Nuclear Medicine and Molecular Imaging (2025) 59:289–305
https://doi.org/10.1007/s13139-025-00936-y

REVIEW

Exploring the Diagnostic and Theranostic Role of FAPI PET in Soft Tissue Sarcoma: A Systematic Review

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Received: 24 May 2025 / Revised: 3 July 2025 / Accepted: 4 July 2025 / Published online: 16 August 2025

Abstract

This systematic review evaluates the diagnostic and theranostic utilities of fibroblast activation protein inhibitor (FAPI PET) in patients with soft tissue sarcomas (STS). PubMed, Scopus, and Web of Science were researched for clinical studies employing FAPI PET in STS, covering literature up to October 15, 2024. This review synthesized 36 studies, involving 316 patients and about 30 STS subtypes. Twenty-one case reports highlighted FAPI's diagnostic utility. Comparative analyses often favored FAPI PET/CT over FDG PET/CT for tumor delineation, showing higher SUVmax and tumor-to-background ratios, especially in vascular tumors. Seven original studies consistently reported reliable FAPI uptake metrics across STS subtypes in 253 patients, strongly correlating with FAP immunohistochemistry. FAPI PET/CT generally demonstrated higher uptake, improved accuracy, and better lesion detection than FDG PET/CT, supporting its use in staging and restaging of recurrent and metastatic STS. Eight studies assessed FAPI PET/CT for FAPI-based radioligand therapy (RLT) eligibility, with posttherapeutic outcome predominantly resulted in disease stabilization (16 out of 36 patients), and a favorable safety profile. FAPI PET/CT outperforms FDG in detecting recