVmax values and improved delineation of tumor margins in primary lesions [6, 10]. Furthermore, peritoneal metastases and stroma-rich implants have been shown to be more conspicuously visualized with FAPI compared with FDG [6, 10]. These advantages may have important clinical implications, particularly in assessing surgical resectability and in radiotherapy planning.

Nevertheless, FAPI uptake is not specific to malignancy. Increased tracer accumulation may also be observed in conditions associated with stromal activation, such as chronic pancreatitis, autoimmune pancreatitis, and other inflammatory pancreatic processes [11]. Therefore, interpretation of FAPI PET/CT findings requires correlation with contrast-enhanced CT, MRI, and clinical as well as laboratory data [11]. A multimodal imaging approach is particularly important in differentiating inflammatory from malignant processes.

Hepatocellular Carcinoma

As the most prevalent primary hepatic malignancy, hepatocellular carcinoma (HCC) remains an important global health challenge owing to its high mortality rate. The majority of cases occur in patients with chronic liver disease and cirrhotic transformation, most commonly resulting from chronic hepatitis B virus infection, chronic hepatitis C virus infection, alcohol-related liver injury, or metabolic dysfunction-associated steatotic liver disease (MASLD). [18].

The diagnostic performance of ^{18}F-FDG PET/CT in HCC is highly variable and largely dependent on tumor differentiation. Well- and moderately differentiated HCCs frequently demonstrate low FDG avidity because of increased glucose-6-phosphatase activity, reduced expression of glucose transporters, and enhanced tracer washout. Consequently, FDG PET/CT may underestimate tumor burden and show limited sensitivity in a substantial proportion of patients, particularly those with well-differentiated tumors [10,14].

In contrast, FAPI PET/CT targets fibroblast activation protein (FAP)-expressing cancer-associated fibroblasts (CAFs) within the tumor microenvironment rather than tumor cell metabolism. Progressive hepatic fibrogenesis, stromal remodeling, and increased CAF density within HCC lesions provide a strong biological rationale for FAPI-based imaging. As a result, FAPI PET/CT may demonstrate intense tracer accumulation even in lesions with limited FDG uptake, potentially improving lesion conspicuity and diagnostic confidence [10,14].

Recent studies have demonstrated promising results for FAPI PET/CT in HCC. Owing to its low physiological hepatic background activity, FAPI imaging may achieve higher tumor-to-background ratios than FDG PET/CT, facilitating the detection of

primary tumors and intrahepatic lesions. Furthermore, improved lesion delineation may contribute to more accurate assessment of tumor extent, particularly in patients undergoing surgical resection, locoregional therapies, or radiotherapy planning [14,20].

Another potential advantage of FAPI PET/CT is its ability to visualize stromal activity associated with tumor progression. Because FAP expression is closely linked to the desmoplastic tumor microenvironment, FAPI uptake may provide complementary biological information beyond conventional metabolic imaging. This characteristic may prove valuable for treatment response assessment and future theranostic applications targeting the tumor microenvironment [10,14].

Nevertheless, interpretation of FAPI PET/CT in HCC requires caution. Increased tracer uptake may also occur in non-malignant fibrotic conditions, including cirrhosis, regenerative nodules, chronic hepatitis, and other fibro-inflammatory liver disorders. Consequently, FAPI uptake alone cannot reliably distinguish malignant from benign hepatic fibrosis. Correlation with contrast-enhanced CT, MRI, laboratory findings, and clinical information therefore remains essential [15].

Although current evidence remains limited, available studies suggest that FAPI PET/CT may represent a valuable complementary imaging modality in HCC, particularly in cases with low FDG avidity or complex underlying liver disease. Larger prospective multicenter studies are needed to establish its diagnostic accuracy, prognostic significance, and potential role in treatment planning and theranostic strategies [10,14,20].

Cholangiocarcinoma

Cholangiocarcinoma (CCA) is an aggressive malignancy arising from the biliary epithelium and is frequently diagnosed at

an advanced stage. Histopathologically, CCA is characterized by a marked desmoplastic reaction and abundant stromal proliferation, resulting in a tumor microenvironment rich in cancer-associated fibroblasts (CAFs). The high density of CAFs and elevated fibroblast activation protein (FAP) expression provide a strong biological rationale for FAPI-based molecular imaging [6, 13].

Conventional imaging modalities, including contrast-enhanced CT, MRI, and 18F-FDG PET/CT, play important roles in the diagnosis and staging of cholangiocarcinoma. However, accurate delineation of tumor extent and detection of metastatic disease may remain challenging, particularly in infiltrative tumors and small metastatic lesions. Furthermore, physiological hepatic background activity may occasionally reduce lesion conspicuity on FDG PET/CT [6, 10].

One of the most important studies evaluating FAPI PET/CT in cholangiocarcinoma was performed by Pabst et al. [14]. In this prospective analysis of patients with histologically confirmed cholangiocarcinoma, 68Ga-FAPI-46 PET/CT demonstrated significantly higher tumor uptake than 18F-FDG PET/CT. The mean SUVmax of primary tumors was significantly higher with FAPI imaging, resulting in superior tumor-to-background contrast. Moreover, FAPI PET/CT detected a greater number of tumor lesions than both FDG PET/CT and conventional contrast-enhanced CT. The superiority of FAPI was particularly evident for primary tumor delineation, lymph node metastases, peritoneal metastases, and distant metastatic lesions [14]. Importantly, Pabst et al. reported that FAPI PET/CT altered TNM staging in a substantial proportion of patients and provided additional clinically relevant information that could potentially influence therapeutic decision-making. The improved lesion conspicuity achieved with FAPI imaging was largely attributed to its low physiological uptake

within normal hepatic parenchyma, allowing excellent visualization of intrahepatic tumor spread and metastatic disease [14].

These findings are consistent with recent review articles demonstrating that cholangiocarcinoma belongs to the group of highly desmoplastic malignancies in which FAPI PET/CT may provide substantial diagnostic advantages over FDG PET/CT [10,14]. Improved lesion delineation may have important implications for surgical planning, radiotherapy target volume definition, treatment response assessment, and patient selection for emerging FAPI-based theranostic approaches.

Nevertheless, FAPI uptake is not entirely tumor-specific. Increased tracer accumulation may also occur in benign biliary disorders associated with fibroblast activation, including cholangitis, biliary obstruction, postoperative fibrosis, and inflammatory changes. Therefore, FAPI PET/CT findings should always be interpreted in conjunction with morphological imaging findings, laboratory parameters, and clinical information [11].

Although current evidence remains limited, the available literature suggests that FAPI PET/CT represents one of the most promising molecular imaging approaches for cholangiocarcinoma. Larger prospective multicenter studies are warranted to further define its diagnostic performance, prognostic significance, and potential role in future theranostic strategies [6, 10, 14].

Clinical Positioning of FAPI PET/CT in Gastrointestinal Malignancies

Gastrointestinal malignancies are characterized by a prominent stromal reaction and a high density of cancer-associated fibroblasts (CAFs). This biological feature provides a strong rationale for the use of fibroblast activation protein (FAP)-targeted imaging agents, particularly within this tumor group. The literature

indicates that FAPI PET/CT achieves a high tumor-to-background ratio in many gastrointestinal cancers and offers a notable contrast advantage, especially in tumors with a desmoplastic phenotype [6, 10, 11].

Current clinical studies and reviews suggest that FAPI PET/CT may demonstrate superiority over FDG PET/CT in specific clinical scenarios. In particular:

- The ability to achieve high contrast in desmoplastic and stroma-rich tumors (e.g., pancreatic ductal adenocarcinoma and cholangiocarcinoma) [6, 10],
- Improved detectability of primary lesions in histological subtypes with low FDG avidity [6, 15],
- Enhanced visualization of liver metastases due to low physiological hepatic background activity [10, 16],
- Increased lesion conspicuity in the assessment of peritoneal metastases and disease recurrence [10, 17, 18],

represent key potential clinical advantages of FAPI PET/CT.

However, FAP expression is not limited to malignant tissues and may also be upregulated in fibrotic, inflammatory, and regenerative processes. This may lead to false-positive findings, particularly in conditions such as cirrhotic liver disease, chronic pancreatitis, cholangitis, gastritis, and postoperative fibrosis [11, 19]. Therefore, FAPI PET/CT findings should be interpreted in conjunction with morphological imaging, clinical data, and, when necessary, histopathological confirmation.

Moreover, a significant amount of the existing evidence is based on small-scale, retrospective studies conducted at single centers, which may limit broader generalizations. The limited availability of large-scale, multicenter prospective studies based on

standardized imaging protocols currently restricts the full integration of FAPI PET/CT into clinical guidelines [6, 10, 15]. In addition, variability in standardized uptake value (SUV) thresholds and optimal imaging timing across institutions highlights the need for further standardization.

Table-1 Comparison of ^{18}F-FDG PET/CT and ^{68}Ga-FAPI PET/CT in oncologic imaging

Parameter	***^{18}F-FDG PET/CT***	***^{68}Ga-FAPI PET/CT***
Biological target	Increased glucose metabolism (GLUT-1 expression, tumor cell proliferation)	Fibroblast activation protein (FAP)-positive cancer-associated fibroblasts (CAFs), stromal activity
Relation to tumor phenotype	Reflects cellular density and metabolic activity	Advantageous in desmoplastic / stroma-rich tumors
Physiological background (liver)	Moderate to high	Low
Physiological bowel activity	Variable, often increased	Generally low
Primary tumor detection	Effective in most gastrointestinal malignancies	Advantageous in FDG-negative or low-FDG-avid subtypes
Lymph node metastasis	Good sensitivity; prone to inflammatory uptake	Higher sensitivity reported in some meta-analyses; uptake may occur in inflammatory nodes
Liver metastasis	May be limited due to hepatic background activity	Low hepatic background → higher tumor-to-background ratio (TBR)
Peritoneal metastasis	Limited in small lesions	Higher contrast → improved detection of small implants
Inflammation sensitivity	High (infection, granulomatous disease)	Uptake may occur in fibrotic and inflammatory tissues
Patient preparation	Requires fasting and blood glucose control	Minimal preparation required
Standardization	Well-established guidelines and	Standardization is ongoing

	standardization	
Level of evidence	Strong evidence accumulated over decades	Increasing but still limited prospective data

Potential Pitfalls and Limitations of FAPI PET/CT

Although FAPI PET/CT has demonstrated considerable diagnostic potential in gastrointestinal cancers, awareness of its limitations is essential for accurate image interpretation. While FAP expression is markedly elevated in cancer-associated fibroblasts, it is also present in activated fibroblasts involved in physiological and pathological tissue remodeling processes. As a result, increased FAPI accumulation may occur not only in malignant lesions but also in benign conditions associated with wound healing, fibrosis, or inflammation, thereby reducing tracer specificity in certain clinical settings [15,21].

One of the principal challenges associated with FAPI PET/CT is the limited specificity resulting from FAP expression in non-neoplastic processes. Increased tracer uptake has been documented in several inflammatory diseases, including gastritis, esophagitis, pancreatitis, cholangitis, inflammatory bowel disease, and peritonitis. Furthermore, conditions characterized by active tissue repair or fibrosis, such as postoperative healing, radiation-induced fibrosis, surgical scars, and chronic fibroinflammatory disorders, may demonstrate prominent FAPI accumulation. Consequently, these benign processes can mimic malignant lesions and should be carefully differentiated during image interpretation [15,21].

The interpretation of FAPI PET/CT may be particularly challenging in hepatopancreatic diseases. In the liver, cirrhosis, regenerative nodules, and ongoing fibrogenesis can produce

increased tracer uptake unrelated to malignant transformation. Likewise, chronic and autoimmune pancreatitis may demonstrate intense FAPI accumulation owing to activated fibroblasts within the inflammatory stroma. Consequently, these benign conditions can mimic malignancy and may limit the specificity of FAPI PET/CT, particularly in the evaluation of pancreatic cancer[14,15].

Another limitation is the presence of physiological or benign uptake in several normal tissues. Variable tracer accumulation has been described in the uterus, breast tissue, salivary glands, healing wounds, arthritic joints, and sites of previous surgical intervention. Awareness of these physiological and benign patterns is essential to avoid overstaging and inappropriate clinical decision-making [15,21].

From a methodological perspective, the current evidence supporting FAPI PET/CT remains relatively limited. Most published studies are retrospective, single-center investigations with modest sample sizes. Furthermore, significant heterogeneity exists regarding patient populations, imaging protocols, radiotracer selection, and reference standards, making direct comparison between studies challenging [5,10,14].

In addition, standardized interpretation criteria have not yet been fully established. Unlike 18F-FDG PET/CT, which benefits from decades of clinical experience and internationally accepted reporting frameworks, FAPI PET/CT lacks universally accepted SUV cut-off values, optimal imaging acquisition protocols, and standardized reporting systems. Variability among different FAPI tracers, including 68Ga-FAPI-04, 68Ga-FAPI-46, and emerging 18F-labeled compounds, may further influence quantitative measurements and diagnostic performance [10,14].

Consequently, FAPI PET/CT should currently be regarded as a complementary imaging modality rather than a stand-alone

diagnostic tool. Correlation with clinical findings, laboratory parameters, histopathological results, and conventional imaging modalities remains essential. Future large-scale prospective studies and standardized imaging protocols are needed to further clarify its diagnostic accuracy, reproducibility, and optimal clinical applications.

Theranostic Approach and Future Perspectives

The remarkable success of FAPI-targeted PET imaging has stimulated growing interest in theranostic applications targeting fibroblast activation protein (FAP). The theranostic concept is based on the use of a common molecular target for both diagnosis and therapy, enabling patient selection, treatment planning, and response monitoring using a single biological pathway [20, 21].

In recent years, several FAP-targeted therapeutic radioligands have been developed by labeling FAPI compounds with beta-emitting radionuclides such as 177Lu and 90Y. Following confirmation of high FAP expression on diagnostic PET imaging, these therapeutic agents can selectively deliver radiation to the tumor microenvironment through cancer-associated fibroblasts (CAFs), which are abundantly present in many gastrointestinal malignancies [20, 22].

Among gastrointestinal tumors, pancreatic ductal adenocarcinoma, cholangiocarcinoma, gastric cancer, and metastatic colorectal cancer appear particularly suitable for FAPI-based radionuclide therapy because of their pronounced desmoplastic reaction and extensive stromal component. Early clinical experiences have demonstrated encouraging tumor targeting, acceptable safety profiles, and preliminary antitumor

activity in heavily pretreated patients with advanced solid malignancies [20, 22].

Beyond conventional beta-emitting radionuclides, alpha-particle-emitting agents targeting FAP are currently under investigation. Owing to their high linear energy transfer and short tissue penetration range, alpha emitters may potentially enhance therapeutic efficacy while minimizing radiation exposure to surrounding normal tissues. Although clinical evidence remains limited, these approaches represent a promising area of ongoing research [21].

Future developments are expected to focus on improving tumor retention, optimizing dosimetry, and enhancing therapeutic efficacy through next-generation FAPI ligands. In addition, combination strategies integrating FAPI-targeted radionuclide therapy with chemotherapy, immunotherapy, or external beam radiotherapy may further improve treatment outcomes. Preclinical studies have suggested that FAP-targeted therapies may enhance antitumor immune responses and potentially synergize with immune checkpoint inhibitors [21, 23].

Despite these promising advances, several challenges remain, including the need for standardized patient selection criteria, optimized treatment protocols, and long-term efficacy data. Ongoing prospective clinical trials evaluating FAPI-based radioligand therapies are expected to further define their role within precision oncology and expand the clinical utility of tumor microenvironment-targeted theranostics. Particularly in desmoplastic gastrointestinal malignancies, FAPI-based theranostics may provide a novel treatment strategy for patients with limited therapeutic options [20-22].

Overall, FAPI-based theranostics represents one of the most rapidly evolving fields in nuclear medicine and may substantially

broaden the clinical impact of FAP-targeted imaging in gastrointestinal malignancies in the near future.

Key Points and Clinical Implications

• FAPI PET/CT targets fibroblast activation protein (FAP)-expressing cancer-associated fibroblasts (CAFs) within the tumor microenvironment, representing a fundamentally different biological approach from 18F-FDG PET/CT, which reflects glucose metabolism [1,10].

• Owing to its low physiological background uptake, FAPI PET/CT frequently provides higher tumor-to-background ratios and improved lesion conspicuity in gastrointestinal malignancies [10,14].

• FAPI PET/CT may be particularly advantageous in tumors characterized by prominent desmoplastic reactions, including pancreatic ductal adenocarcinoma, cholangiocarcinoma, diffuse-type gastric cancer, and peritoneal carcinomatosis [10,14,16].

• Compared with FDG PET/CT, FAPI PET/CT has demonstrated improved detection rates for primary tumors, lymph node metastases, liver metastases, and peritoneal implants in selected gastrointestinal cancers [5,6].

• The low physiological hepatic and abdominal background activity of FAPI tracers may facilitate the detection of small liver metastases and peritoneal lesions that are difficult to identify with FDG PET/CT [4,19].

• FAPI uptake is not tumor-specific and may occur in inflammatory, fibrotic, regenerative, and postoperative conditions. Therefore,

imaging findings should always be interpreted in conjunction with clinical, histopathological, and conventional imaging data [15,21].

• Current evidence supports the role of FAPI PET/CT as a complementary imaging modality rather than a replacement for FDG PET/CT. Appropriate patient selection remains essential for maximizing its clinical benefit [5,10,14].

• Future developments in FAPI-targeted imaging and theranostic applications may further expand the role of tumor microenvironment-targeted strategies in precision oncology and personalized radionuclide therapy [14].

Conclusion

As a cutting-edge molecular imaging tool, FAPI PET/CT focuses on the tumor microenvironment instead of cellular metabolic activity, introducing an innovative approach to assessing gastrointestinal cancers. This technique binds to cancer-associated fibroblasts that exhibit fibroblast activation protein (FAP), resulting in exceptional tumor-to-background contrast and sharper lesion visibility across various GI tract malignancies especially those with significant stromal density and strong desmoplastic responses.

A growing body of research indicates that FAPI PET/CT can outperform ^{18}F-FDG PET/CT in specific clinical settings, such as pancreatic ductal adenocarcinoma, diffuse-type gastric cancer, cholangiocarcinoma, peritoneal carcinomatosis, and hepatic metastases. Because FAPI radiotracers display minimal physiological background uptake, they can reveal lesions that typically remain hidden on standard metabolic scans, thereby refining initial staging, therapeutic choices, and the evaluation of treatment efficacy.

Nevertheless, several limitations remain. FAPI uptake is not specific to malignant tissues and may occur in inflammatory,

fibrotic, regenerative, and postoperative conditions, potentially resulting in false-positive findings. Furthermore, the current evidence base is still largely derived from retrospective studies, and standardized imaging protocols and interpretation criteria have yet to be fully established.

Beyond diagnostic imaging, the development of FAPI-targeted theranostic approaches represents an exciting future direction in nuclear oncology. The integration of FAPI-based imaging with targeted radionuclide therapy may further expand the clinical utility of tumor microenvironment-targeted strategies and contribute to the advancement of precision medicine.

In conclusion, FAPI PET/CT should currently be regarded as a complementary imaging modality with significant potential in gastrointestinal oncology. Ongoing prospective multicenter studies and future theranostic developments will be crucial in defining its optimal clinical role and determining its long-term impact on patient management and outcomes. As the field continues to evolve, FAPI-based imaging and theranostic applications have the potential to become integral components of precision oncology in gastrointestinal malignancies.

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FAPI PET/CT IN GYNECOLOGİCAL AND UROLOGİCAL MALİGNANCİES

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Gynecological and urological malignancies constitute a substantial proportion of the global cancer burden and remain among the leading causes of cancer-related morbidity and mortality worldwide. In addition to ovarian, cervical, and endometrial cancers, prostate, bladder, and renal tumors are frequently encountered in clinical practice and represent a heterogeneous group of diseases characterized by diverse biological behavior and variable clinical courses. Despite significant advances in diagnostic and therapeutic strategies, early detection remains challenging in many cases, while accurate staging continues to be of critical importance for appropriate treatment planning.

Molecular imaging modalities play a central role in the evaluation of these malignancies. In particular, positron emission tomography (PET)-based imaging is widely used for tumor detection, staging, restaging, and assessment of treatment response. Fluorodeoxyglucose (FDG) PET has held a prominent position for many years due to its ability to reflect tumor glucose metabolism and has demonstrated high diagnostic accuracy across a variety of gynecological and urological malignancies. However, variable FDG uptake among certain tumor subtypes, as well as physiological tracer accumulation in normal tissues, may limit its sensitivity and specificity in specific clinical settings.

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To overcome these limitations, interest in novel radiopharmaceuticals has increased considerably in recent years. Fibroblast activation protein inhibitors (FAPI), which target cancer-associated fibroblasts within the tumor microenvironment, have emerged as promising PET tracers. By targeting not only tumor cell metabolism but also the stromal components of the tumor microenvironment, FAPI-based imaging provides higher tumor-to-background contrast and offers the potential to improve lesion detection across a broad spectrum of malignancies.

This chapter reviews the applications of FAPI PET in gynecological and urological malignancies, with particular emphasis on its clinical advantages and potential limitations.

1. FAPI PET/CT in Gynecological Malignancies

1.1. General Overview

Radiolabeled fibroblast activation protein inhibitors (FAPI) represent a novel class of radiopharmaceuticals that have demonstrated promising diagnostic performance across a variety of tumor types (Vahidfar et al., 2021a).

Fibroblast activation protein (FAP), a type II serine protease, is expressed by cancer-associated fibroblasts (CAFs), which are key components of the tumor microenvironment. These CAFs are present within the stromal architecture of many solid tumors and are generally associated with tumor progression and poor prognosis. Owing to this distinctive expression pattern, FAPI-based imaging agents have attracted increasing interest as an alternative or complementary approach to conventional PET tracers in oncologic imaging (Vahidfar et al., 2021b; Barbazan et al., 2019).

Currently, the most widely used PET/CT radiopharmaceutical in clinical oncology is 18F-FDG, which accumulates in tissues primarily according to glucose metabolism and cellular glucose

consumption. Consequently, 18F-FDG uptake may be influenced by various physiological and external factors, including blood glucose levels, physical activity, and nutritional status (Almuhaideb et al., 2011).

18F-FDG PET/CT is a well-established imaging modality that demonstrates high diagnostic performance in the detection of metastatic lymph nodes and distant metastases and is widely used in routine clinical practice. Several studies have shown that it provides higher sensitivity than magnetic resonance imaging (MRI) and contrast-enhanced computed tomography (CT) for the detection of lymph node metastases (Fischerova et al., 2024; Rahman et al., 2019). However, its diagnostic specificity may be limited by high physiological background activity in certain tissues and by uptake related to blood glucose levels, physical activity, and inflammatory or infectious processes (Lakhani et al., 2017). Furthermore, reduced sensitivity for the detection of micrometastases and lymph nodes smaller than 1 cm is considered a significant limitation (Wei et al., 2025; Amant et al., 2005). Therefore, there is growing interest in the development of novel PET/CT radiopharmaceuticals capable of providing greater specificity and diagnostic accuracy.

In addition, 68Ga-FAPI PET/CT imaging can be performed without requiring patients to fast or undergo prolonged resting periods, and its diagnostic performance is not affected by blood glucose levels. Moreover, this imaging modality can be completed within a relatively short time and demonstrates lower off-target uptake compared with 18F-FDG, potentially resulting in improved image quality and diagnostic clarity (Cescato et al., 2008; Siripongsatian et al., 2022).

In a clinical study conducted by Wang et al., PET/CT findings obtained with 18F-FDG and 68Ga-FAPI-04 were compared, and

physiological ovarian uptake of 68Ga-FAPI-04 was found to be unaffected by the menstrual cycle. In contrast, 18F-FDG demonstrated uptake in both malignant lesions and functional (hormonally active) ovarian tissue, which may lead to diagnostic uncertainty. Overall, these findings suggest that 68Ga-FAPI may serve as a promising radiopharmaceutical with higher specificity for the evaluation of gynecological malignancies (Sirinpongsatian et al., 2022).

Considering the well-recognized limitations of 18F-FDG, the use of radiolabeled FAPI-based tracers in PET/CT imaging has been proposed to offer superior diagnostic performance, particularly in gynecological malignancies as well as in various malignant and benign conditions (Promteangtrong et al., 2022).

Supporting this view, a multicenter study evaluated the diagnostic performance of 68Ga-FAPI PET/CT across different gynecological malignancies and demonstrated its potential utility in a variety of neoplasms, including breast, ovarian, cervical, endometrial, and fallopian tube tumors, as well as uterine leiomyosarcoma. These findings suggest that 68Ga-FAPI PET/CT may have a broad range of clinical applications in gynecologic oncology practice (Dendl et al., 2021).

1.2. FAPI PET/CT in Ovarian Malignancies

Among gynecological cancers, ovarian cancer ranks behind cervical and uterine cancers in incidence; however, it is associated with the highest mortality rate and the poorest prognosis. Although less common than breast cancer, it is associated with an approximately threefold higher mortality rate (Coburn et al., 2017). The primary reason for this disparity is the lack of specific symptoms during the early stages of the disease, resulting in the majority of cases being diagnosed at an advanced stage. Consequently, treatment success is often limited. Furthermore,

ovarian cancer–related mortality is projected to increase substantially by 2040, further emphasizing the importance of early diagnosis and effective therapeutic strategies (Yoneda et al., 2012).

Epidemiological data indicate that ovarian cancer predominantly affects older women, particularly those in the postmenopausal period. The median age at diagnosis is generally between 50 and 65 years, although the disease may also occur in younger individuals. The lifetime risk of developing ovarian cancer in women is approximately 1–2% (Momenimovahed et al., 2019).

Ovarian cancer typically spreads through peritoneal, lymphatic, or hematogenous routes and frequently disseminates extensively through the circulation of ascitic fluid within the peritoneal cavity. From an imaging perspective, 18F-FDG PET/CT is an effective modality for detecting small metastatic lesions and metastatic foci that may be difficult to identify using conventional imaging techniques.

Nevertheless, several limitations should be considered in clinical practice. One of the major drawbacks of 18F-FDG PET/CT is the potential for false-positive findings resulting from physiological FDG uptake in normal ovarian tissue. This issue is particularly pronounced in premenopausal women due to the physiological activity of the ovaries (Kessler et al., 2022; Li et al., 2024; Kitajima et al., 2011).

Although FDG PET remains one of the cornerstone imaging modalities for ovarian cancer, its limitations in certain clinical settings have prompted the search for alternative approaches. In this context, FAPI PET, which targets the tumor microenvironment, has emerged as a promising imaging modality capable of providing complementary diagnostic information.

Zheng et al. reported that 68Ga-FAPI PET/CT demonstrated higher sensitivity than 18F-FDG PET/CT for the detection of ovarian cancer lesions. Their findings were as follows:

Primary ovarian tumors:

- 68Ga-FAPI PET/CT: 100% (14/14)
- 18F-FDG PET/CT: 78% (11/14)

Lymph node metastases:

- 68Ga-FAPI PET/CT: 100% (75/75)
- 18F-FDG PET/CT: 80% (60/75)

Peritoneal and pleural metastases:

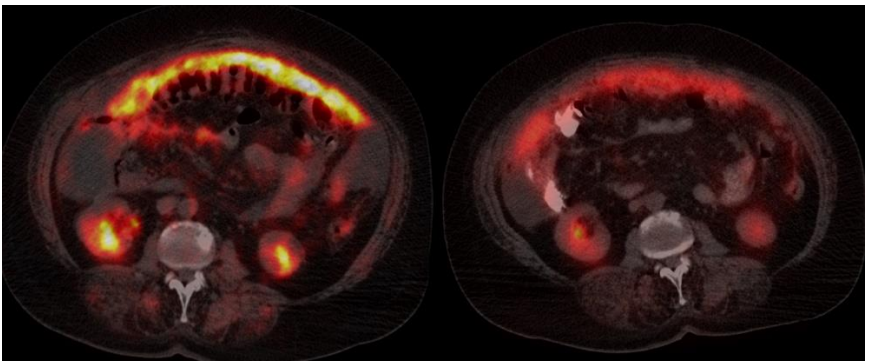
- 68Ga-FAPI PET/CT: 100% (9/9)
- 18F-FDG PET/CT: 56% (5/9)

Overall, these results indicate that 68Ga-FAPI PET/CT provides superior diagnostic sensitivity and may serve as a complementary imaging modality to 18F-FDG PET/CT in the evaluation of ovarian cancer (Zheng et al., 2023).

Peritoneal dissemination represents one of the most common metastatic patterns in ovarian cancer and poses significant challenges in disease management. In this context, Liu et al. compared the diagnostic performance of 68Ga-FAPI PET/CT and 18F-FDG PET/CT in patients with suspected platinum-sensitive recurrent ovarian cancer. The findings demonstrated that 68Ga-FAPI PET/CT provided higher tumor-to-background contrast and significantly greater sensitivity and specificity, particularly for the detection of peritoneal metastases and recurrent lesions. Furthermore, the study suggested that this modality may also offer clinical value in the assessment of treatment response. Overall,

these results indicate that 68Ga-FAPI PET/CT may provide substantial advantages over 18F-FDG PET/CT, especially in the evaluation of peritoneal disease burden in ovarian cancer (Liu et al., 2023).

Figure 1. Comparative imaging of peritoneal metastases in a patient with ovarian cancer using FAPI PET/CT and FDG PET/CT; FAPI PET images are shown on the left, and FDG PET images on the right.



Current evidence suggests that FAPI PET may improve diagnostic accuracy and enable a more comprehensive assessment of disease extent. This may facilitate more accurate staging and contribute to more effective treatment planning. Consequently, FAPI PET has the potential to support personalized patient management and improve clinical outcomes. These characteristics highlight its growing importance and suggest potential advantages over FDG PET in the evaluation of ovarian cancer.

1.3. FAPI PET/CT in Cervical Malignancies

Cervical cancer ranks as the fourth leading cause of cancer-related mortality among women and remains a significant global health concern. Although its incidence has declined in recent years due to improvements in healthcare services and the widespread implementation of screening programs, early diagnosis and

accurate staging continue to be essential for effective treatment planning and prognostic assessment (Shi et al., 2025).

In the FIGO staging system for cervical cancer, lymph node involvement is recognized as a major prognostic factor. According to this classification, the presence of regional lymph node metastases is categorized as stage IIIC disease. Pelvic lymph node involvement is classified as stage IIIC1, whereas para-aortic lymph node involvement is classified as stage IIIC2 (Bhatla et al., 2019).

Therefore, accurate assessment of lymph node status through imaging modalities and other diagnostic approaches is critical for reliable disease staging and the selection of appropriate treatment strategies in cervical cancer. Since lymph node metastases have a direct impact on both treatment planning and prognosis, their early and reliable detection plays a pivotal role in clinical management.

In a study evaluating patients with cervical cancer, FAPI PET and FDG PET imaging were directly compared. The results demonstrated no substantial differences between the two modalities with respect to SUVmax and SUVmean values. However, significant differences were observed in tumor-to-background ratio (TBR) measurements. In the evaluation of primary lesions, TBR values calculated relative to both the blood pool and liver background were higher with FAPI than with FDG. Similarly, metastatic lymph nodes exhibited higher TBR values on FAPI imaging compared with FDG. Collectively, these findings indicate that FAPI, owing to its lower background activity, enables clearer delineation of lesions from surrounding tissues and may therefore offer advantages over FDG in terms of lesion detectability (Bollineni et al., 2016).

Table 1. In a comparative analysis of patients with metastatic lymph node involvement, 18F-FAPI PET/CT detected a greater number of metastatic lymph nodes overall than 18F-FDG PET/CT.

These findings suggest that FAPI-based imaging may provide higher sensitivity, particularly in the assessment of lymph node metastases. This advantage may be attributable to the ability of FAPI to target tumor stroma and cancer-associated fibroblast activity, resulting in enhanced lesion-to-background contrast.

Nevertheless, 18F-FDG PET/CT identified additional metastatic lymph nodes in certain cases. In particular, FDG imaging appeared to offer an advantage in the detection of very small lymph nodes.

Overall, the available data support the high diagnostic performance of 18F-FAPI PET/CT for the detection of metastatic lymph node involvement. However, the potential complementary value of 18F-FDG PET/CT in the evaluation of very small lymph node metastases should also be taken into consideration (Bollineni et al., 2016).

Table 1. Number of Metastatic Lymph Nodes Detected by ^{18}F-FAPI-04 PET/CT and ^{18}F-FDG PET/CT in Patients with Metastatic Lymph Nodes

Patient No.	Number of Metastatic LN		
	FAPI	FDG	Total
1	7	5	7
2	4	3	4
3	2	1	2
4	1	2	2
5	22	7	22
6	25	3	25
7	21	23	23
Total	**82**	**44**	**85**

1.4. FAPI PET/CT in Endometrial Malignancies

Endometrial cancer is the sixth most common malignancy among women worldwide. At the time of diagnosis, approximately 70% of patients present with disease confined to the uterine corpus, a finding generally associated with early-stage disease and a favorable prognosis. Although treatment outcomes are generally successful, recurrence occurs in approximately 15–20% of cases (Zhang et al., 2022).

18F-FDG PET/CT is widely used in the staging of endometrial carcinoma and has demonstrated high diagnostic accuracy for both the preoperative detection of lymph node metastases and the identification of postoperative recurrence (Usmani et al., 2025).

In contrast, the role of radiolabeled FAPI in the diagnosis and staging of endometrial cancer has not yet been clearly established. Available evidence suggests that its diagnostic utility may be limited by relatively high uptake in normal uterine tissue and comparatively lower uptake in metastatic endometrial lesions (Kessler et al., 2022).

Physiological FAPI uptake within normal endometrial tissue may represent a limitation in the assessment of primary endometrial tumors. Owing to the dynamic nature of the endometrium and its dependence on hormonal cycling, variable levels of FAP expression may occur in normal tissue, leading to physiological uterine uptake and potentially complicating the differentiation between benign and malignant processes. Consequently, image interpretation may be particularly challenging in small or low-grade tumors.

Nevertheless, because FAPI PET/CT targets the tumor microenvironment rather than solely cellular metabolism, it may enable the visualization of lesions with relatively low metabolic activity. Despite its limitations in the assessment of primary tumors, this characteristic may make FAPI PET/CT a valuable complementary modality for evaluating metastatic disease burden.

However, current clinical evidence remains limited, and larger studies are required to better define its role in endometrial cancer.

On the other hand, 18F-FDG PET/CT remains an important imaging modality in gynecologic oncology, although its specificity may occasionally be limited by uptake associated with benign conditions. Therefore, the combined interpretation of FAPI PET/CT and FDG PET/CT may improve diagnostic accuracy by providing complementary information regarding different aspects of tumor biology.

Through this integrated imaging approach, both the metabolic activity and stromal component of the primary tumor can be evaluated simultaneously, allowing for a more comprehensive characterization of tumor heterogeneity. The contribution of FAPI may be particularly valuable in mucinous or low-grade tumors that exhibit low FDG avidity, whereas FDG imaging may retain an advantage in the detection of certain very small metastatic lymph nodes. Furthermore, lesions demonstrating FAPI positivity but FDG negativity may reflect stromal-dominant tumor regions, while areas with intense FDG uptake may indicate more aggressive metabolic activity.

From a treatment-planning perspective, the combined use of both modalities may contribute to more accurate assessment of disease extent, improved identification of target lesions, and optimization of therapeutic strategies. Multimodal PET imaging may be especially beneficial for surgical planning, delineation of radiotherapy target volumes, and assessment of response to systemic therapies. In addition, combined evaluation may improve diagnostic confidence in differentiating residual disease from post-treatment fibrotic or inflammatory changes.

1.5. Pitfalls and Interpretative Challenges of FAPI PET/CT in Gynecological Malignancies

Because fibroblast activation protein expression is not restricted to malignant tissues and may also occur in various physiological and benign conditions, several interpretative challenges may arise during image analysis. Therefore, FAPI uptake should not be considered synonymous with malignancy in all circumstances.

1.5.1. Physiological Uterine Uptake

The uterus is a dynamic organ that undergoes continuous remodeling throughout life under hormonal influence. Consequently, variable degrees of physiological FAPI uptake may be observed in both the endometrium and myometrium, particularly in premenopausal women. In some cases, marked physiological uptake may lead to false-positive interpretations during the evaluation of primary uterine malignancies.

1.5.2. Benign Uterine and Ovarian Lesions

Leiomyomas, adenomyosis, and certain benign ovarian lesions may demonstrate increased FAPI uptake due to enhanced stromal activity. In lesions with a prominent fibrotic component, tracer accumulation may reach levels comparable to those observed in malignant tumors. Therefore, correlation of FAPI PET/CT findings with ultrasonography and magnetic resonance imaging (MRI) is essential for accurate interpretation.

1.5.3. Endometriosis and Inflammatory Processes

Endometriosis represents one of the most important pitfalls of FAPI PET/CT in gynecological imaging. Owing to chronic inflammation and fibrotic tissue formation, endometriotic lesions may exhibit intense FAPI uptake. Peritoneal endometriotic implants, in particular, may mimic peritoneal metastases associated with

ovarian cancer or other gynecological malignancies. Similarly, pelvic inflammatory disease and infectious processes may also result in false-positive findings.

1.5.4. Post-Treatment Changes

As FAP expression plays a role in wound healing and tissue repair, increased FAPI uptake may be observed following surgery or radiotherapy. Postoperative granulation tissue and radiation-induced fibrotic changes may mimic residual tumor or local recurrence. Therefore, detailed knowledge of the patient's treatment history is crucial for accurate image interpretation.

1.5.5. Lymph Node and Peritoneal Assessment

FAPI uptake may be observed in reactive or inflammatory lymph nodes, potentially leading to false-positive findings during nodal staging. Similarly, peritoneal fibrotic changes resulting from prior surgery, inflammation, or endometriosis may be difficult to distinguish from metastatic implants. This issue is particularly relevant in ovarian cancer, where peritoneal dissemination is common and careful image interpretation is essential.

1.6. FAPI-Based Theranostic Approaches in Gynecological Malignancies

FAPI-based agents have attracted considerable attention as an important theranostic platform because they target fibroblast activation protein (FAP), which is highly expressed within the tumor stroma. Consequently, these agents are not only valuable for diagnostic imaging but also hold promise for radionuclide therapy applications. Characterized by high tumor uptake and low background activity, FAPI tracers can be labeled with therapeutic radioisotopes and potentially used for targeted treatment. However,

clinical experience in gynecological malignancies remains limited, and the currently available evidence is largely derived from early-phase studies.

Ovarian cancer is among the gynecological malignancies most in need of novel therapeutic strategies because of its aggressive biological behavior and high recurrence rates. Although primary debulking surgery followed by platinum-based chemotherapy remains the current standard of care, a substantial proportion of patients eventually experience disease recurrence (du Bois et al., 2009). Therefore, FAPI-targeted radionuclide therapies are being investigated, particularly in patients with advanced-stage disease who have exhausted conventional treatment options. In a study involving patients with advanced metastatic cancers, 177Lu-FAPI-04 demonstrated lower radiation doses to critical organs compared with currently available peptide receptor–targeted radionuclide therapies. However, due to the relatively limited tumor retention time of the tracer, the authors emphasized the need for the development of novel FAPI derivatives with improved tumor retention characteristics (Kuyumcu et al., 2021). Furthermore, early clinical studies using 177Lu-FAP-2286 reported that the treatment was generally well tolerated and was not associated with significant toxicity. These findings suggest that FAPI-based radionuclide therapy may represent a feasible therapeutic option for ovarian cancer in the future (Baum et al., 2022).

In cervical cancer, surgery and radiotherapy constitute the main treatment modalities for early-stage disease, whereas systemic therapies play a more prominent role in advanced stages. At present, no clinical studies have directly evaluated the therapeutic use of radiolabeled FAPI agents in cervical cancer. Nevertheless, the promising results achieved with radioimmunotherapy approaches targeting HPV-related antigens suggest that FAPI-based therapies may also warrant future investigation in this setting.

For endometrial cancer, current treatment options include surgery, radiotherapy, brachytherapy, and chemotherapy. With the increasing incorporation of molecular classification into clinical practice, targeted therapeutic strategies have gained growing importance. However, data regarding the role of FAPI-based radionuclide therapies in endometrial cancer remain extremely limited. Consequently, further clinical studies are needed to determine the efficacy, safety, and optimal patient selection criteria for FAPI-targeted therapeutic approaches.

Based on the currently available evidence, the most established application of FAPI agents in gynecological malignancies remains diagnostic imaging. Nevertheless, the use of FAPI derivatives labeled with therapeutic radioisotopes, particularly in tumors exhibiting high FAP expression, may become an integral component of personalized theranostic strategies in the future. Early clinical experience indicates an acceptable safety profile for these agents, and ongoing studies are expected to further clarify their true clinical value in gynecological cancers.

1.7. Future Perspectives of FAPI in Gynecological Malignancies

The role of stromal remodeling and cancer-associated fibroblasts in tumor progression is becoming increasingly well understood in ovarian, cervical, and endometrial cancers. Accordingly, establishing the relationship between FAPI imaging findings and tumor biology, aggressiveness, and treatment response may pave the way for the future use of FAPI as both a prognostic and predictive biomarker.

Particularly in ovarian cancer, accurate assessment of peritoneal dissemination, planning of cytoreductive surgery, and evaluation of recurrent disease represent major clinical challenges. If the utility of FAPI PET/CT in these settings is confirmed in larger patient cohorts, it may assume an important role in patient selection and

treatment decision-making. In endometrial and cervical cancers, investigation of the relationship between imaging findings and molecular classification systems or risk stratification models may contribute to more refined risk assessment and personalized management strategies in the future.

1.8. Limitations of FAPI in Gynecological Malignancies

Current evidence regarding the use of FAPI PET/CT in gynecological malignancies is derived predominantly from studies involving ovarian cancer, with relatively limited data available for cervical and endometrial cancers. Consequently, its diagnostic performance and clinical utility across different histological subtypes have not yet been adequately defined. In particular, the heterogeneity of FAP expression among rare gynecological tumors and distinct molecular subgroups remains an important area of uncertainty.

The inherently dynamic physiological nature of gynecological organs may also influence image interpretation. Factors such as the menstrual cycle, hormonal fluctuations, postoperative changes, and radiotherapy-induced stromal reactions may affect FAPI uptake patterns. As a result, differentiation between benign and malignant processes may be challenging in certain clinical scenarios.

In addition, the prognostic significance of FAPI uptake and its value in predicting treatment response remain unclear. Most available studies have relatively short follow-up periods and limited clinical outcome data. Therefore, the impact of FAPI PET/CT on patient survival, long-term outcomes, and treatment decision-making has not yet been conclusively established. To define the true clinical value of this modality in gynecological malignancies, large-scale, multicenter, prospective studies with long-term follow-up are required.

2. FAPI PET/CT in Urological Malignancies

2.1. General Overview

Accurate staging of genitourinary malignancies is critical for optimizing treatment planning and improving patient outcomes. In recent years, advances in molecular imaging modalities, particularly 18F-FDG PET/CT and prostate-specific membrane antigen (PSMA)-based PET/CT, have led to significant improvements in the staging of genitourinary cancers compared with conventional imaging techniques. These modalities have demonstrated high diagnostic performance for detecting metastatic disease, even in cases without anatomically apparent abnormalities (Hofman et al., 2020; Richters et al., 2023; Ottenhof et al., 2022).

Despite these advances, several important limitations remain. Incomplete detection of metastatic lesions, reduced sensitivity of 18F-FDG PET/CT and 68Ga-PSMA PET/CT in certain clinical settings, false-positive findings related to physiological tracer uptake or postoperative inflammation, and the absence or heterogeneity of PSMA expression are among the major challenges encountered in clinical practice. Consequently, there is increasing interest in exploring alternative imaging approaches that may improve staging accuracy and facilitate more effective treatment decision-making (Einerhand et al., 2023; Leijte et al., 2009; Jansen et al., 2021).

Like many other malignancies, genitourinary cancers are not composed solely of neoplastic cells but rather exist within a complex tumor microenvironment containing multiple cellular components (Valkenburg et al., 2018). Activated fibroblasts and myofibroblasts, collectively referred to as cancer-associated fibroblasts (CAFs), are abundant within the tumor microenvironment and play important roles in tumor growth, cellular invasion and metastasis, angiogenesis, and immune

regulation (Mueller et al., 2004). Unlike normal fibroblasts, a substantial proportion of CAFs exhibit marked overexpression of fibroblast activation protein (FAP), making it an attractive and targetable biomarker for noninvasive molecular imaging (Dendl et al., 2021; Costa et al., 2018).

Conventional 18F-FDG PET/CT is based on glucose metabolism and is limited in the evaluation of urinary tract and pelvic malignancies because of intense physiological urinary excretion of the tracer. In contrast, FAPI PET/CT demonstrates relatively low physiological urinary activity, allowing clearer visualization of primary tumors, local recurrences, and metastatic lesions in urological malignancies such as prostate, bladder, renal, and testicular cancers. Furthermore, higher lesion detection rates have been reported in certain tumors with low FDG avidity. Consequently, FAPI-based imaging is increasingly recognized as a promising modality in uro-oncology, both for diagnostic purposes and potential theranostic applications.

2.2. FAPI PET/CT in Renal Cell Carcinoma (RCC)

Renal cell carcinoma (RCC) is the 14th most common malignancy worldwide, with incidence rates increasing markedly between the ages of 60 and 70 years. Major risk factors implicated in its pathogenesis include obesity, tobacco use, and hypertension. (Capitanio et al., 2016; Hancock et al., 2016).

The relatively low expression of glucose transporter-1 (GLUT-1) in RCC, combined with the physiological renal excretion of 18F-FDG, may reduce lesion conspicuity by decreasing the contrast between tumor tissue and normal renal parenchyma. Owing to these biological and physiological limitations, the diagnostic and clinical utility of 18F-FDG PET/CT in RCC remains relatively restricted (Aide et al., 2003; Liu, 2016; Nakajima et al., 2016; Lindenberg et al., 2019).

In one study, 68Ga-FAPI PET/CT demonstrated multiple FAPI-positive metastatic lesions involving the vertebral column, together with a focus of intense tracer uptake within the kidney. Subsequent renal biopsy confirmed the diagnosis of renal cell carcinoma. The authors reported that 68Ga-FAPI PET/CT exhibited higher sensitivity than 18F-FDG PET/CT, particularly for the detection of osseous metastases (Pang et al., 2021).

Another study reported superior diagnostic performance of FAPI PET/CT compared with 18F-FDG PET/CT in patients with RCC. FAPI PET/CT demonstrated higher lesion detection sensitivity and provided more intense and consistent uptake in primary tumors, recurrent lesions, and pulmonary metastases. In addition, the modality offered higher tumor-to-background contrast, facilitating clearer lesion delineation and potentially improving the assessment of disease extent compared with 18F-FDG PET/CT (Civan et al., 2024).

Several studies have reported successful visualization of both primary tumors and metastatic lesions across different histopathological subtypes of RCC using FAPI PET/CT. In the setting of metastatic disease, the combination of high tumor uptake and low background activity has been shown to improve lesion conspicuity. Furthermore, some reports have suggested that the low physiological uptake of FAPI tracers in the brain may facilitate the detection of rare central nervous system metastases (Kratocwil et al., 2019; Pang et al., 2021; Yang et al., 2022).

Studies directly comparing FAPI PET/CT with 18F-FDG PET/CT have demonstrated that FAPI imaging can reveal a similar or greater number of metastatic lesions while providing superior lesion visibility owing to higher tumor-to-background ratios. In some cases, primary tumors that were inadequately visualized on FDG imaging were successfully identified using FAPI PET/CT.

Histopathological confirmation in selected studies further demonstrated that FAPI-positive lesions corresponded to metastatic disease (Yang et al., 2022).

2.3. FAPI PET/CT in Prostate Cancer

The high tumor-to-background ratios (TBRs) achieved by FAPI PET/CT, resulting from intense tracer uptake and low background activity, have enabled successful visualization of metastatic prostate cancer lesions, including lymph node, bone, and visceral metastases. Similarly, in newly diagnosed prostate cancer, the primary tumor has been reported to demonstrate prominent radiotracer uptake, allowing clear lesion visualization (Cai et al., 2023; Pang et al., 2022; Tatar et al., 2023a; Tatar et al., 2023b).

When compared with 18F-FDG PET/CT and 68Ga-PSMA PET/CT, FAPI PET/CT has shown variable diagnostic performance. Some studies have reported superior diagnostic efficacy, whereas others have demonstrated lower performance, particularly regarding the detection of metastatic lesions (Cai et al., 2023; Pang et al., 2022; Tatar et al., 2023b; Aryana et al., 2022; Kessel et al., 2022; Isık et al., 2022; Khreish et al., 2020).

Nevertheless, evidence suggests that FAPI PET/CT may provide greater diagnostic value in patients with advanced-stage prostate cancer (Aryana et al., 2022; Kesch et al., 2021; Kessel et al., 2022).

Importantly, several reports have demonstrated successful visualization of both local and metastatic disease using FAPI PET/CT in tumors that were negative for PSMA expression (Pang et al., 2022; Aryana et al., 2022).

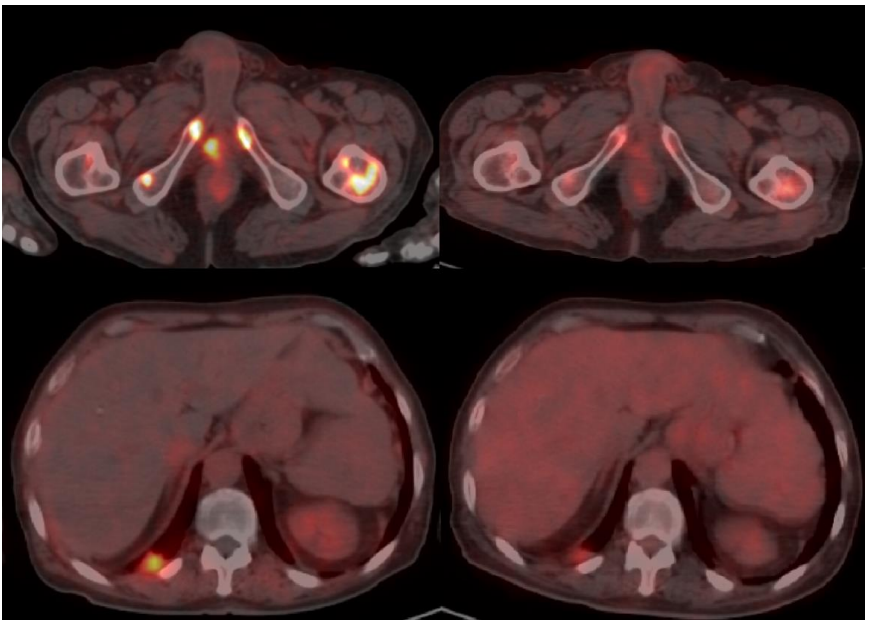
These findings indicate that FAPI PET/CT may serve as a valuable complementary imaging modality, particularly in clinical scenarios where PSMA-targeted imaging has limited utility.

2.4. FAPI PET/CT in Bladder Cancer

Although 18F-FDG PET/CT can be used in the evaluation of bladder cancer, its role in primary staging is limited by intense physiological renal excretion and accumulation of the tracer within the urinary bladder. In addition, its sensitivity for detecting lymph node involvement is relatively modest. Because accurate assessment of lymph node metastases is closely linked to tumor staging and treatment planning, reliable differentiation between T2 and ≥T3 disease is of particular clinical importance.

While 18F-FDG PET/CT is known to produce false-positive findings due to pseudoprogression, 68Ga-FAPI PET/CT may offer advantages in this setting. By reflecting the population of cancer-associated fibroblasts (CAFs) within the tumor microenvironment and potentially correlating with treatment-induced reductions in CAF density, FAPI PET/CT may facilitate differentiation between true disease progression and pseudoprogression (Galgano et al., 2020; Girard et al., 2020).

Figure 2. Metastatic bladder cancer showing multiple metastatic lesion on comparative FAPI PET/CT and FDG PET/CT imaging. The upper panels demonstrate pelvic bone metastases (left: FAPI PET, right: FDG PET), while the lower panels depict the pulmonary lesion (left: FAPI PET, right: FDG PET).



2.5. FAPI PET/CT in Other Urological Malignancies and Pathological Conditions

In addition to renal malignancies, chronic kidney disease (CKD) represents a major health problem with a high prevalence in clinical practice. Key factors contributing to its development include diabetes mellitus, hypertension, obesity, and advanced age. Current therapeutic strategies are primarily aimed at slowing disease progression; however, irreversible nephron loss and the eventual development of end-stage renal disease often remain unavoidable (Zahir et al., 2021).

Renal fibrosis is a pathological process that plays a central role in the progression of CKD and is characterized by the accumulation of activated myofibroblasts and excessive extracellular matrix deposition. Consequently, therapeutic strategies targeting myofibroblast activation and collagen degradation pathways have emerged as promising approaches for reversing or attenuating the fibrotic process (Ruiz-Ortega et al., 2020).

In one study, 68Ga-FAPI PET/CT demonstrated increased tracer uptake in patients with renal fibrosis, reflecting underlying fibrotic activity. Notably, SUVmax values showed a positive correlation with the severity of fibrosis. The findings indicated a progressive increase in radiotracer uptake from mild to advanced stages of fibrosis. These results suggest that 68Ga-FAPI PET/CT may have potential as a noninvasive alternative or complementary approach to renal biopsy for assessing fibrosis burden and monitoring disease progression (Zhou et al., 2021).

Additionally, noteworthy findings have been reported regarding the use of FAPI PET/CT in penile squamous cell carcinoma. In one study, all histopathologically confirmed lymph node metastases were successfully detected by FAPI PET/CT (Eismann et al., 2025). These observations indicate that FAPI-based imaging may have diagnostic applications extending beyond the malignancies discussed in this chapter and may provide clinical value across a broader spectrum of urological tumor subtypes.

2.6. Pitfalls and Interpretative Challenges of FAPI PET/CT in Urological Malignancies

In renal tumors, FAPI uptake may vary according to histological subtype. Because stromal composition and fibroblast activation differ among tumor subtypes, the degree of tracer uptake may not always correlate directly with tumor burden or biological behavior. Furthermore, different uptake patterns may be observed between primary tumors and metastatic lesions within the same patient.

In bladder cancer, previous surgical interventions, transurethral resection procedures, and radiotherapy-induced stromal alterations may result in increased FAPI uptake. This may complicate the distinction between residual tumor and treatment-related changes, particularly during post-treatment evaluation.

In prostate cancer, the relationship between FAPI uptake, tumor grade, and clinical aggressiveness has not yet been fully elucidated. Moreover, heterogeneous tracer uptake among different tumor foci may complicate the assessment of disease extent.

In lymph node evaluation, small metastatic deposits may exhibit low FAPI uptake, whereas reactive or inflammatory lymph nodes may demonstrate increased uptake. Therefore, lymph node findings should be interpreted with caution.

FAPI uptake in bone metastases may also be variable. In particular, uptake patterns in the sclerotic metastases commonly observed in prostate cancer may differ according to the biological characteristics of individual lesions. In addition, post-treatment bone remodeling processes may further complicate image interpretation.

For these reasons, FAPI PET/CT findings in urological malignancies should not be interpreted in isolation. Instead, imaging results should be evaluated in conjunction with the patient's clinical history, prior treatments, and findings from other imaging modalities. Such an integrated approach may reduce interpretative errors and improve diagnostic accuracy.

2.7. FAPI-Based Theranostic Approaches in Urological Malignancies

FAPI-based theranostic strategies represent an emerging field that targets cancer-associated fibroblasts within the tumor microenvironment for both diagnostic imaging and therapeutic applications. The demonstration of FAP expression in various urological malignancies, particularly prostate cancer, suggests that FAPI agents may also have therapeutic utility.

The limited expression of FAP in normal tissues provides an important advantage for the therapeutic application of radiolabeled

FAPI compounds (Novruzov et al., 2022). To this end, FAPI derivatives labeled with beta- and alpha-emitting radionuclides such as 177Lu and 225Ac are currently under investigation. These FAPI-targeted radionuclide therapies may offer a novel treatment option, particularly for patients with advanced disease or resistance to standard therapies (Yang et al., 2022).

Nevertheless, clinical experience with FAPI-based therapies in urological malignancies remains very limited. Current evidence is derived largely from early-phase studies and case series, and more comprehensive investigations are required to establish treatment efficacy, optimal dosing regimens, and long-term clinical outcomes.

2.8. Future Perspectives of FAPI in Urological Malignancies

One of the most promising future applications of FAPI PET/CT in urological malignancies may be its ability to complement information obtained from existing imaging modalities with insights into the tumor microenvironment. In prostate cancer, a better understanding of the relationship between FAP expression and tumor aggressiveness, metastatic potential, and treatment response may contribute significantly to patient management.

In renal and bladder cancers, characterization of FAP expression patterns across different histological subtypes may help identify patient populations most likely to benefit from FAPI PET/CT. Furthermore, correlating imaging findings with molecular and histopathological features may facilitate the development of more refined risk stratification models.

In the future, theranostic approaches integrating FAPI-based imaging and radionuclide therapy within a single platform are expected to become part of personalized treatment strategies, particularly for patients with advanced-stage or treatment-resistant

urological malignancies. In addition, potential synergistic effects of combining FAPI-targeted approaches with chemotherapy, hormonal therapy, and immunotherapy continue to be actively investigated.

2.9. Limitations of FAPI in Urological Malignancies

A substantial portion of the current literature regarding FAPI PET/CT in urological malignancies consists of studies with limited patient numbers and case series. Consequently, larger investigations are required to establish its clinical performance across different tumor types and patient subgroups.

Another important limitation is the heterogeneous nature of FAP expression in urological tumors. In renal neoplasms in particular, marked differences may exist among histological subtypes, and heterogeneous expression may even occur within the same tumor. This variability complicates image interpretation and limits the generalizability of current findings.

Furthermore, the prognostic significance of FAPI uptake and its role in predicting treatment response in prostate, bladder, and renal cancers have not yet been fully elucidated. Additional limitations of existing studies include the inability to obtain histopathological confirmation for all detected lesions and the scarcity of long-term follow-up data.

For these reasons, the precise clinical role of FAPI PET/CT in urological malignancies remains to be established. Multicenter, prospective studies with larger patient populations and long-term outcome data are required to fully define its diagnostic and therapeutic value.

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BÖLÜM 10
TUMOR MICROENVIRONMENT–TARGETED IMAGING in HEMATOLOGIC MALIGNANCIES: The EMERGING ROLE of FAPI PET/CT

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Introduction

Hematologic malignancies comprise a biologically heterogeneous group of neoplastic disorders involving the bone marrow, lymphoid tissues, and peripheral circulation. This group is broadly categorized into lymphomas, leukemias, and plasma cell neoplasms. While lymphomas originate from lymphoid tissues, leukemias arise from the bone marrow and frequently involve peripheral blood dissemination. Plasma cell disorders, such as multiple myeloma, predominantly affect the bone marrow and skeletal system, exhibiting distinct clinical and radiological characteristics. This marked heterogeneity necessitates disease-specific diagnostic and therapeutic approaches [1, 2].

In hematologic malignancies, imaging modalities play a critical role not only in evaluating anatomical disease distribution but also in characterizing underlying biological activity. In current clinical practice, ^{18}F-fluorodeoxyglucose (FDG) PET/CT has become the standard imaging modality, particularly in lymphoma,

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by reflecting increased glucose metabolism of tumor cells. FDG PET/CT is widely utilized for staging, treatment response assessment, and detection of recurrence. However, important limitations exist, including increased uptake in inflammatory processes, reduced sensitivity in low-proliferative tumors, and challenges in interpreting physiological uptake in tissues such as bone marrow [3, 4].

In recent years, it has become increasingly evident that tumor biology extends beyond malignant cells alone, with the tumor microenvironment (TME) playing a crucial role in disease progression and therapeutic response. This paradigm shift has led to the development of novel imaging agents targeting tumor stroma. Fibroblast activation protein (FAP), which is predominantly expressed in cancer-associated fibroblasts (CAFs), represents a key component of the tumor microenvironment. Radiopharmaceuticals targeting FAP, known as fibroblast activation protein inhibitors (FAPI), have emerged as a novel imaging approach enabling visualization of stromal activity [4, 5].

FAPI PET/CT provides complementary information to FDG PET/CT by reflecting stromal rather than metabolic activity. Particularly in malignancies with prominent stromal components, FAPI imaging offers potential advantages such as low background activity and high tumor-to-background ratios [4, 5]. Considering the importance of lymph node microenvironment and bone marrow stroma in hematologic malignancies, FAPI PET/CT may provide a novel imaging perspective in this disease group.

In this chapter, the biological basis, current literature findings, and potential clinical applications of FAPI PET/CT in hematologic malignancies are discussed in light of recent evidence.

Tumor Microenvironment and FAP

The tumor microenvironment (TME) is not a passive structure composed solely of neoplastic cells; rather, it represents a complex and dynamic biological system consisting of stromal cells, immune cells, vascular components, and extracellular matrix elements. Increasing evidence has demonstrated that tumor progression, invasion, metastasis, and treatment response are not exclusively determined by tumor cells, but are significantly modulated by microenvironmental factors [4, 6]. Accordingly, the TME has evolved from a pathophysiological concept into a critical diagnostic and therapeutic target in modern oncology.

Among the microenvironmental components, fibroblast activation protein (FAP) has attracted considerable attention. FAP is a type II transmembrane serine protease with both dipeptidyl peptidase and endopeptidase activity. Under physiological conditions, its expression in adult tissues is minimal; however, it is markedly upregulated in pathological states such as malignancy, fibrosis, and tissue remodeling. FAP is predominantly expressed in cancer-associated fibroblasts (CAFs), which constitute a major cellular component of tumor stroma and actively contribute to tumor progression [4, 7].

CAFs promote tumor development through multiple mechanisms, including extracellular matrix remodeling, secretion of growth factors, induction of angiogenesis, and modulation of immune responses. Furthermore, CAFs have been shown to enhance tumor invasiveness and contribute to chemotherapy resistance. Therefore, FAP expression represents not only an imaging target but also an important biomarker reflecting tumor biology [7].

Although the microenvironment in hematologic malignancies has historically been considered less prominent than

in solid tumors, it plays a crucial role in disease pathophysiology. In lymphomas, the lymph node stroma—comprising fibroblastic reticular cells, follicular dendritic cells, and immune components—forms a supportive niche that facilitates tumor cell proliferation and survival. Notably, in Hodgkin lymphoma, malignant cells constitute only a small fraction of the tumor mass, while the majority consists of reactive and stromal elements, highlighting the importance of stromal activity in this disease [8].

Similarly, the bone marrow microenvironment plays a central role in both leukemias and multiple myeloma. Stromal cells, cytokine networks, and cell–cell interactions within the bone marrow provide a supportive milieu that promotes malignant cell proliferation and resistance to apoptosis. In this context, increased FAP expression within the bone marrow microenvironment may be reflected by FAPI imaging.

A prospective study by Jin et al. demonstrated that FAP expression assessed by immunohistochemistry in lymphoma patients correlated with FAPI PET/CT findings. Higher FAP expression was observed in Hodgkin lymphoma and aggressive non-Hodgkin lymphoma subtypes, supporting the biological basis of FAPI uptake in these diseases [9]. These findings suggest that FAPI imaging may serve as a functional biomarker reflecting microenvironmental activity in hematologic malignancies.

FAPI Radiopharmaceuticals and Imaging Principles

The development of FAP-targeted radiopharmaceuticals has been recognized as a major advancement in nuclear medicine. These agents are derived from small molecules with high affinity for FAP, and the most commonly used derivatives include FAPI-02, FAPI-04, and FAPI-46. These ligands are generally labeled with radionuclides such as ^{68}Ga or ^{18}F and are utilized in PET imaging [4, 5].

The pharmacokinetic properties of FAPI agents provide several important advantages compared to conventional PET tracers. Following injection, these agents demonstrate rapid and intense uptake within tumor tissue, while exhibiting fast clearance from the blood pool and low nonspecific binding, resulting in high-contrast images. In the study conducted by Giesel et al., FAPI agents were shown to provide high tumor-to-background ratios (TBR), which may facilitate improved detection of small lesions [5].

From a practical standpoint, the FAPI PET/CT imaging protocol is more convenient than FDG PET/CT. The absence of a fasting requirement and the relatively short uptake time (typically 10–60 minutes after injection) offer significant advantages in clinical practice, particularly in high-volume centers.

Semi-quantitative parameters used in FAPI PET/CT include SUVmax, SUVmean, and tumor-to-background ratio (TBR). High TBR values may enable superior lesion detectability, especially in anatomical regions with low inherent contrast. However, standardization of these parameters has not yet been fully achieved, and variability between studies persists [4].

Another important advantage of FAPI PET/CT in hematologic malignancies is its relatively low physiological uptake in bone marrow. In FDG PET/CT, physiological or reactive bone marrow activity may complicate interpretation, whereas FAPI PET/CT appears to be less affected by this limitation, potentially allowing clearer assessment in diseases such as multiple myeloma.

Biological Basis of FAPI Uptake in Hematologic Malignancies

The primary biological feature of FAPI PET/CT is that it targets the tumor microenvironment rather than tumor cells themselves. This indicates that FAPI uptake is directly associated

with stromal activation and reflects the biological activity of tumor-supporting structures. Therefore, FAPI PET/CT differs from conventional metabolic imaging by revealing the “supportive biological infrastructure” of the tumor [4, 7].

In hematologic malignancies, FAPI uptake varies depending on histological subtype, stromal density, and microenvironmental characteristics. Higher uptake is expected in diseases with a prominent stromal component, such as Hodgkin lymphoma, whereas lower uptake may be observed in indolent lymphomas. This variability highlights the potential of FAPI imaging to reflect tumor heterogeneity [9].

However, it should be emphasized that FAPI uptake is not specific to malignant processes. Increased FAP expression may also occur in inflammatory conditions, fibrotic diseases, and tissue repair processes. Therefore, FAPI PET/CT findings must always be interpreted in conjunction with clinical, laboratory, and other imaging findings [10].

This biological distinction supports the concept that FAPI PET/CT and FDG PET/CT should be considered complementary imaging modalities. While FDG reflects metabolic activity, FAPI reflects stromal activation, and the combined use of these methods may enable a more comprehensive evaluation of tumor biology.

FAPI PET/CT in Lymphomas

Lymphomas constitute the most extensively studied group of hematologic malignancies in the context of FAPI PET/CT. Although FDG PET/CT remains the standard imaging modality in lymphoma management, FAPI PET/CT has attracted increasing attention due to its ability to reflect tumor microenvironment characteristics [11].

1. Hodgkin Lymphoma

Hodgkin lymphoma is characterized by a highly prominent tumor microenvironment, in which malignant cells represent only a small fraction of the total tumor mass. This feature highlights the critical role of stromal activity in disease biology.

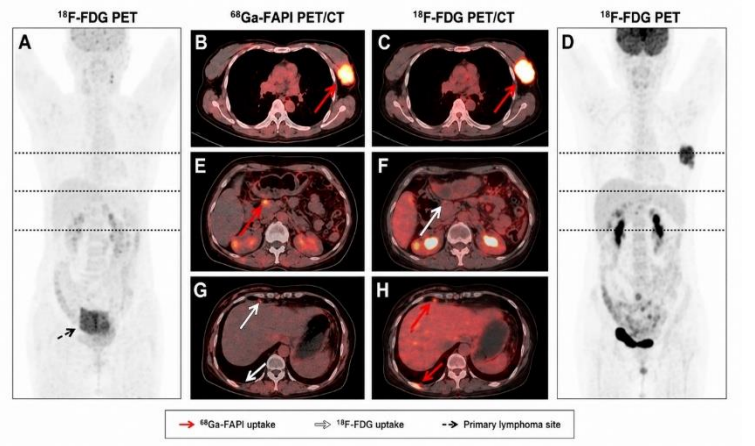
The ability of FAPI PET/CT to visualize stromal activation provides a theoretical advantage in Hodgkin lymphoma. In the study by Jin et al., high levels of FAPI uptake were observed in Hodgkin lymphoma lesions, and these findings were found to be consistent with immunohistochemical FAP expression [9]. These results suggest that FAPI PET/CT may contribute not only to lesion detection but also to the biological characterization of the disease.

2. Non-Hodgkin Lymphoma

Non-Hodgkin lymphomas represent a heterogeneous group of diseases, and FAPI uptake may vary across subtypes. In aggressive lymphoma subtypes, higher stromal activity and consequently more pronounced FAPI uptake may be observed, whereas in indolent lymphomas uptake may be relatively lower [9].

This variability suggests that FAPI PET/CT may have the potential to reflect biological differences among lymphoma subtypes. However, further large-scale prospective studies are required to validate this hypothesis.

Figure-1 Comparative 68Ga-FAPI PET/CT and 18F-FDG PET/CT Demonstrating Distinct Patterns of Disease Involvement in Lymphoblastic Leukemia/Lymphoma



Comparative ^{68}Ga-FAPI PET/CT and ^{18}F-FDG PET/CT findings in a 46-year-old woman with lymphoblastic leukemia/lymphoma. (A) Maximum-intensity projection (MIP) image obtained from ^{68}Ga-FAPI PET. (B, E, G) Representative axial ^{68}Ga-FAPI PET/CT images. (C, F, H) Corresponding axial ^{18}F-FDG PET/CT images. (D) MIP image obtained from ^{18}F-FDG PET. Intense tracer uptake is observed in the left breast lesion on both ^{68}Ga-FAPI and ^{18}F-FDG PET/CT images (B and C). A focal pancreatic lesion demonstrates increased ^{68}Ga-FAPI uptake, whereas no appreciable ^{18}F-FDG uptake is evident at the corresponding site (E and F). In contrast, uptake-positive internal mammary and subpleural lymph nodes are visualized on ^{18}F-FDG PET/CT but show no significant ^{68}Ga-FAPI accumulation (G and H). Prominent uterine ^{68}Ga-FAPI uptake is also observed on the MIP image (A). Adapted from [12].

3. Comparison of FAPI and FDG in Lymphoma

FDG PET/CT remains the gold standard imaging modality in lymphoma. In systematic evaluations, it has been reported that FAPI PET/CT may demonstrate lower sensitivity compared with FDG PET/CT in certain lymphoma subtypes [11].

Nevertheless, the low background activity and stromal-targeting characteristics of FAPI PET/CT may provide additional information in selected clinical scenarios. Therefore, FAPI PET/CT should be considered a complementary imaging modality rather than a replacement for FDG PET/CT.

Plasma Cell Disorders and Multiple Myeloma: FAPI PET/CT

Multiple myeloma is a complex hematologic malignancy characterized by clonal plasma cell proliferation, with involvement of the bone marrow, osteolytic bone lesions, and potential extramedullary dissemination. In current clinical practice, imaging has become essential not only for the assessment of skeletal involvement but also for initial staging, evaluation of treatment response, and detection of residual disease. In this context, ^{18}F-FDG PET/CT is a well-established imaging modality; however, it has several limitations, including challenges in detecting diffuse bone marrow infiltration, lesions with low metabolic activity, and variability due to physiological bone marrow uptake in certain cases. Recent reviews on PET-based imaging in multiple myeloma emphasize that although FDG is a valuable tool, it is not without limitations, and there remains a need for novel radiopharmaceuticals that better reflect underlying disease biology [13, 14].

The growing interest in FAPI PET/CT in multiple myeloma is primarily related to the central role of the bone marrow microenvironment in myeloma biology. A dynamic interaction exists between myeloma cells, bone marrow stromal cells, fibroblast-like stromal components, cytokine networks, and the extracellular matrix. Therefore, imaging approaches targeting FAP expression may indirectly reflect not only tumor burden but also the stromal activity that supports disease progression. Within this biological framework, FAPI has been suggested as a

complementary imaging modality in multiple myeloma, particularly due to its low background activity [13, 14].

The clinical study published by Elboğa et al. in 2022 represents one of the most important early human datasets in this field. In this retrospective series, ^{68}Ga-FAPI PET/CT was compared with ^{18}F-FDG PET/CT in 14 patients with multiple myeloma. While both modalities failed to detect bone lesions in some patients, FAPI demonstrated higher SUVmax values in a subset of cases. In addition, bone lesions that were not detected by FDG were identified by FAPI in two patients, and FAPI revealed a greater number of bone lesions in five patients. However, the authors concluded that FAPI did not demonstrate a statistically clear superiority over FDG, but rather may serve as a complementary imaging modality, particularly in cases with low FDG avidity or inconclusive findings. Furthermore, low background activity, reduced nonspecific diffuse bone marrow uptake, and low physiological brain uptake were highlighted as practical advantages of FAPI imaging [15].

These findings allow several clinically relevant interpretations. First, FAPI PET/CT may increase lesion conspicuity in multiple myeloma by enhancing the contrast of bone lesions. Second, in the evaluation of extramedullary disease, FAPI may demonstrate higher uptake in certain lesions; in the series by Elboğa et al., examples included extramedullary involvement in the lung and presacral lymph nodes. Third, it cannot be concluded that FAPI PET/CT has become a standard imaging modality in multiple myeloma, as current evidence remains limited and is based on small patient cohorts. Therefore, the most balanced interpretation is that FAPI PET/CT should not be considered a replacement for FDG PET/CT, but rather a complementary technique that may provide additional biological and visual information in selected clinical scenarios [13, 15].

Accordingly, FAPI PET/CT may be considered a problem-solving imaging tool, particularly in patients with FDG-negative or heterogeneous uptake patterns in multiple myeloma.

Leukemias and Myeloid Sarcoma: FAPI PET/CT

The current literature regarding the use of FAPI PET/CT in leukemias is considerably more limited compared to lymphoma and multiple myeloma. Most available data consist of case reports, and therefore conclusions in this field should be interpreted with caution. In particular, the evaluation of diffuse bone marrow disease burden remains an unresolved issue in FAPI imaging, due to the unique biological characteristics of leukemia and the complexity of the bone marrow microenvironment. Accordingly, the role of FAPI PET/CT in leukemias should currently be considered investigational [16, 17].

Within this context, the most notable evidence has been derived from cases of myeloid sarcoma, which represents extramedullary myeloid disease. In a case report published by Wu et al. in 2022, ^{68}Ga-FAPI PET/CT was shown to provide significantly superior tumor-to-background contrast compared to ^{18}F-FDG PET/CT in a biopsy-proven breast myeloid sarcoma. In the same case, follow-up FAPI PET/CT after chemotherapy demonstrated both a reduction in lesion size and decreased tracer uptake, suggesting that FAPI may have potential not only in lesion detection but also in treatment response assessment. However, this observation is based on a single case and cannot be generalized to routine clinical practice [16].

Similarly, in another case of myeloid sarcoma reported in 2023, ^{68}Ga-DOTA-FAPI-04 PET/CT demonstrated increased uptake in chest wall and mediastinal masses, which were subsequently confirmed as myeloid sarcoma by biopsy. Such reports suggest that FAPI imaging may enhance lesion conspicuity

in extramedullary myeloid disease; however, the current level of evidence remains limited to case-based observations. Therefore, these findings should be considered primarily as proof-of-concept data [17].

From a broader perspective, the key unanswered questions in leukemias include the ability of FAPI PET/CT to reliably detect diffuse bone marrow infiltration, to differentiate post-treatment stromal remodeling from active disease, and to identify residual extramedullary foci. The currently available evidence is insufficient to address these questions.

Accordingly, the most appropriate interpretation at present is that FAPI PET/CT represents a promising but still very early-stage research area in leukemias, with its potential role likely to emerge first in extramedullary manifestations such as myeloid sarcoma [16, 17].

Therefore, the clinical role of FAPI PET/CT in leukemias has not yet been clearly defined, and existing data should be regarded as hypothesis-generating rather than practice-changing.

Comparative Evaluation of FAPI and FDG PET/CT

The most fundamental consideration in comparing FAPI PET/CT and FDG PET/CT is the clear recognition that these two modalities do not measure the same biological processes. While FDG reflects glucose metabolism and, consequently, metabolically active tumor cell populations, FAPI primarily targets fibroblast activation and stromal components within the tumor microenvironment. Therefore, differences observed between these two modalities should not be interpreted as technical shortcomings but rather as the natural consequence of their distinct biological targets. This distinction is particularly important in hematologic malignancies, where certain subtypes are dominated by tumor cell

burden, whereas in others the microenvironmental component plays a more decisive role [11, 15].

From a lymphoma perspective, recent systematic reviews have demonstrated that FAPI PET/CT may exhibit lower diagnostic sensitivity compared with FDG PET/CT, particularly in lymphomas with low FAP expression. These findings support the continued role of FDG PET/CT as the gold standard imaging modality in lymphoma. However, FAPI may provide additional information regarding stromal characteristics and may serve a complementary role in selected subgroups. Furthermore, a pilot study published in 2025 reported that baseline ^{68}Ga-FAPI uptake levels in patients with non-Hodgkin lymphoma undergoing chemotherapy may be associated with the prediction of metabolic response, suggesting that FAPI could provide prognostic information beyond lesion detection alone [11, 18].

In multiple myeloma, the comparative framework differs. The principal advantage of FAPI in this setting may be its low background activity and reduced nonspecific diffuse bone marrow uptake. In the study by Elboğa et al., although FAPI demonstrated higher contrast and detected a greater number of bone lesions in some patients, no clear overall superiority over FDG was established. Therefore, the most appropriate positioning of FAPI in multiple myeloma is as a complementary imaging modality, particularly in cases with low FDG avidity, inconclusive PET findings, or when improved characterization of extramedullary disease is required [14, 15].

Within this comparative framework, the potential advantages of FAPI include low physiological background activity, high tumor-to-background contrast in certain lesions, the ability to reflect stromal biology, and improved visualization in some extramedullary disease sites. Conversely, its limitations include

reduced specificity due to FAP expression in inflammation, fibrosis, and tissue repair processes; small and heterogeneous study populations in hematologic malignancies; lack of standardized interpretation criteria; and limited prognostic data [11, 15, 16].

In light of current evidence, it appears more rational to position FAPI PET/CT not as a replacement for FDG PET/CT, but rather as a complementary imaging modality, particularly in diseases with low FDG avidity or complex biological behavior.

Clinical Applications and Potential Use Scenarios of FAPI PET/CT

In hematologic malignancies, the potential clinical applications of FAPI PET/CT can theoretically be categorized as diagnosis, staging, treatment response assessment, evaluation of residual or recurrent disease, and prognostic stratification. However, the level of evidence supporting each of these applications is not uniform. Current data are predominantly concentrated in lymphoma and multiple myeloma, whereas in leukemias the available evidence is largely limited to case-based observations, particularly involving extramedullary disease. Therefore, the current position of FAPI PET/CT should be considered not as a method integrated into standard diagnostic algorithms, but rather as an innovative molecular imaging tool that may be utilized in selected clinical scenarios [11, 15, 16].

From a diagnostic perspective, FAPI PET/CT may be particularly valuable in diseases with a prominent stromal component or in situations where low background activity enhances lesion conspicuity. In lymphoma, this may contribute to the characterization of the tumor microenvironment. In multiple myeloma, FAPI may have a supportive diagnostic role by improving the visual contrast of certain bone lesions and enabling clearer depiction of selected extramedullary sites. Reports of

myeloid sarcoma further suggest that FAPI PET/CT may demonstrate notable performance in selected cases of extramedullary leukemic involvement [15-17].

Treatment response assessment represents one of the most promising future applications of FAPI PET/CT. In a pilot study conducted in patients with non-Hodgkin lymphoma, baseline ^{68}Ga-FAPI PET/CT parameters were found to be associated with metabolic response to CHOP-like therapy, suggesting a potential role for FAPI as a prognostic biomarker. In addition, case-based evidence from myeloid sarcoma has demonstrated a reduction in FAPI uptake following treatment, indicating that this modality may also be explored for response monitoring. Nevertheless, these findings are still preliminary and are not yet sufficient to influence standardized treatment algorithms [16, 18].

Table-1 Summary of key studies evaluating FAPI PET/CT in hematologic malignancies

Study	**Patient population**	**Key findings**	**Conclusion**
Jin et al. (2022)	Lymphoma	High FAPI uptake correlated with FAP expression	Reflects tumor microenvironment activity
Elboga et al. (2022)	Multiple myeloma	Higher uptake in some lesions compared to FDG	Complementary imaging modality
Wu et al. (2022)	Myeloid sarcoma	High tumor-to-background contrast	Potential in extramedullary disease
Quartuccio et al. (2025)	Lymphoma (review)	FDG generally superior to FAPI	FAPI has a complementary role

Abbreviations: FAPI, fibroblast activation protein inhibitor; FDG, fluorodeoxyglucose; PET/CT, positron emission tomography/computed tomography. This table summarizes representative studies evaluating the role of FAPI PET/CT in hematologic malignancies.

Potential Pitfalls and Limitations of FAPI PET/CT

FAPI PET/CT is an innovative imaging modality targeting the tumor microenvironment; however, it is associated with important limitations and potential pitfalls that must be carefully considered during interpretation. The most significant limitation is that FAP expression is not specific to malignant tissues. Fibroblast activation protein may also be upregulated in conditions such as inflammation, fibrosis, and tissue repair. Therefore, increased tracer uptake observed on FAPI PET/CT should not be interpreted as synonymous with malignancy [4, 5, 10].

This issue becomes particularly relevant in hematologic malignancies. Reactive lymph node hyperplasia, treatment-related regenerative changes in the bone marrow, post-radiotherapy fibrotic processes, and concomitant infectious or inflammatory conditions may all demonstrate increased FAPI uptake. In this context, interpretation of FAPI PET/CT findings must be performed in conjunction with clinical evaluation, laboratory parameters, and other imaging modalities [4, 8].

Another important limitation is the currently limited level of evidence supporting the use of FAPI PET/CT in hematologic malignancies. A substantial proportion of the available literature consists of small cohort studies, retrospective analyses, and case reports. In particular, data regarding leukemias and extramedullary hematologic diseases remain scarce, and existing evidence is largely hypothesis-generating in nature [11, 16].

In addition, the lack of standardization in FAPI imaging represents a major challenge. Variability in the use of different

FAPI derivatives (e.g., FAPI-02, FAPI-04, FAPI-46), differences in imaging acquisition timing, and heterogeneity in SUV-based measurements complicate comparisons across studies. Unlike FDG PET/CT, standardized interpretation criteria have not yet been fully established, leading to uncertainty in clinical practice [4, 5].

Another potential limitation is that the relationship between FAPI uptake and tumor burden is not always linear. Since FAPI reflects stromal activity rather than tumor cell mass, discordant scenarios may be encountered, such as low FAPI uptake in the presence of high tumor burden or, conversely, high uptake in lesions with relatively limited tumor cell density [5].

Finally, practical considerations such as cost, availability, and limited clinical experience also constitute important barriers. The fact that FAPI agents have not yet been widely integrated into routine clinical practice further restricts their widespread adoption.

In this context, it should be strongly emphasized that although FAPI PET/CT is a promising imaging modality in hematologic malignancies, the current evidence base remains heterogeneous and limited; therefore, large-scale, multicenter studies with standardized protocols and histopathological correlation are required before routine clinical use can be recommended [11].

Theranostic Approach and Future Perspectives

The development of FAP-targeted agents holds significant potential not only for diagnostic imaging but also for theranostic applications. The theranostic concept refers to the use of the same molecular target for both diagnostic and therapeutic purposes. In this context, FAPI agents can be labeled with appropriate radionuclides, enabling not only imaging but also targeted

radioligand therapy, thereby providing a versatile platform for integrated diagnostic and therapeutic strategies [4, 19].

In recent years, increasing attention has been directed toward labeling FAP-targeted agents with therapeutic radionuclides such as ^{177}Lu, ^{90}Y, and ^{225}Ac. Early-phase studies, particularly in solid tumors, have suggested that this approach may be safe and potentially effective. However, in hematologic malignancies, this field remains at a very early stage, and no standardized treatment strategies have yet been established for routine clinical use [7, 19].

One of the most important theoretical advantages of FAPI-based theranostic approaches in hematologic malignancies is the targeting of the tumor microenvironment rather than tumor cells themselves. This feature may offer a potential advantage in treatment-resistant disease by disrupting microenvironmental support mechanisms. Given that stromal cells contribute to tumor cell survival in lymphomas, targeting the tumor microenvironment may enable the development of novel therapeutic strategies [7, 8].

From a future perspective, one of the most promising areas is the integration of combined molecular imaging approaches. While FDG PET/CT reflects tumor cell metabolic activity, FAPI PET/CT visualizes stromal components. The combined use of these modalities may allow simultaneous evaluation of both metabolic and microenvironmental characteristics, thereby enabling a more comprehensive assessment of tumor biology. This approach may facilitate improved characterization of tumor heterogeneity and support the development of patient-specific treatment strategies [4, 11].

In particular, stromal phenotyping in lymphomas may contribute to a better understanding of disease subtypes. Studies investigating the relationship between FAPI uptake levels and disease aggressiveness, treatment response, and prognosis suggest

that FAPI PET/CT may serve as a potential prognostic biomarker in the future. However, current data remain limited, and validation through large-scale prospective studies is required [11].

In addition, the integration of radiomics and artificial intelligence–based imaging approaches with FAPI PET/CT may further enhance its clinical utility. Quantitative assessment of stromal heterogeneity represents an important research area that may contribute to personalized treatment strategies [19].

Although FAPI-based imaging and theranostic approaches are still in the early stages of development in hematologic malignancies, this paradigm—targeting the tumor microenvironment—has the potential to significantly influence future diagnostic and therapeutic strategies. Nevertheless, based on current evidence, it is clear that further scientific validation is required before widespread clinical implementation can be recommended [4, 11].

Key Points and Clinical Implications

- FAPI PET/CT reflects fibroblast activation within the tumor microenvironment (i.e., stromal activity), rather than tumor cell metabolism, whereas FDG PET/CT demonstrates glucose metabolism and proliferative activity of tumor cells. Therefore, these two modalities represent distinct biological processes and should be considered complementary rather than interchangeable.
- Based on current evidence, FDG PET/CT remains the gold standard imaging modality in lymphoma. In contrast, FAPI PET/CT may provide additional biological insight, particularly in subtypes characterized by prominent

microenvironmental activity, and should be regarded as a complementary imaging approach.

- In multiple myeloma, FAPI PET/CT offers potential advantages due to its low physiological background activity and, in some cases, higher lesion-to-background contrast. Accordingly, it may serve as a problem-solving imaging modality, particularly in patients with FDG-negative or heterogeneous uptake patterns.
- The available data regarding the use of FAPI PET/CT in leukemias are extremely limited and are largely based on case reports. Therefore, current evidence remains hypothesis-generating, and a clearly defined clinical role has not yet been established.
- FAP-targeted imaging holds significant promise not only for diagnostic purposes but also for theranostic applications. The labeling of FAPI agents with therapeutic radionuclides may enable the development of novel treatment strategies targeting the tumor microenvironment in the future.

Conclusion

FAPI PET/CT represents a novel and distinct molecular imaging approach in hematologic malignancies by targeting the tumor microenvironment rather than tumor cell metabolism. Current literature indicates that this modality has been most extensively investigated in lymphoma and multiple myeloma, whereas in leukemias, early but intriguing data are primarily limited to extramedullary manifestations such as myeloid sarcoma. In lymphoma, existing evidence supports that FDG PET/CT remains the reference standard imaging modality, while FAPI PET/CT may provide complementary information, particularly in relation to stromal biology. Similarly, in multiple myeloma, FAPI

PET/CT demonstrates potential as an adjunctive imaging technique due to its low background activity and, in some cases, improved lesion contrast; however, a clear superiority over FDG PET/CT has not yet been established [11, 15, 16, 18].

Based on current evidence, FAPI PET/CT cannot be considered a new standard imaging modality replacing FDG PET/CT in hematologic malignancies. Rather, it should be positioned as a complementary tool that may provide additional insight into stromal biology, tumor-to-background contrast, and potentially prognostic information in selected patients. Future multicenter studies with larger patient cohorts, histopathological correlation, and direct comparative designs will be essential to clarify in which disease subtypes, clinical scenarios, and treatment settings FAPI PET/CT offers the greatest clinical value. Accordingly, FAPI PET/CT should currently be regarded as a rapidly evolving yet scientifically robust field of research in hematologic malignancies [11, 13, 15, 16, 18].

Although FAPI PET/CT is not yet a standard imaging modality in hematologic malignancies, its unique biological approach—targeting the tumor microenvironment—introduces a new paradigm that extends beyond conventional metabolic imaging.

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FAPI IN SOFT TISSUE AND BONE SARCOMAS

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Introduction

Sarcomas are a heterogeneous group of malignant tumors arising from embryologically derived mesenchymal tissues, including bone, muscle, adipose tissue, fibrous tissue, cartilage, vascular structures, and peripheral nerve sheaths. Although they account for approximately 1% of adult malignancies, sarcomas demonstrate substantial variability in biological behavior, molecular characteristics, and clinical course due to the existence of more than 100 histological subtypes. Genomic instability, chromosomal translocations, gene amplifications, and loss of tumor suppressor genes play important roles in sarcoma pathogenesis. Recent studies have demonstrated that sarcoma progression is not solely dependent on tumor cells themselves but is also critically influenced by the tumor microenvironment. This microenvironment, composed of cancer-associated fibroblasts (CAFs), immune cells, extracellular matrix components, and tumor vasculature, substantially contributes to tumor growth, invasion, metastasis, and the development of treatment resistance. Particularly in high-grade soft tissue and bone sarcomas, prominent stromal remodeling, extracellular matrix production, and fibroblast activation are observed, resulting in increased expression of fibroblast activation protein (FAP). This marked overexpression of FAP within the tumor stroma has led to the emergence of fibroblast

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activation protein inhibitors (FAPI)-based molecular imaging and radioligand therapy approaches as promising biomarkers and therapeutic targets in sarcomas.

In nuclear medicine, particularly in the field of PET imaging, significant advances continue to emerge. One of these developments is the radiotracer fibroblast activation protein inhibitor (FAPI), which enables visualization of the tumor microenvironment. Fibroblast activation protein (FAP) is a type II transmembrane serine protease possessing dipeptidyl peptidase and endopeptidase activity and is known to be overexpressed in the stroma of numerous epithelial cancers, including more than 90% of sarcomas (Giammarile et. al., 2024; Lindner et. al., 2018; Loktev et. al., 2018). Traditionally, 18F-FDG PET/CT has been widely used for diagnosis and staging in soft tissue and bone sarcomas by reflecting metabolic activity and continues to play an important role. However, this modality has limitations in certain subtypes characterized by low FDG uptake, such as low-grade fibromyxoid sarcoma or well-differentiated osteosarcoma.

Because of its relatively low sensitivity in several subtypes of soft tissue sarcomas (STS), particularly low-grade sarcomas, 18F-FDG is not recommended in certain clinical scenarios. In contrast, due to FAP overexpression in many sarcomas, FAPI tracers labeled with [18F] or [68Ga] have increasingly been preferred. For example, a meta-analysis investigating soft tissue sarcomas reported that 68Ga-FAPI demonstrated higher sensitivity and specificity than 18F-FDG, along with superior positive predictive value, negative predictive value, and greater accuracy in detecting recurrent lesions (Guglielmo et. al., 2023).

Furthermore, because FDG reflects cellular metabolism, assessment of bone structures may be challenging, particularly in

pathological conditions associated with bone marrow activation, where increased uptake can complicate interpretation. In contrast, the low physiological background uptake and high tumor-to-background ratio observed with FAPI facilitate the evaluation of these regions and improve lesion detection within both bone and soft tissue structures (Chandekar et. al., 2023; Gu et. al., 2022).

Considering these advantages, FAPI -which targets the tumor microenvironment- has gained increasing importance not only because of its diagnostic value but also because of its potential role in treatment planning and in the assessment of therapeutic response and disease recurrence.

This chapter aims to discuss the comparative diagnostic performance of FAPI PET/CT and FDG PET/CT in soft tissue and bone sarcomas, as well as the clinical contributions of FAPI imaging in various applications.

1. Soft Tissue Sarcomas

Soft tissue sarcomas (STSs) are a relatively rare and heterogeneous group of tumors derived from mesenchymal tissue elements. Although they most commonly occur in the upper and lower extremities, they may also develop in the abdomen, thorax, and retroperitoneal regions. More than 50 histological subtypes have been identified, among which liposarcoma, leiomyosarcoma, and synovial sarcoma are the most recognized. STSs can occur at any age, accounting for less than 1% of all adult solid tumors and approximately 7% of pediatric malignancies. Consequently, STSs are responsible for nearly 2% of all cancer-related deaths (Burningham et. al., 2012; Katal et. al., 2018; Weitz et. al., 2003).

Although the exact etiology of soft tissue sarcomas remains unclear, several major contributing factors have been identified:

a) Genetic Factors:

- •Li-Fraumeni syndrome
- • Neurofibromatosis type 1 (NF1)
- • Retinoblastoma

b) Environmental and Acquired Factors:

- • Radiation exposure
- • Chemical agents such as vinyl chloride

c) Molecular Pathogenesis:

- •Chromosomal translocations
- • Gene amplifications
- • Proto-oncogene activation
- • Tumor suppressor gene inactivation

Although the clinical presentation of soft tissue sarcomas varies according to tumor location, they generally manifest as rapidly enlarging, painless masses producing compressive symptoms. Weight loss, fatigue, and paraneoplastic syndromes may also accompany the disease. The most important components of the diagnostic process are detailed history taking and physical examination. Subsequently, the suspicious region is evaluated using magnetic resonance imaging (MRI), which remains the gold standard modality for the assessment of soft tissue sarcomas, and diagnosis is confirmed by biopsy.

Treatment strategies are primarily guided by the TNM staging system (Tanaka & Ozaki, 2019). MRI is used to assess tumor size and local extension, while biopsy provides information regarding nodal involvement. For evaluation of regional and distant metastases, PET/CT is frequently utilized. In routine clinical

practice, FDG remains the most commonly used tracer and continues to represent the first-line option for detecting distant metastases in metabolically active sarcoma subtypes. However, it may provide insufficient information in tumors characterized by limited glucose utilization. In such circumstances, 68Ga-FAPI has gained considerable attention because of the high levels of FAP activity observed in sarcomas.

Abdulrahman M. et al. synthesized data from 36 studies involving 316 patients and approximately 30 soft tissue sarcoma subtypes to investigate the diagnostic and therapeutic role of FAPI. Their analysis demonstrated that FAPI PET/CT showed higher tracer uptake, improved diagnostic accuracy, and superior lesion detection compared with FDG PET/CT. Furthermore, FAPI imaging appeared to outperform FDG in detecting recurrent soft tissue sarcomas (Abdulrahman et. al., 2025).

1.1 Liposarcoma

Liposarcomas are among the most common soft tissue sarcoma subtypes. They are malignant mesenchymal tumors exhibiting adipocytic differentiation and arising from adipose tissue. They most frequently occur in the retroperitoneum and extremities and generally present as slowly enlarging masses. Liposarcomas include several histological subtypes, including well-differentiated, dedifferentiated, and myxoid variants. Although studies investigating FAPI uptake remain limited and largely consist of early reports or isolated case studies (Wang et. al., 2025), the heterogeneous nature of FDG uptake across liposarcoma subtypes has long been demonstrated in the literature (Fu et. al., 2019; Schwarzbach et. al., 2001).

1.2 Leiomyosarcoma

Leiomyosarcomas are malignant tumors derived from smooth muscle tissue. They are most commonly observed in the retroperitoneum, uterus, large vessels, and extremities. Because of their tendency toward hematogenous spread, pulmonary metastases are frequently encountered. Although leiomyosarcomas are generally considered highly FDG-avid tumors, their prominent stromal remodeling also suggests significant potential for FAPI uptake. For example, one study reported that in a patient with the extremely rare diagnosis of primary osseous leiomyosarcoma, FAPI imaging detected more lesions and demonstrated higher uptake values compared with FDG (Jiang et. al., 2025).

1.3 Undifferentiated Pleomorphic Sarcoma (UPS)

Previously referred to as malignant fibrous histiocytoma, undifferentiated pleomorphic sarcoma (UPS) is typically a high-grade tumor predominantly localized to the extremities. It is among the soft tissue sarcoma subtypes demonstrating the highest FDG uptake. While necrotic regions may contribute to heterogeneous FDG distribution, the abundant fibrotic stroma may also result in intense FAPI accumulation. Case reports have demonstrated the supportive role of FDG PET/CT in diagnosing UPS alongside ultrasonography, CT, and MRI findings (Utsunomiya et. al., 2024).

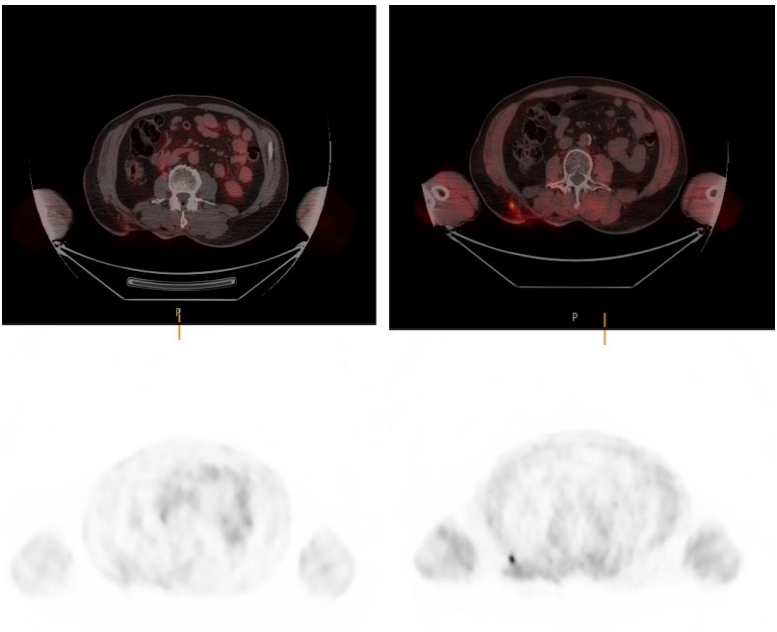

Figure 1. In a patient who underwent surgery for undifferentiated pleomorphic sarcoma, the lesion corresponding to residual tumor tissue demonstrates no FDG uptake on the left image, whereas the corresponding FAPI image is shown on the right.

1.4 Synovial Sarcoma

Synovial sarcoma is an important soft tissue sarcoma subtype predominantly affecting young adults. It most commonly occurs around the extremities and is characterized by the t(X;18) chromosomal translocation. Although these tumors generally demonstrate substantial FDG uptake, studies evaluating FAPI remain limited. In one reported case involving duodenal synovial sarcoma, FDG and FAPI demonstrated comparable uptake; however, FAPI provided superior delineation of lesion margins, suggesting its potential utility as an imaging radiopharmaceutical (Zhan et. al., 2025).

2. Bone Sarcomas

Bone sarcomas are malignant mesenchymal tumors originating from bone tissue and are generally rare. They most commonly arise in long bones such as the femur, tibia, and humerus. Their major clinical manifestations include persistent bone pain, restricted mobility, and pathological fractures. Risk factors include both environmental/acquired causes, such as previous radiotherapy exposure, and hereditary syndromes including Werner syndrome and Bloom syndrome (Strauss et. al., 2021).

FDG remains one of the most frequently utilized radiopharmaceuticals for diagnosis, staging, treatment monitoring, and follow-up of bone sarcomas (Oh et. al., 2023). However, due to limitations including low glucose metabolism in certain subtypes and the occurrence of false-positive FDG findings, there has been increasing interest in novel imaging agents capable of overcoming these limitations. In this context, fibroblast activation protein-α (FAPα), a type II transmembrane glycoprotein, has emerged as an important target. Various radiolabeled FAP inhibitors (FAPI) have subsequently been developed for molecular imaging and potential therapeutic applications (Sollini et. al., 2021).

2.1 Osteosarcoma

Osteosarcoma is the most common primary malignant bone tumor and represents a high-grade mesenchymal neoplasm characterized by malignant osteoid production. It predominantly affects adolescents and young adults. Osteosarcoma biology is characterized by complex genomic alterations, marked chromosomal instability, high proliferative activity, and intense interactions within the tumor microenvironment. Cancer-associated fibroblasts, immune cells, osteoblastic reaction zones, and

extracellular matrix components constitute important elements of the tumor stroma. This stromal complexity contributes both to the aggressive biological behavior and imaging characteristics of osteosarcoma. Osteosarcoma occurs slightly more frequently in males and most commonly involves the metaphyseal regions of long bones, particularly the distal femur, proximal tibia, and proximal humerus.

Due to their high metabolic activity, osteosarcomas generally demonstrate substantial FDG uptake. Simultaneously, fibroblast activation and osteoid matrix formation suggest that FAPI imaging may also represent a valuable imaging modality. The identification of high FAP expression in osteosarcoma provides an important biological rationale for future therapeutic applications involving radiolabeled FAPI derivatives such as 177Lu-FAPI and 225Ac-FAPI.

2.2 Chondrosarcoma

Chondrosarcomas are malignant mesenchymal tumors characterized by production of cartilaginous matrix and represent the second most common primary malignant bone tumor in adults after osteosarcoma. They typically occur between 40 and 70 years of age and most frequently involve the pelvis, femur, and ribs.

A defining characteristic of chondrosarcoma is abundant extracellular cartilaginous matrix production. This matrix is rich in type II collagen, proteoglycans, and glycosaminoglycans. The dense matrix contributes to the formation of hypoxic regions within the tumor microenvironment. Consequently, hypoxia-inducible-factors particularly HIF-1α become activated and contribute to tumor progression, angiogenesis, and treatment resistance.

FDG uptake correlates closely with tumor grade and has proven useful for differentiating benign enchondromas from malignant lesions and for predicting tumor grade. Because FAPI-related evidence remains extremely limited in chondrosarcoma, its exact role remains unclear; however, emerging studies investigating dedifferentiated chondrosarcoma suggest potential future utility in selected subtypes (Liu et. al., 2017).

2.3 Ewing Sarcoma

Ewing sarcoma is the second most common primary malignant bone tumor in children and adolescents and belongs to the group of small round blue cell tumors. It most frequently occurs during the second decade of life and involves both axial and appendicular skeletal regions, including the pelvis, femur, tibia, and chest wall.

The biology of Ewing sarcoma is largely determined by specific chromosomal translocations. Approximately 85% of tumors harbor the EWSR1-FLI1 fusion gene resulting from the t(11;22)(q24;q12) translocation. Additional molecular studies have identified other genetic alterations, including tumors characterized by CIC and BCOR rearrangements (PDQ Pediatric Treatment Editorial Board, 2002).

Histologically, Ewing sarcoma demonstrates high cellularity with relatively limited stromal content. Tumor cells consist of uniform small round cells with glycogen-rich cytoplasm, while CD99 membrane positivity remains a characteristic immunohistochemical finding. Unlike osteosarcoma and high-grade pleomorphic sarcomas, prominent desmoplastic reactions and abundant extracellular matrix production are generally absent. Consequently, the clinical role of FDG remains considerably stronger than that of FAPI in this tumor type.

3. Treatment

Studies investigating the use of FAPI not only as an imaging agent but also as a therapeutic agent are ongoing. For example, in the study conducted by Helena L. et al. regarding the theranostic use of 90Y-FAPI-46 in sarcomas and other solid tumors, 23 of the 30 patients (77%) had sarcoma, 3 (10%) had pancreatic cancer, 1 (3%) had prostate cancer, 1 (3%) had gastric cancer, 1 (3%) had non-melanoma skin cancer, and 1 (3%) had cholangiocarcinoma. Post-treatment responses were evaluated using RECIST (n = 25) and PERCIST (n = 20). According to RECIST, disease control was 48% (12/25), including 3 partial responses (12%). According to PERCIST, metabolic response was observed in 12 of 20 patients (60%). As a result of the study, they stated that "disease stabilization was observed in nearly half of the patients, especially in sarcomas. Our findings support the role of FAP-targeted radiopharmaceutical therapy in patients with metastatic sarcoma" (Lanzafame et. al., 2026).

Although there are still insufficient cases regarding the use of FAPI in treatment, no adverse effect profile that would prevent its use has been observed, and it has been noted that the tolerability profile is favorable (Sidrak et. al., 2023).

In a study conducted on sarcomas, it was reported that:

"Importantly, among all therapeutic strategies evaluated in sarcoma to date, the current treatment evidence is limited to small, non-randomized cohorts and compassionate-use experiences. No study has yet demonstrated a survival advantage, durable tumor control, or improvement in patient-reported outcomes. At present, no therapeutic approach can be accepted as part of standard sarcoma management, and all radionuclide therapies discussed in

this review should be considered investigational and restricted to research settings." (Appana et. al., 2026).

Table 1. Comparative Features of FDG and FAPI PET/CT in Soft Tissue Sarcomas

Feature	FDG	FAPI
Primary tumor detection	●●●●○	●●●●●
Tumor-to-background contrast	●●●○○	●●●●●
Small lesion visibility	●●●○○	●●●●●
Local recurrence detection	●●●○○	●●●●●
Bone metastasis detection	●●●●○	●●●●●
Lung metastasis detection	●●●●○	●●●●○
Treatment response assessment	●●●●●	●●○○○
Theranostic suitability	●○○○○	●●●●●
Ease of patient preparation	●●●○○	●●●●●
Level of evidence	●●●●●	●●○○○

Scoring: ●○○○○ = Very low, ●●○○○ = Low, ●●●○○ = Moderate, ●●●●○ = High, ●●●●● = Very high.

4. Pitfalls

One important point that should not be forgotten is that FAP expression does not increase only within the tumor microenvironment. For example, Qin C. et al. investigated increased FAPI uptake in bones and joints and identified a total of 295 lesions in 82 cases; among these, 94 (31.9%) were malignant lesions (all metastases), whereas 201 (68.1%) were benign lesions. Benign lesions included 13 cases of osteofibrous dysplasia, 48 cases of degenerative bone disease, 33 cases of periodontitis, 56 cases of arthritis, and 51 other inflammatory or trauma-related abnormalities. In the conclusion section, they stated:

"68Ga-FAPI accumulated in both bone metastases and some benign diseases of bone and joints. Although uptake of 68Ga-FAPI was generally higher in bone metastases, this finding cannot be used to differentiate benign and malignant lesions." (Qin et. al., 2022).

In another interesting study, a 72-year-old male patient who had been experiencing right hip pain for 3 months underwent FAPI PET/CT imaging. Because of increased uptake, malignant processes were initially suspected; however, following biopsy, the diagnosis was found to be myositis ossificans (Gong et. al., 2022).

5. Future Perspectives

Although fibroblast activation protein inhibitor (FAPI)-based imaging methods in soft tissue and bone sarcomas are still an emerging field, current evidence suggests that FAPI PET may become an important complementary imaging modality in the evaluation of mesenchymal malignancies in the future.

One of the most promising potential applications of FAPI PET in sarcomas is more accurate delineation of tumor margins. Especially in tumors with extensive stromal remodeling, such as dedifferentiated liposarcoma, undifferentiated pleomorphic sarcoma, and osteosarcoma, lesion borders may be better defined due to the high tumor-to-background contrast.

In the future, FAPI PET is also expected to play an important role in treatment response assessment. In particular, combined use with FDG PET may allow simultaneous evaluation of both metabolic activity and stromal activity.

6. Conclusion

Fibroblast activation protein inhibitor (FAPI)-based imaging methods are increasingly attracting attention as a novel molecular imaging approach that enables evaluation of the tumor microenvironment in soft tissue and bone sarcomas. The ability to visualize cancer-associated fibroblasts, stromal remodeling, and extracellular matrix dynamics which play important roles in the biological behavior of sarcomas provides FAPI PET/CT with a distinct and complementary biological perspective compared with conventional imaging methods targeting tumor metabolism.

Current evidence suggests that FAPI PET/CT can provide superior tumor-to-background contrast due to high tumor uptake and low physiological background activity, particularly in subtypes with prominent stromal activity such as osteosarcoma, undifferentiated pleomorphic sarcoma, leiomyosarcoma, and dedifferentiated liposarcoma. These characteristics highlight the potential applications of FAPI in various clinical scenarios including primary tumor evaluation, detection of metastatic spread, identification of recurrence, and monitoring of treatment response.

However, most currently available evidence comes from retrospective studies with limited patient numbers and heterogeneous patient populations. The fact that sarcomas represent an extremely heterogeneous group of tumors in terms of histology, molecular features, and microenvironmental composition leads to considerable variability in FAP expression and consequently FAPI uptake among different subtypes.

Further studies are especially needed to clarify the clinical value of FAPI in tumors with more limited stromal components, such as Ewing sarcoma and low-grade chondrosarcoma. Therefore, large-scale, prospective, multicenter studies using standardized imaging protocols are required to determine the diagnostic accuracy, prognostic value, and role of FAPI PET/CT in predicting treatment response.

Beyond diagnostic applications, the theranostic potential of FAPI represents one of the most remarkable areas of sarcoma research. Noninvasive visualization of FAP expression may allow identification of suitable patients for FAP-targeted radioligand therapies. Particularly in advanced-stage, metastatic, or treatment-resistant sarcomas, FAPI derivatives labeled with 177Lu and 225Ac may become important therapeutic options in the future.

In addition, integration of FAPI imaging data with radiomic analyses, artificial intelligence-based prognostic models, and personalized treatment strategies appears to be a promising research area that may open new horizons in sarcoma management.

In conclusion, FAPI PET/CT stands out as an innovative imaging modality capable of evaluating not only the metabolic aspect of tumor biology but also the tumor microenvironment and stromal activity in soft tissue and bone sarcomas. Based on current evidence, FAPI appears more likely to complement FDG PET/CT

and increase biological insight rather than replace it in the near future. However, results from ongoing clinical studies will reveal the true clinical value of FAPI in diagnostic, prognostic, and theranostic applications and will more clearly define its role in the routine management of sarcomas.

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BÖLÜM 0

GA-68 FAPI PET IMAGING in CARDIAC and SYSTEMIC FIBROTIC DISEASES: FROM MOLECULE to CLINIC

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Introduction

Fibrosis is a fundamental pathological process underlying a wide spectrum of cardiovascular and systemic diseases and is characterized by excessive extracellular matrix deposition and persistent fibroblast activation. Recent advances in molecular imaging have highlighted fibroblast activation protein (FAP) as an important biomarker of active fibrogenesis and tissue remodeling (Lindner et al., 2021; Schmidkonz et al., 2022). In this context, Ga-68 fibroblast activation protein inhibitor (FAPI) PET imaging has emerged as a promising modality by enabling high-contrast visualization of activated fibroblasts with low physiological background uptake. Initially introduced in oncologic imaging, FAPI PET has rapidly expanded into non-malignant diseases, particularly fibrotic and chronic inflammatory conditions, where it may provide molecular assessment of ongoing fibroblast-driven remodeling beyond conventional structural imaging approaches (Dong et al., 2023).

In cardiovascular diseases, myocardial fibrosis is recognized as one of the fundamental pathophysiological mechanisms underlying ventricular remodeling, progressive heart

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failure, and arrhythmogenesis. Ga-68 FAPI PET enables visualization of activated fibroblast activity, allowing assessment of ongoing myocardial remodeling processes at early stages (Diekmann et al., 2022; Heckmann et al., 2020). Under normal physiological conditions, myocardial FAPI uptake is relatively low. However, increased myocardial FAPI uptake has been demonstrated in various cardiovascular conditions, including myocardial infarction, heart failure, and valvular heart disease, and has been associated with disease severity and functional outcomes (Diekmann et al., 2023; Notohamiprodjo et al., 2022; Wang et al., 2026).

Beyond cardiac applications, FAPI PET has emerged as a promising imaging modality in systemic fibrotic diseases such as pulmonary fibrosis, systemic sclerosis, IgG4-related disease, and liver fibrosis. By enabling whole-body assessment of fibroblast activity, it provides insights into disease burden and activity across multiple organs, supporting its potential role in early diagnosis, disease characterization, and treatment response assessment (Rosenkrans et al., 2022; Schmidkonz et al., 2022; Windisch et al., 2021).

Recent systematic reviews and meta-analyses further support the clinical utility of FAPI PET in non-oncologic settings, emphasizing its high sensitivity and potential prognostic value (Wang et al., 2026; Windisch et al., 2021). Moreover, emerging evidence suggests that FAPI imaging may enable theranostic approaches targeting fibrotic pathways (Palihati et al., 2025).

This chapter aims to define the emerging role of Ga-68 FAPI PET in cardiac and systemic fibrotic diseases by integrating current evidence, highlighting its value in early detection, disease characterization, and clinical decision-making, while outlining future directions for its use in medicine.

FAPI Applications In Cardiovascular Diseases

Myocardial Infarction and Post-Infarction Remodeling

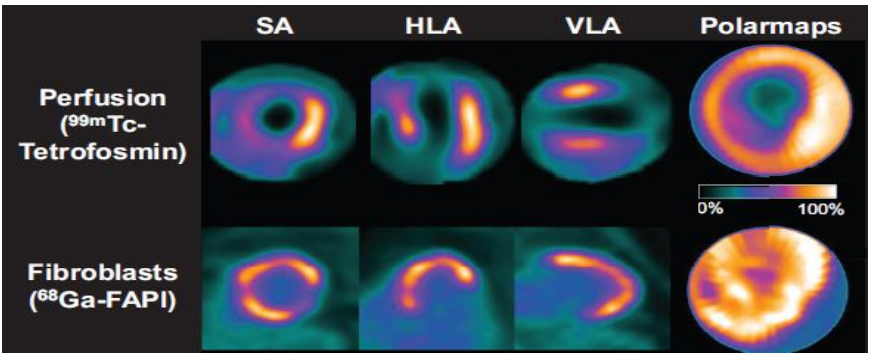
Myocardial infarction (MI) results from acute ischemic injury leading to irreversible cardiomyocyte death and initiates a complex sequence of inflammatory and reparative processes within the myocardium. The early phase is characterized by infiltration of inflammatory cells, including neutrophils and macrophages, which release cytokines and growth factors that activate resident cardiac fibroblasts. These activated fibroblasts subsequently differentiate into myofibroblasts, contributing to extracellular matrix deposition and scar formation, which are essential for maintaining structural integrity of the infarcted myocardium (Frangogiannis, 2018; Lindner et al., 2021).

Although fibroblast activation is essential for maintaining structural integrity after myocardial infarction, excessive or prolonged activation may lead to diffuse myocardial fibrosis, contributing to adverse ventricular remodeling, impaired contractile function, and progression to heart failure. This maladaptive process highlights the importance of identifying active fibrotic remodeling rather than established scar tissue. In this regard, FAPI PET enables detection of ongoing fibrotic activity, providing information on disease progression and allowing earlier risk assessment (Notohamiprodjo et al., 2022).

In myocardial infarction, increased FAPI uptake has been observed in both infarcted and peri-infarct regions, reflecting ongoing repair and fibrogenesis (Diekmann et al., 2022; Notohamiprodjo et al., 2022) (Figure1). While conventional imaging modalities such as cardiac magnetic resonance (CMR) primarily demonstrate irreversible fibrosis and structural alterations, FAPI PET can detect fibroblast activation at earlier stages of myocardial remodeling, allowing identification of active

disease processes before overt structural changes become apparent (Heckmann et al., 2020; Diekmann et al., 2022).

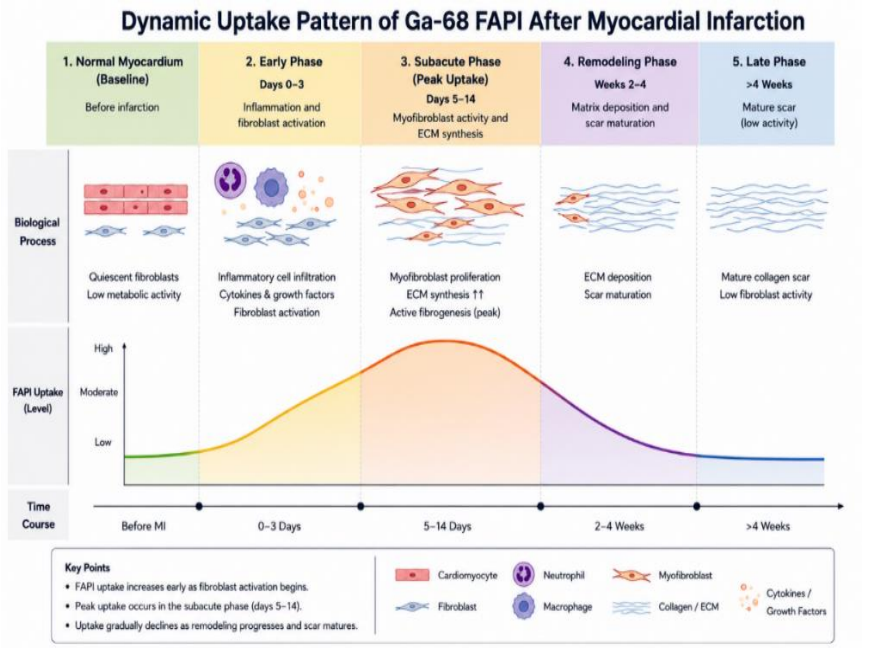
Figure 1: Myocardial perfusion scintigraphy and Ga-68 FAPI PET images in a patient with MI



Myocardial perfusion images using 99mTc-tetrofosmin at rest and 68Ga-FAPI PET. Area of fibroblast activation as indicated by 68Ga-FAPI-46 PET signal exceeds infarct area, the most common type of myocardial FAP distribution. HLA: Horizontal long axis; SA:short axis; VLA:vertical long axis. (Used with permission from Diekmann et al., Journal of Nuclear Medicine 2022)

Ga-68 FAPI uptake after myocardial infarction changes over time according to the progression of fibroblast activation. Uptake is typically low in normal myocardium but begins to increase within the first few days after infarction, corresponding to the early reparative phase characterized by fibroblast proliferation. Peak uptake is generally observed during the subacute phase, approximately between days 5 and 14, when myofibroblast activity and extracellular matrix synthesis are most prominent. Thereafter, uptake gradually declines over subsequent weeks as remodeling progresses toward mature scar formation (Figure 2), (Diekmann et al., 2022; Varasteh et al., 2019).

Figure 2: Dynamic pattern of Ga-68 FAPI uptake following myocardial infarction (Schematic representation based on data reported by Diekmann et al. and Varasteh et al.)



From a clinical perspective, dynamic uptake pattern of Ga-68 FAPI is critical for interpretation. Persistently elevated or prolonged FAPI uptake beyond the expected subacute phase may indicate ongoing maladaptive remodeling and has been associated with adverse ventricular remodeling and impaired functional recovery. Conversely, low or absent uptake in later stages is generally consistent with stabilized scar tissue and reduced fibroblast activity (Notohamiprodjo et al., 2022; Wang et al., 2026).

These findings also have potential implications for treatment guidance. Identification of ongoing fibroblast activation may help select patients who could benefit from antifibrotic or remodeling-targeted therapies. In addition, changes in FAPI uptake over time may provide a means to monitor treatment response,

particularly in the early phases of intervention. Such an approach may support more individualized management by distinguishing active disease from stabilized fibrosis (Heckmann et al., 2020; Schmidkonz et al., 2022; Windisch et al., 2021).

In summary, Ga-68 FAPI PET provides a novel approach for assessing myocardial remodeling by enabling visualization of active fibroblast activity. By distinguishing ongoing fibrogenesis from established scar, it offers clinically relevant information beyond conventional imaging. This capability may improve disease characterization and support more informed clinical decision-making in patients following myocardial infarction.

Non-Ischemic Cardiomyopathies

Non-ischemic cardiomyopathies comprise a heterogeneous group of myocardial disorders characterized by structural and functional abnormalities in the absence of significant coronary artery disease. Despite their diverse etiologies and phenotypic presentations, progressive myocardial remodeling and interstitial fibrosis represent common pathological features contributing to ventricular dysfunction, arrhythmogenesis, and adverse clinical outcomes. In many cases, fibrotic remodeling develops as a diffuse and dynamic process that may not be fully characterized by conventional imaging techniques, particularly during early or biologically active stages of disease (Heckmann et al., 2020; Wang et al., 2026).

CMR remains central to the evaluation of non-ischemic cardiomyopathies, particularly through late gadolinium enhancement (LGE) and parametric mapping techniques. These methods provide important information regarding myocardial tissue composition and fibrosis burden; however, they primarily reflect structural and extracellular matrix alterations rather than ongoing cellular activity. In this context, Ga-68 FAPI PET has emerged as a

promising molecular imaging approach for assessing fibroblast-related activity associated with myocardial remodeling. Preliminary studies suggest that myocardial FAPI uptake may provide complementary information regarding disease activity, remodeling heterogeneity, and potential risk stratification in patients with non-ischemic cardiomyopathies (Cui et al., 2023; Wang et al., 2026).

Dilated Cardiomyopathy

Dilated cardiomyopathy (DCM) is characterized by ventricular dilation and systolic dysfunction accompanied by progressive interstitial fibrosis, which plays a central role in disease progression and adverse remodeling, often presenting as a diffuse and heterogeneous process that complicates accurate assessment with conventional imaging techniques. In this setting, Ga-68 FAPI PET may provide molecular characterization of fibroblast activity associated with active myocardial remodeling.

Recent studies have demonstrated increased myocardial FAPI uptake in patients with DCM, reflecting active fibroblast activity and correlating with impaired left ventricular function. Notably, FAPI uptake may extend beyond areas identified by conventional imaging, suggesting that it can capture early or subclinical fibrotic processes not detectable by CMR alone. These findings support the role of Ga-68 FAPI PET as a potential tool for assessing disease activity and improving risk stratification in patients with dilated cardiomyopathy (Shi et al., 2022; Wang et al., 2023; Cui et al., 2023).

In dilated cardiomyopathy, Ga-68 FAPI uptake typically demonstrates a diffuse and heterogeneous distribution throughout the myocardium, reflecting varying degrees of fibroblast activation across different regions. This pattern often does not conform to coronary territories and may involve both septal and lateral walls, highlighting the non-ischemic nature of the disease. In some

patients, more pronounced or focal areas of increased uptake may be observed, potentially indicating regions of intensified remodeling activity. Such spatial heterogeneity suggests that fibroblast activation is a dynamic and regionally variable process in DCM (Shi et al., 2022; Wang et al., 2023).

From a clinical perspective, these uptake patterns may provide valuable information for patient management. Increased and widespread FAPI uptake may indicate active disease progression, whereas lower or more limited uptake could reflect a relatively stable phase. This distinction may help identify patients who require closer follow-up or more aggressive medical therapy. Furthermore, serial FAPI imaging has the potential to monitor changes in fibroblast activity over time, offering a non-invasive approach to assess treatment response and guide individualized management strategies (Cui et al., 2023; Wang et al., 2026).

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is characterized by myocardial hypertrophy, myocyte disarray, and varying degrees of interstitial and replacement fibrosis, all of which contribute to diastolic dysfunction, arrhythmogenesis, and an increased risk of sudden cardiac death. Unlike dilated cardiomyopathy, structural alterations in HCM are often regionally accentuated, most prominently involving the interventricular septum, although fibrotic remodeling may extend beyond hypertrophied segments. While CMR plays a central role in detecting focal fibrosis through late gadolinium enhancement, its ability to identify early or diffuse fibroblast activity remains limited (Song et al., 2026; Cui et al., 2023).

Ga-68 FAPI PET offers a complementary approach by visualizing fibroblast-related activity. Increased myocardial FAPI uptake has been demonstrated in patients with HCM, typically

showing a heterogeneous and regionally accentuated distribution that often involves hypertrophied segments but is not confined to them. This pattern indicates that fibroblast activation may extend beyond structural abnormalities detectable by conventional imaging and reflects a dynamic, multifocal remodeling process. These findings suggest that FAPI PET may provide additional insight into disease activity and underlying biological mechanisms (Wang et al., 2023-a; Cui et al., 2023).

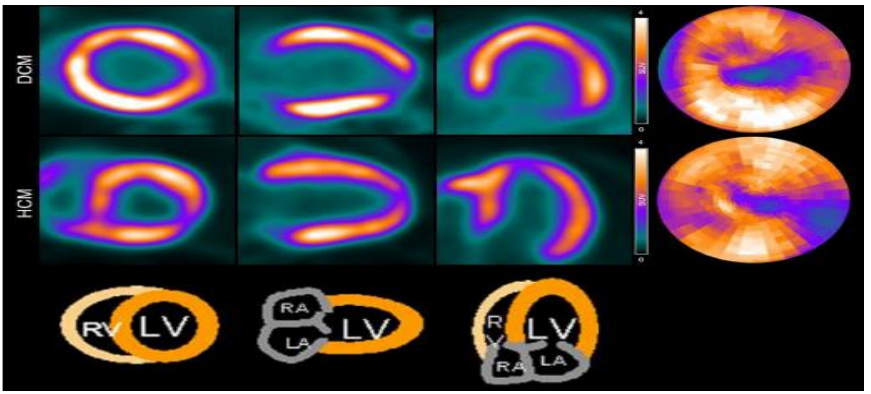
From a clinical perspective, these uptake characteristics may provide important prognostic information. Higher and more heterogeneous FAPI uptake has been associated with markers of disease severity, including impaired myocardial strain and increased arrhythmic risk. Notably, recent studies suggest that fibroblast-related activity detected by FAPI PET may be linked to an increased risk of sudden cardiac death, potentially offering incremental value beyond conventional risk stratification models. In addition, its ability to reflect early and active remodeling may help identify patients who require closer monitoring or more aggressive therapeutic strategies (Song et al., 2026; Wang et al., 2023-a).

A comparative overview of FAPI PET findings in DCM and HCM is presented in Table 1 and Ga-68 FAPI images in Figure 3.

Table-1: Comparison of FAPI PET Findings in Dilated Cardiomyopathy and Hypertrophic Cardiomyopathy

Features	**Dilated Cardiomyopathy (DCM)**	**Hypertrophic Cardiomyopathy (HCM)**
Primary Pathology	**Ventricular dilation and systolic dysfunction**	**Myocardial hypertrophy and myocyte disarray**
Fibrosis Type	**Predominantly diffuse interstitial fibrosis**	**Interstitial and perivascular fibrosis**
FAPI Uptake Pattern	**Diffuse and heterogeneous uptake with widespread ventricular involvement**	**Predominantly regional uptake with frequent septal predominance that may extend beyond hypertrophic segments**
Complementary Value to CMR	**May detect diffuse remodeling potentially underestimated by CMR**	**FAPI-positive regions may exceed hypertrophic areas detected by CMR**
Potential Clinical Value	**Potential utility for monitoring disease progression and remodeling activity**	**Potential prognostic value in clinical risk assessment**

Figure 3: Ga-68 FAPI uptake in DCM and HCM



DCM:Dilated cardiomyopathy; HCM:Hypertrophic cardiomyopathy; SA:Short axis; HLA:Horizontal long axis; VLA: Vertical long axis; RV:Right ventricle; LV:Left ventricle; RA:Right atrium; LA:Left atrium (Reproduced from Wang et al., EJNMMI Research (2023-b), distributed under the terms of the Creative Commons Attribution 4.0 International License (CC BY 4.0)

Cardiotoxicity

Cardiotoxicity refers to myocardial injury that occurs as a consequence of cancer therapies, including chemotherapy, targeted agents, and immunotherapies. While these treatments have significantly improved cancer survival, they may adversely affect the myocardium through mechanisms such as oxidative stress, mitochondrial dysfunction, and immune-mediated injury (Zamorano et al., 2016; Lyon et al., 2022; Caforio et al., 2013). Depending on the type of agent and duration of exposure, myocardial damage may present as acute dysfunction or evolve into a chronic process characterized by progressive remodeling.

A key feature of cardiotoxicity is the activation of cardiac fibroblasts and the development of interstitial fibrosis, which contribute to ventricular dysfunction and heart failure. Importantly, these changes may begin at a subclinical stage before measurable alterations in left ventricular function become apparent. This

highlights the need for imaging approaches capable of detecting early myocardial injury and ongoing remodeling beyond conventional functional assessment (Lyon et al., 2022).

Conventional imaging modalities play a central role in the monitoring of cardiotoxicity, with echocardiography being the most widely used tool for serial assessment of left ventricular function. In particular, global longitudinal strain has emerged as a sensitive marker for detecting early myocardial dysfunction before a decline in ejection fraction becomes apparent (Lyon et al., 2022). CMR provides additional value through detailed tissue characterization, allowing detection of myocardial edema and fibrosis, especially in selected clinical scenarios.

Despite these advantages, current imaging approaches have important limitations. Most techniques primarily detect functional impairment or established structural changes, which may occur relatively late in the disease course. As a result, early subclinical injury and ongoing cellular processes such as fibroblast activation may remain undetected. This gap is particularly relevant in patients receiving cardiotoxic therapies, where timely identification of myocardial involvement is critical for preventing irreversible damage (Zamorano et al., 2016; Lyon et al., 2022). In this context, imaging strategies that can directly reflect active myocardial remodeling may provide additional clinical value.

Ga-68 FAPI PET offers a complementary approach by directly targeting activated fibroblasts. Unlike conventional imaging, it enables visualization of early cellular activity associated with myocardial injury and repair, which may occur before overt ventricular dysfunction becomes apparent (Heckmann et al., 2020; Frangogiannis, 2021).

Recent experimental data provide important insight into the temporal pattern of FAPI uptake in cardiotoxicity. In a preclinical

model of anthracycline-induced injury, myocardial Ga-68 FAPI uptake was shown to increase as early as 2 weeks after doxorubicin exposure, preceding the onset of measurable functional impairment (Lee et al., 2025). Notably, conventional echocardiographic parameters remained unchanged at early time points, while ventricular dysfunction became evident only at later stages (Lee et al., 2025). This temporal dissociation highlights that FAPI uptake reflects early fibroblast activation and molecular remodeling rather than established structural or functional damage.

In addition to its early onset, FAPI uptake appears to persist during the progression of myocardial injury, remaining elevated during phases when functional decline begins to emerge (Lee et al., 2025). This pattern supports the concept that FAPI PET captures a dynamic remodeling process, providing a window into ongoing myocardial injury that is not accessible with conventional imaging approaches (Heckmann et al., 2020; Lyon et al., 2022).

Taken together, these findings suggest that FAPI PET may serve as a sensitive imaging modality for the early detection of cardiotoxicity by enabling identification of subclinical myocardial injury before irreversible damage occurs. This capability may allow earlier identification of at-risk patients and support more timely and individualized clinical management.

Aortic Stenosis

Aortic stenosis imposes a chronic pressure overload on the left ventricle, leading to progressive hypertrophy and structural remodeling. Although this initial response helps preserve cardiac output, sustained mechanical stress promotes myocyte injury and activation of cardiac fibroblasts, resulting in interstitial fibrosis. Over time, these changes increase myocardial stiffness, impair diastolic function, and contribute to the development of heart failure. Importantly, the extent of myocardial remodeling varies

among patients and plays a key role in determining clinical outcomes following valve intervention (Dweck et al., 2012; Treibel et al., 2018).

In patients with severe aortic stenosis, accurate assessment of myocardial involvement before intervention is essential, particularly in the context of transcatheter aortic valve replacement (TAVR). Although valve replacement effectively reduces afterload, clinical recovery varies considerably, with a substantial proportion of patients demonstrating persistent symptoms or limited reverse remodeling despite technically successful procedures (Xue et al., 2026). This variability is largely attributed to differences in the extent and activity of myocardial fibrosis, which may not be fully captured by conventional imaging techniques.

Current imaging modalities provide important structural and functional information but have inherent limitations. Echocardiography reflects hemodynamic severity and ventricular performance, while CMR allows quantification of fibrosis through late gadolinium enhancement and parametric mapping. However, these techniques primarily depict established structural changes and may not adequately reflect ongoing fibrogenic activity or the dynamic nature of myocardial remodeling (Diekmann et al., 2023). As a result, there is increasing interest in imaging approaches that can identify active biological processes and better predict myocardial recovery following TAVR.

Ga-68 FAPI PET enables direct visualization of activated fibroblasts by reflecting pressure overload–induced myocardial remodeling in aortic stenosis. In addition, it may demonstrate ongoing fibrogenic activity even in patients with preserved ventricular function (Diekmann et al., 2023).Recent clinical studies have demonstrated increased and heterogeneous myocardial FAPI uptake in patients with severe aortic stenosis, often with a predilection for septal and basal segments, reflecting regional

differences in wall stress and remodeling . Importantly, quantitative measures such as the myocardium-to-blood pool ratio (TBR) have shown strong associations with biomarkers of hemodynamic stress, including N-terminal pro-brain natriuretic peptide (NT-proBNP), suggesting that FAPI uptake reflects active myocardial remodeling rather than static fibrosis (Xue et al., 2026).

Beyond its diagnostic role, FAPI PET may provide important prognostic information in patients undergoing TAVR. Increased pre-procedural myocardial FAPI uptake has been linked to variable clinical response, reflecting differences in myocardial remodeling activity (Diekmann et al., 2023). More recent evidence shows that higher myocardium-to-blood pool ratios are associated with reduced improvement after TAVR, suggesting that active fibroblast-driven remodeling may limit functional recovery (Xue et al., 2026).

These findings highlight the potential of FAPI PET to identify patients with advanced or less reversible myocardial disease. In aortic stenosis, Ga-68 FAPI PET provides additional insight beyond structural assessment, supporting more refined risk stratification and individualized patient management before TAVR.

Atherosclerosis

Atherosclerosis is a chronic progressive disease of the arterial wall characterized by lipid accumulation, endothelial dysfunction, immune cell infiltration, and extracellular matrix remodeling. Beyond luminal stenosis, atherosclerosis is increasingly recognized as a biologically active fibro-inflammatory process involving persistent vascular inflammation and remodeling (Hansson & Hermansson, 2011; Libby et al., 2019).

The disease is initiated by endothelial injury triggered by cardiovascular risk factors such as hypertension, dyslipidemia, diabetes mellitus, and smoking. Subsequent retention and oxidation

of low-density lipoprotein (LDL) particles promote recruitment of inflammatory cells, cytokine release, smooth muscle cell activation, and fibroblast-related extracellular matrix remodeling, leading to progressive plaque formation and vascular remodeling (Libby, 2021).

Progressive atherosclerotic plaque formation may lead to arterial luminal narrowing, impaired tissue perfusion, and ischemic cardiovascular events, including myocardial infarction, stroke, and peripheral arterial disease. Importantly, clinical events are often determined not only by the degree of stenosis but also by plaque vulnerability and biological activity within the arterial wall. Vulnerable plaques are characterized by intense inflammatory activity, a large lipid-rich necrotic core, thinning of the fibrous cap, extracellular matrix degradation, and increased susceptibility to rupture or erosion. These processes promote thrombosis and acute vascular events, highlighting the importance of identifying biologically active plaques beyond structural assessment (Bentzon et al., 2014; Libby, 2021).

Given the central role of plaque biology in determining cardiovascular risk, accurate characterization of atherosclerotic activity has become an important clinical objective. Conventional imaging modalities such as computed tomography angiography (CTA), vascular ultrasound, invasive coronary angiography, and CMR provide important anatomical and functional information regarding plaque burden, luminal stenosis, vascular calcification, and vessel wall morphology. In particular, CTA enables assessment of coronary plaque composition and calcification, while vascular ultrasound allows evaluation of carotid intima-media thickness and plaque characteristics. CMR may additionally provide information regarding vessel wall composition and inflammatory changes in selected settings. However, these techniques primarily depict structural abnormalities and have limited ability to directly assess

ongoing biological processes associated with plaque activity and vascular remodeling (Kosmala et al., 2023).

Molecular imaging techniques, particularly PET, have gained increasing interest for the non-invasive assessment of biological activity within atherosclerotic plaques. Among molecular imaging techniques, fluorine-18 fluorodeoxyglucose (18F-FDG) PET has been the most extensively investigated modality for imaging vascular inflammation in atherosclerosis. FDG uptake reflects glucose metabolism associated with activated inflammatory cells, particularly macrophages, and increased arterial FDG uptake has been associated with plaque inflammation and cardiovascular risk. Several studies have demonstrated correlations between FDG uptake and histopathological markers of inflammatory activity within atherosclerotic plaques, supporting its role as a marker of biologically active disease (Tawakol et al., 2006; Joshi et al., 2014).

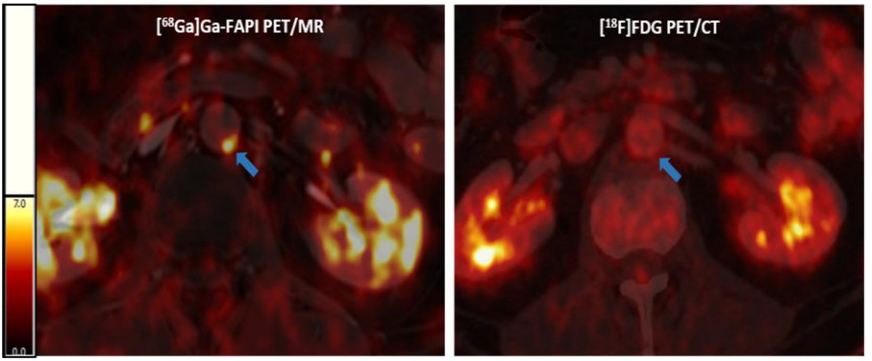
Despite these advantages, FDG PET has important limitations in vascular imaging. FDG uptake is not specific for atherosclerotic inflammation and may be influenced by systemic metabolic activity, blood glucose levels, and physiologic background uptake. In addition, FDG provides limited information regarding fibroblast activation and extracellular matrix remodeling, which are key components of plaque progression and vascular remodeling (Calabretta et al., 2025).

Ga-68 FAPI PET has emerged as a promising molecular imaging technique for evaluating fibroblast-related vascular remodeling in atherosclerosis. FAP is highly expressed in activated fibroblasts and increased FAP expression has particularly been demonstrated in thin-cap fibroatheromas and unstable plaques prone to rupture, suggesting a potential role of Ga-68 FAPI PET in identifying vulnerable atherosclerotic lesions (Wu et al., 2022).

Ga-68 FAPI uptake is most commonly observed in the abdominal and thoracic aorta, iliac arteries, and carotid bifurcations, corresponding to regions exposed to low endothelial shear stress where atherosclerosis preferentially develops (Kosmala et al., 2023; Bentzon et al., 2014). Imaging studies have demonstrated that FAPI uptake is more prominent in non-calcified or mildly calcified lesions, whereas heavily calcified plaques tend to show lower tracer activity (Wu et al., 2022). Moreover, increased FAP expression within thin fibrous caps supports the concept that Ga-68 FAPI PET may reflect active plaque remodeling rather than late-stage stable calcification.

Compared with FDG PET, Ga-68 FAPI PET offers several potential advantages in vascular imaging. Physiological myocardial FDG uptake often limits coronary artery assessment. In contrast, Ga-68 FAPI demonstrates low background myocardial activity, allowing improved visualization of vascular wall lesions. Furthermore, FAPI uptake appears to be less influenced by metabolic conditions. Recent studies have shown that Ga-68 FAPI detects a greater number of active arterial lesions and demonstrates significantly higher target-to-background ratios compared with FDG PET (Calabretta et al., 2025)(Figure-4) Nevertheless, important limitations remain, including the relatively limited clinical experience, lack of standardized interpretation criteria, and the possibility that part of the vascular uptake may be influenced by image noise rather than true biological activity (Kosmala et al., 2023).

Figure-4: Representative Ga-68 FAPI and 18F-FDG PET findings in atherosclerotic arterial lesions.



An arterial lesion (blue arrows) with a higher [68Ga] Ga-FAPI expression and without significant [18F] FDG activity in a cancer patient (Reproduced from Calabretta et al. (2025) under the terms of the Creative Commons Attribution License (CC BY 4.0).

In conclusion, Ga-68 FAPI PET appears to be a promising molecular imaging modality for evaluating atherosclerotic plaque activity and vulnerability; however, further large-scale studies and standardized interpretation criteria are required before its routine clinical implementation.

Systemıc Diseases and GA-68 FAPI PET

Pulmonary Fibrosis and FAPI PET Imaging

Pulmonary fibrosis comprises a heterogeneous group of chronic interstitial lung diseases characterized by progressive fibroblast activation, excessive extracellular matrix deposition, and irreversible architectural distortion of the lung parenchyma. Fibrotic remodeling of the lungs may develop in association with a

wide spectrum of conditions, including idiopathic pulmonary fibrosis (IPF), connective tissue disease–associated interstitial lung diseases, chronic hypersensitivity pneumonitis, occupational and environmental exposures such as asbestos and silica, drug-induced lung injury, radiation exposure, and post-inflammatory lung damage (King et al., 2011; Raghu et al., 2018). Among these entities, IPF represents the most severe and progressive form, typically associated with poor prognosis and progressive respiratory failure (King et al., 2011).

Conventional imaging modalities, particularly high-resolution computed tomography (HRCT), remain the cornerstone for the diagnosis and structural evaluation of pulmonary fibrosis. HRCT provides detailed assessment of fibrotic patterns such as reticulation, traction bronchiectasis, and honeycombing, and plays a central role in the identification of usual interstitial pneumonia patterns in idiopathic pulmonary fibrosis (Lynch et al., 2018). In addition to HRCT, FDG PET has been investigated for the evaluation of pulmonary fibrosis because increased FDG uptake may reflect inflammatory and metabolically active tissue processes. Several studies have demonstrated elevated pulmonary FDG uptake in patients with interstitial lung diseases and suggested potential associations with disease progression and prognosis (Groves et al., 2009; Win et al., 2018). However, despite its essential diagnostic role, HRCT primarily reflects established structural abnormalities rather than ongoing fibrogenic activity, whereas FDG PET mainly provides information about inflammatory processes and is not specific for fibrosis.

Ga-68 FAPI PET enables molecular imaging of activated fibroblasts within fibrotic lung tissue by targeting FAP expression associated with active fibrogenesis. Increased pulmonary FAPI uptake has been demonstrated in patients with interstitial lung diseases, with tracer accumulation corresponding to fibrotic lung

involvement identified on HRCT. Importantly, FAPI uptake may extend beyond areas of established fibrosis, suggesting that FAPI PET could provide additional information regarding ongoing fibroblast-driven remodeling and active disease activity. Furthermore, preliminary findings suggest that Ga-68 FAPI PET may detect fibrotic injury at earlier stages of disease, when conventional diagnostic tools such as HRCT and spirometry may still demonstrate limited sensitivity (Rosenkrans et al., 2022; Röhrich et al., 2022).

From a clinical perspective, FAPI uptake appears to correlate with disease activity and may provide additional value for assessing disease progression. By reflecting active remodeling, FAPI PET has the potential to improve disease characterization, support early diagnosis, and enable monitoring of therapeutic response. This may be particularly relevant in the era of antifibrotic therapies, where identification of active disease is critical for optimizing treatment strategies

Renal Fibrosis and FAPI PET Imaging

Renal fibrosis represents the common final pathway of chronic kidney diseases and is a major determinant of progressive renal dysfunction and irreversible nephron loss. Histologically, it is characterized by excessive extracellular matrix deposition and expansion of the tubulointerstitial compartment secondary to persistent fibroblast activation and maladaptive tissue repair processes. Progressive fibrotic remodeling contributes to deterioration of renal function regardless of the underlying etiology, including diabetic nephropathy, hypertensive nephrosclerosis, glomerulonephritis, obstructive nephropathy, and autoimmune kidney diseases (Humphreys, 2018). Importantly, renal fibrosis often develops before substantial decline in

conventional functional parameters becomes apparent, creating a major challenge for early diagnosis and disease monitoring.

Current diagnostic approaches for renal fibrosis remain limited. Conventional imaging modalities such as ultrasonography and computed tomography primarily provide structural and anatomical information but lack sensitivity for detecting early or active fibrotic remodeling. Functional parameters including estimated glomerular filtration rate (eGFR) and serum creatinine reflect overall renal function rather than ongoing molecular and cellular processes within the renal parenchyma. Although renal biopsy remains the reference standard for fibrosis assessment, its invasive nature, sampling variability, and limited suitability for serial monitoring restrict its routine use in evaluating dynamic fibrotic progression (Farris & Alpers, 2014).

Ga-68 FAPI PET enables molecular imaging of activated fibroblasts within the renal parenchyma by targeting FAP expression associated with active fibrogenesis. Increased renal FAPI uptake has been demonstrated in patients with chronic kidney disease and renal fibrosis, with tracer accumulation correlating with histopathological fibrosis severity, renal functional impairment, and advanced disease stages characterized by higher SUVmax and target-to-background ratios (Conen et al., 2022; Zhou et al., 2021). Moreover, an inverse relationship between renal FAPI uptake and glomerular filtration rate has been reported, supporting the association between fibroblast activation, fibrotic burden, and progressive renal dysfunction (Conen et al., 2022). Nevertheless, several important limitations of renal FAPI imaging should be considered. Physiological renal tracer activity and urinary excretion may complicate image interpretation, while increased FAP expression in inflammatory conditions such as pyelonephritis may reduce specificity. In addition, the lack of standardized interpretation criteria and limited validation studies currently

restrict the routine clinical application of FAPI PET in renal fibrosis.

From a clinical perspective, FAPI PET may provide a non-invasive approach for assessing renal fibrotic activity, monitoring disease progression, and evaluating response to antifibrotic therapies. By enabling visualization of ongoing fibroblast activation, FAPI imaging may offer functional information beyond conventional structural and laboratory-based assessments. Nevertheless, larger prospective studies are still required to establish standardized imaging criteria and clarify its role in routine clinical practice (Schmidkonz et al., 2022; Windisch et al., 2021).

Liver Fibrosis and FAPI PET Imaging

Liver fibrosis represents a dynamic wound-healing response to chronic liver injury characterized by excessive extracellular matrix deposition and progressive architectural remodeling of the liver. Persistent fibrogenesis disrupts normal hepatic structure and may ultimately progress to cirrhosis, portal hypertension, and hepatic failure. Chronic viral hepatitis, metabolic dysfunction-associated steatotic liver disease, alcohol-related liver disease, and autoimmune liver disorders constitute the major etiological causes of liver fibrosis worldwide (Bataller & Brenner, 2005; Friedman, 2003). Importantly, liver fibrosis is potentially reversible, particularly in earlier stages, emphasizing the clinical importance of timely detection and accurate assessment of active fibrogenesis before irreversible structural damage develops (Schuppan & Afdhal, 2008).

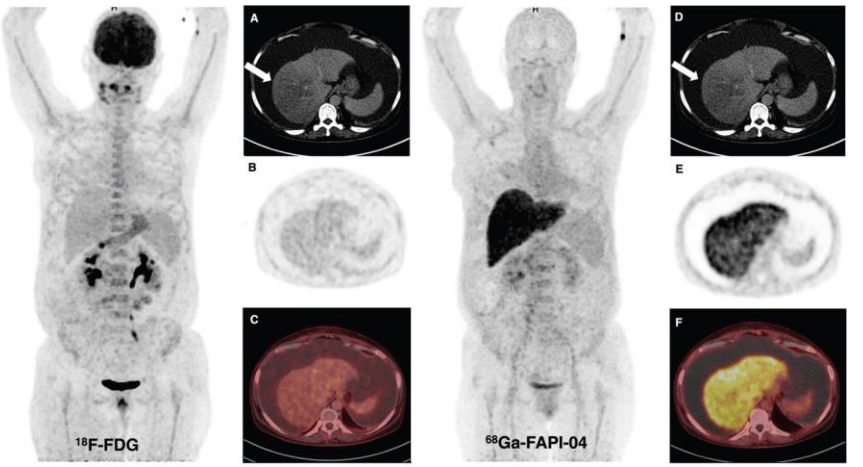
Conventional imaging modalities such as ultrasonography, CT, and MRI primarily provide structural assessment of liver fibrosis. In addition, non-invasive techniques including elastography enable fibrosis staging through the evaluation of liver stiffness and fibrotic burden. However, these approaches primarily

reflect accumulated fibrosis rather than ongoing fibrogenic activity, limiting evaluation of active disease (Barr et al., 2015). In addition, elastography measurements may be influenced by inflammation, congestion, obesity, and technical factors, potentially affecting diagnostic accuracy in certain clinical settings (Barr et al., 2015).

Although liver biopsy remains the reference standard for fibrosis assessment, its invasive nature, sampling variability, interobserver variability, and limited suitability for serial monitoring restrict routine evaluation of disease progression and treatment response.

In this context, Ga-68 FAPI PET enables non-invasive assessment of fibroblast activity and ongoing fibrogenesis within the liver. Preliminary clinical and translational studies have demonstrated increased hepatic FAPI uptake in patients with liver fibrosis and cirrhosis (Mori et al., 2025; Song et al., 2024). Compared with FDG PET, which may demonstrate relatively low or non-specific hepatic uptake in cirrhotic livers, FAPI PET may better reflect fibroblast-related fibrogenic activity (Figure-5). Hepatic FAPI uptake has also been reported to correlate with fibrosis severity and indirect fibrosis markers such as the aspartate aminotransferase-to-platelet ratio index (APRI) (Song et al., 2024). In a pilot prospective study, Li et al. demonstrated a correlation between Ga-68 FAPI PET/CT findings and histopathological fibrosis staging, supporting the potential role of FAPI imaging in the non-invasive assessment of liver fibrosis (Li et al., 2026). Nevertheless, several limitations of hepatic FAPI imaging should be considered. Physiological hepatic tracer uptake and heterogeneous parenchymal remodeling in cirrhotic livers may complicate image interpretation. In addition, inflammatory hepatic conditions may also demonstrate increased FAP expression, potentially limiting specificity for fibrosis assessment.

Figure-5: Comparative FDG and Ga-68 FAPI PET/CT images in a patient with liver cirrhosis



A 50-year-old woman patient presented with abdominal pain and was found to have massive ascites and had undergone ^{18}F-FDG and ^{68}Ga-FAPI-04 PET/CT imaging for a suspected gastric tumor. Abnormal liver activity was not observed on ^{18}F-FDG PET/CT, but diffuse intense FAPI uptake was seen in the liver on 68Ga-FAPI-04 PET/CT. The hypodense area detected in CT sections [(A, D) arrow] at the right lobe of the liver did not show prominent 18F-FDG [(B) PET, (C) fusion images] or FAPI uptake [(E) PET, (F) fusion images] in the parenchyma. Also, no malignant cells were found in the peritoneal aspiration fluid. The patient is being followed up with the diagnosis of decompensated alcoholic cirrhosis. (Reproduced from: Tatar et al., 2023; Licensed under CC BY-NC-ND 4.0.)

From a clinical perspective, FAPI PET may provide a non-invasive approach for assessing active fibrogenesis, monitoring disease progression, and evaluating response to antifibrotic therapies in chronic liver disease. In addition, whole-liver

assessment with FAPI imaging may offer advantages over liver biopsy, which is invasive and subject to sampling variability. However, currently available evidence remains limited, and larger prospective studies with histopathological validation are required to establish standardized imaging criteria and clarify the clinical role of FAPI PET in liver fibrosis.

Pitfalls and Limitations of FAPI PET Imaging

Although the clinical applications of FAPI PET imaging are rapidly expanding, several important pitfalls and limitations should be considered during image interpretation. The main limitations include:

- Increased FAP expression is not specific to malignant or fibrotic processes and may also be observed in inflammatory, infectious, and reparative conditions.
- Physiological tracer uptake and organ-specific background activity may complicate image interpretation in certain anatomical regions.
- Standardized imaging protocols have not yet been fully established. In addition, differences in radiotracers, acquisition timing, reconstruction methods, and interpretation criteria may affect reproducibility across studies.
- Most currently available studies are based on relatively small patient cohorts.

Theranostic Applications

Beyond its diagnostic role, FAPI-based imaging has increasingly attracted attention as a theranostic platform, particularly in oncology, where significant advances have been achieved with FAPI-targeted radionuclide therapies. Favorable

biodistribution characteristics and selective targeting of activated fibroblasts have supported the development of therapeutic radioligands in various malignancies. In parallel with these oncologic advances, growing evidence suggests that FAPI-directed therapies may also hold potential in fibrotic diseases.

In this context, Zhao et al. demonstrated the potential therapeutic application of Lu-177-labeled FAPI in a rat model of myocardial infarction. In their study, targeted radionuclide therapy was associated with reduced myocardial fibrosis, attenuation of adverse ventricular remodeling, and improvement in left ventricular function without significant systemic toxicity (Zhao et al., 2025). These findings suggest that fibroblast-directed therapies may represent a promising future strategy for modulating post-infarction remodeling.

Nevertheless, theranostic applications of FAPI in cardiovascular and systemic fibrotic diseases remain at an early stage of development. Current evidence is largely limited to preclinical investigations, and further studies are needed to establish long-term safety, optimal therapeutic protocols, and clinical efficacy before routine clinical application can be achieved.

Conclusion

Ga-68 FAPI PET imaging has emerged as a promising modality for the evaluation of cardiac and systemic fibrotic diseases. Visualization of activated fibroblasts enables earlier detection of disease, improved characterization of active remodeling processes, and more accurate assessment of disease burden across different organs. In addition, by providing a dynamic whole-body evaluation, FAPI PET has the potential to complement and, in selected scenarios, provide advantages over conventional imaging methods in diagnosis, risk stratification, and treatment monitoring.

Beyond its diagnostic applications, the expanding role of FAPI-targeted imaging has also introduced potential theranostic implications, particularly with the development of fibroblast-targeted radionuclide therapies.

Nevertheless, several important limitations remain, including the lack of standardized imaging protocols, variability in physiological and inflammatory uptake patterns, and the limited availability of large prospective multicenter studies. Therefore, further translational and clinical investigations are required to clarify the diagnostic, prognostic, and therapeutic applications of FAPI imaging before its routine integration into clinical practice.

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LIMITATIONS, PITFALLS, and FUTURE DIRECTIONS OF FAPI PET/CT
BÖLÜM 0

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1. Introduction

Fibroblast activation protein inhibitor (FAPI) PET/CT has rapidly gained attention as a promising imaging modality in oncologic nuclear medicine, primarily due to its high tumor-to-background contrast and favorable pharmacokinetics. However, despite these advantages, the clinical role of FAPI PET/CT remains incompletely defined. Most available data originate from retrospective and single-center studies, often with limited histopathological validation. Therefore, a critical and balanced evaluation of its limitations, pitfalls, and future directions is essential for appropriate clinical integration.

2. Lack of Tumor Specificity

2.1 Biological Basis

FAP is not a tumor-specific marker; rather, it is a marker of activated fibroblasts. Consequently, FAPI uptake reflects stromal activation rather than malignancy itself (Loktev et al., 2018; Kratochwil et al., 2019). Activated fibroblasts are present in multiple physiological and pathological processes, including tissue repair, inflammation, and fibrosis.

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2.2 Clinical Implications

Increased FAPI uptake has been reported in several benign conditions, including:

- Chronic inflammatory diseases (e.g., pancreatitis, arthritis)
- Fibrotic conditions (e.g., liver cirrhosis, pulmonary fibrosis)
- Post-surgical and post-radiation tissue remodeling

This overlap significantly limits specificity and may lead to false-positive interpretations (Acharya et al., 2006; Terry et al., 2016; Waumans et al., 2015)

In addition to these conditions, it should be noted that the intensity and pattern of FAPI uptake in benign processes may overlap considerably with malignant lesions. While malignant lesions often demonstrate focal and intense uptake, inflammatory or fibrotic processes may also exhibit similar patterns, particularly in active phases. Therefore, reliance solely on uptake intensity may be misleading, and pattern recognition combined with clinical context becomes essential for accurate interpretation. FAPI uptake should be interpreted as a marker of fibroblast activation rather than malignancy per se.

3. False-Positive Findings

3.1 Inflammation and Fibrosis

Inflammatory and fibrotic processes are among the most common causes of false-positive FAPI uptake. For example:

- Active inflammation may demonstrate intense uptake comparable to malignancy
- Fibrotic lesions often show diffuse uptake patterns

Granulomatous diseases such as sarcoidosis may further complicate interpretation (Gu et al., 2020; Hao et al., 2021). Another important consideration is the temporal behavior of FAPI uptake in inflammatory conditions. Acute inflammatory processes may demonstrate higher uptake due to active fibroblast proliferation, whereas chronic fibrotic lesions may show more stable or diffuse uptake patterns. This temporal variability may provide additional clues but also introduces complexity in interpretation, particularly in the absence of prior imaging.

3.2 Post-Treatment Changes

FAPI uptake is frequently observed in:

- Surgical scars
- Anastomotic sites
- Radiotherapy fields

This is particularly relevant in early post-treatment imaging, where reactive fibroblast activity is prominent (Acharya et al., 2006; Terry et al., 2016; Waumans et al., 2015). The timing of imaging relative to treatment is therefore critical. Early post-treatment imaging may overestimate disease activity due to transient fibroblast activation, whereas delayed imaging may better reflect residual or recurrent disease. This highlights the need for standardized imaging intervals, which are currently lacking.

3.3 Practical Considerations

To minimize misinterpretation:

- Correlation with morphological imaging (CT/MRI) is essential

- Clinical history (recent surgery, radiotherapy) must be considered
- Temporal evolution should be evaluated in follow-up imaging

Common causes of false-positive FAPI uptake are summarized in Table 1.

Table 1. Major Sources of False-Positive FAPI Uptake

Category	**Examples**	**Potential Interpretation Pitfall**
Chronic inflammation	Pancreatitis, arthritis	Mimics active malignancy
Fibrotic diseases	Pulmonary fibrosis, liver cirrhosis	Diffuse uptake may resemble tumor infiltration
Granulomatous disease	Sarcoidosis, tuberculosis	Intense uptake despite benign nature
Post-surgical changes	Surgical scars, anastomotic sites	Reactive fibroblast activity
Post-radiotherapy changes	Radiation fields	May overestimate residual disease
Degenerative processes	Musculoskeletal remodeling	Incidental uptake

4. False-Negative Findings and Tumor Heterogeneity

4.1 Variability of FAP Expression

Not all tumors demonstrate high FAP expression. Tumor heterogeneity can result in variable or low FAPI uptake in:

- Hematological malignancies
- Tumors with low stromal content
- Certain well-differentiated or early-stage tumors (Sharma et al., 2021).
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Table 2. Potential Sources of False-Negative Findings in FAPI PET/CT

Cause	Examples	Clinical Impact
Low stromal content	Some early-stage tumors	Underestimation of disease
Low FAP expression	Hematologic malignancies	Reduced lesion detectability
Tumor heterogeneity	Variable intratumoral expression	Discordant imaging findings
Small-volume disease	Micrometastases	Potential false-negative interpretation

4.2 Clinical Impact

This heterogeneity may lead to underestimation of disease burden. Consequently, FAPI PET/CT should not be considered universally superior to FDG PET/CT but rather complementary.

Moreover, intratumoral heterogeneity may lead to discordant findings between FAPI and FDG PET/CT. While FDG uptake reflects viable tumor cell metabolism, FAPI uptake reflects stromal response, which may persist even after effective therapy. This discrepancy should be carefully considered in response assessment, as persistent FAPI uptake does not necessarily indicate treatment failure.

5. Lack of Standardization

5.1 Radiotracer Variability

Multiple FAPI tracers are currently in use, including FAPI-02, FAPI-04, and FAPI-46. These tracers differ in tumor retention, pharmacokinetics, and imaging characteristics (Sharma et al., 2021; Lindner et al., 2018; Loktev et al., 2019).

5.2 Imaging Protocols

There is no consensus regarding:

- Optimal injected activity
- Imaging time points
- Acquisition protocols

This variability complicates inter-study comparisons and limits reproducibility.

In addition, variability in imaging timing may significantly influence measured uptake values. Early imaging may favor high tumor-to-background contrast, whereas delayed imaging may provide different quantitative metrics. The absence of standardized timing protocols limits comparability across studies and complicates the interpretation of quantitative parameters.

5.3 Quantitative Parameters

Although standardized uptake value (SUV) is widely used, its clinical relevance in FAPI imaging is not fully established. Tumor-to-background ratio (TBR) may provide additional value, but further validation is needed.

Furthermore, the relationship between quantitative FAPI parameters and clinical outcomes remains insufficiently defined. Unlike FDG PET/CT, where SUV-based metrics have established prognostic value in many malignancies, the prognostic and predictive significance of FAPI-derived parameters is still under investigation. Quantitative metrics in FAPI imaging remain exploratory rather than standardized.

Current limitations related to tracer selection, acquisition protocols, and quantitative interpretation are summarized in Table 3.

Table 3. Current Challenges in Standardization of FAPI PET/CT

Domain	Current Limitation
Tracer selection	Multiple FAPI compounds in use
Injected activity	No consensus
Imaging timing	Variable acquisition windows
Quantitative metrics	SUV/TBR not standardized
Reporting criteria	Lack of unified systems
Inter-study comparison	Limited reproducibility

6. Limited Histopathological Validation

A significant limitation of the current literature is the lack of lesion-based histopathological confirmation. Many studies rely on:

- Imaging follow-up
- Clinical correlation
- Limited biopsy sampling

This is particularly problematic for:

- Lymph node staging
- Detection of micrometastases
- Assessment of small lesions (Sollini et al., 2021)

This limitation is particularly relevant in the evaluation of small lymph nodes and suspected micrometastases, where imaging

findings may not be routinely confirmed histologically. As a result, the true diagnostic accuracy of FAPI PET/CT in these settings remains uncertain and may be overestimated in imaging-based studies.

7. Comparison with FDG PET/CT: A Balanced Perspective

7.1 Complementary Roles

FDG PET/CT remains the established standard imaging modality in many oncologic indications due to its well-validated role in staging, treatment response assessment, and prognostication. In contrast, FAPI PET/CT provides complementary biological information by targeting stromal activation and tumor microenvironment remodeling rather than glucose metabolism alone.

The complementary nature of these modalities may be particularly valuable in biologically heterogeneous tumors, where a single imaging approach may not fully capture the complexity of disease behavior. In such settings, a dual-tracer approach combining FDG and FAPI imaging may provide a more comprehensive assessment of both tumor metabolism and stromal involvement.

Importantly, discordant findings between FDG and FAPI PET/CT should not necessarily be interpreted as contradictory, but rather as reflections of different biological processes within the tumor microenvironment.

7.2 Clinical Scenarios Favoring FAPI

FAPI PET/CT may offer advantages in several clinical scenarios, particularly in tumors characterized by prominent stromal or desmoplastic components. Reported areas of potential superiority include:

- pancreatic and gastric cancers,
- peritoneal carcinomatosis,
- liver metastases,
- and tumors with low or heterogeneous FDG avidity.

In addition, FAPI PET/CT may be particularly useful in cases where FDG PET/CT yields equivocal findings, especially in anatomically complex regions or in lesions with relatively low metabolic activity (Kratochwil et al., 2019; Kuyumcu et al., 2021). The lower physiologic background activity observed with FAPI tracers may improve lesion conspicuity in selected organs and disease patterns.

However, the currently available evidence remains insufficient to establish universal superiority of FAPI PET/CT over FDG PET/CT across all tumor types and clinical indications.

7.3 Clinical Scenarios Favoring FDG

Despite the growing interest in FAPI imaging, FDG PET/CT continues to demonstrate superior performance in multiple clinical contexts. Highly proliferative tumors, hematologic malignancies, and several aggressive thoracic malignancies often exhibit strong FDG avidity and remain well characterized by metabolic imaging.

Moreover, FDG PET/CT benefits from decades of clinical validation, standardized interpretation criteria, widespread availability, and established prognostic value across numerous malignancies. In contrast, many aspects of FAPI imaging—including quantitative interpretation, optimal timing, and long-term clinical impact—remain under active investigation. Therefore, at the current stage of evidence, FAPI PET/CT should be considered a

complementary imaging modality rather than a replacement for FDG PET/CT.

Selected clinical scenarios in which FAPI PET/CT or FDG PET/CT may provide relative advantages are summarized in Table 4.

Table 4. Clinical Scenarios Favoring FAPI PET/CT versus FDG PET/CT

FAPI PET/CT Potential Advantages	**FDG PET/CT Potential Advantages**
Pancreatic cancer	Hematologic malignancies
Gastric cancer	Highly proliferative tumors
Peritoneal carcinomatosis	Aggressive thoracic tumors
Liver metastases	Established prognostic indications
Low/heterogeneous FDG avidity	Standardized response assessment
Low-background imaging regions	Broad clinical validation

8. Economic and Practical Considerations

Despite its promising results, FAPI PET/CT faces several practical challenges:

- Limited global availability
- Lack of standardized reimbursement
- Higher costs compared to FDG in many settings

These factors currently limit widespread clinical adoption.

Furthermore, the widespread implementation of FAPI PET/CT will depend not only on clinical performance but also on logistical and economic factors, including tracer production, regulatory approval, and reimbursement policies. These considerations may vary significantly across different healthcare systems.

9. Theranostic Challenges

FAPI-based theranostics is an emerging field; however, several challenges remain:

- Short tumor retention time may limit therapeutic efficacy
- Limited dosimetry data
- Lack of established treatment protocols

Despite the promising preliminary data, several important limitations remain. One of the major challenges is the relatively rapid clearance of current FAPI compounds from tumor tissue, which limits the achievable radiation dose during therapy (Langbein et al., 2019). To address this issue, multiple molecular modifications, including dimerization and albumin-binding strategies, are being investigated to prolong tumor retention time and optimize pharmacokinetics.

Another important limitation is the lack of complete tumor specificity. Increased FAPI uptake has been observed not only in malignant lesions but also in chronic inflammatory and fibrotic conditions. Consequently, benign processes may lead to false-positive findings, and careful interpretation of FAPI PET/CT images is required. Furthermore, many currently available studies are retrospective, involve relatively small and heterogeneous

patient populations, and often lack comprehensive histopathological validation. Follow-up durations are also limited in most reports.

In addition, FAP expression may vary significantly according to tumor type and disease stage. Emerging evidence suggests that FAP-related pathways may play a more prominent role during early tumor development, whereas other biological pathways may become dominant in advanced disease. Therefore, it remains unclear whether FAPI imaging consistently outperforms ^{18}F-FDG PET/CT throughout all stages of tumor progression.

10. Future Directions

The rapidly expanding field of FAPI imaging continues to evolve beyond initial proof-of-concept studies toward broader clinical and translational applications. Future developments will likely focus not only on improving diagnostic performance but also on optimizing theranostic strategies, quantitative assessment, and integration with emerging technologies. However, the long-term clinical value of FAPI PET/CT will ultimately depend on robust prospective validation and standardized implementation. Major areas of ongoing research and emerging applications that may shape the future development of FAPI imaging are summarized in Table 5.

Table 5. Future Directions in FAPI Imaging

Research Area	Potential Future Impact
Novel tracer development	Improved tumor retention
FAPI-74 and 18F tracers	Broader availability
Theranostic applications	Targeted radionuclide therapy
Radiomics	Prognostic assessment
Artificial intelligence	Automated interpretation
Precision oncology	Personalized treatment strategies
Prospective multicenter studies	Clinical validation

10.1 Radiopharmaceutical Development

Efforts are ongoing to develop novel FAPI tracers with improved pharmacokinetic and imaging characteristics. One of the major goals is the development of compounds with prolonged tumor retention, which may improve both diagnostic imaging and therapeutic efficacy. Molecular modifications such as dimerization, albumin-binding strategies, and structural optimization are currently under investigation to enhance tumor uptake and retention time.

In addition, increasing attention is being directed toward ^{18}F-labeled FAPI tracers, including FAPI-74, which may offer several practical advantages over ^{68}Ga-based compounds. The longer half-life of ^{18}F enables centralized production and large-scale distribution, potentially facilitating broader clinical implementation

and multicenter standardization. Furthermore, ^{18}F-based tracers may provide improved image resolution and higher production capacity in high-volume centers.

Beyond conventional PET imaging, future radiopharmaceutical development may also focus on theranostic applications using therapeutic radionuclides such as ^{177}Lu, ^{90}Y, and ^{225}Ac. These approaches may expand the role of FAPI from diagnostic imaging to targeted radionuclide therapy, particularly in tumors with prominent stromal components.

10.2 Clinical Trials and Standardization

Despite encouraging preliminary data, most currently available studies remain retrospective and heterogeneous. Therefore, large-scale prospective multicenter trials are critically needed to establish the true clinical value of FAPI PET/CT across different tumor types and clinical scenarios.

Future studies should aim to:

- define evidence-based clinical indications,
- establish standardized imaging protocols,
- determine optimal acquisition timing,
- validate quantitative imaging biomarkers,
- and directly compare FAPI PET/CT with established modalities such as ^{18}F-FDG PET/CT.

Standardization will be particularly important for improving reproducibility and facilitating cross-study comparisons. International consensus recommendations regarding tracer selection, imaging timing, interpretation criteria, and reporting

systems may become increasingly necessary as clinical utilization expands.

10.3 Quantitative Imaging and Artificial Intelligence

Emerging quantitative imaging approaches may significantly enhance the clinical utility of FAPI PET/CT. Advanced imaging biomarkers, including volumetric parameters and tumor-to-background metrics, may provide additional prognostic and predictive information beyond simple SUV measurements.

In particular, radiomics-based approaches may enable extraction of high-dimensional imaging features that are not visually appreciable, potentially improving lesion characterization, response assessment, and outcome prediction. Artificial intelligence (AI)-based interpretation algorithms may further improve reproducibility, reduce observer variability, and assist in automated lesion detection and segmentation.

However, these technologies remain in relatively early stages of development and require extensive external validation before routine clinical implementation. Variability in acquisition protocols and limited availability of large annotated datasets currently represent important challenges.

10.4 Integration into Precision Oncology

Another important future direction is the integration of FAPI PET/CT into precision oncology frameworks. Because FAPI imaging reflects tumor microenvironment activity rather than solely tumor metabolism, it may provide complementary biological information that could influence individualized treatment planning.

Potential applications may include:

- selection of patients for stromal-targeted therapies,
- monitoring of treatment-induced stromal changes,
- assessment of tumor heterogeneity,
- and integration with molecular and genomic biomarkers.

In the future, combined evaluation of metabolic, stromal, and molecular imaging data may allow a more comprehensive characterization of tumor biology than any single modality alone.

10.5 Future Perspective and Clinical Outlook

Although FAPI PET/CT remains an evolving imaging modality, its rapid development suggests substantial future potential in oncologic imaging and theranostics. Nevertheless, enthusiasm should be balanced with careful scientific validation. Important questions regarding specificity, standardization, cost-effectiveness, and long-term clinical impact remain unresolved.

Ultimately, the future role of FAPI PET/CT will likely depend on its ability to provide clinically actionable information beyond existing imaging techniques while maintaining reproducibility, accessibility, and cost-effectiveness.

11. Conclusion

FAPI PET/CT has emerged as a highly promising imaging modality that provides unique insight into tumor-associated stromal activity and the tumor microenvironment. Its favorable pharmacokinetics, high tumor-to-background contrast, and potential advantages in selected tumor types have generated considerable interest in both diagnostic and theranostic applications.

Nevertheless, several important limitations remain. Lack of tumor specificity, variability in FAP expression, limited histopathological validation, and the absence of standardized imaging protocols continue to represent major challenges for widespread clinical implementation. In addition, many currently available studies remain retrospective and heterogeneous, limiting the strength of current evidence.

Rather than replacing ^{18}F-FDG PET/CT, FAPI imaging should currently be viewed as a biologically complementary modality capable of providing additional information regarding stromal remodeling and tumor-host interactions. The integration of metabolic and stromal imaging approaches may ultimately allow a more comprehensive characterization of tumor biology than either technique alone.

Future progress in FAPI imaging will likely depend on continued radiopharmaceutical development, prospective multicenter validation, standardized interpretation criteria, and integration with emerging technologies such as radiomics and artificial intelligence. As evidence continues to evolve, FAPI PET/CT may become an increasingly important component of precision oncology and theranostic imaging strategies. As understanding of tumor–stroma interactions continues to evolve, FAPI imaging may play an increasingly important role in the future landscape of precision oncology.

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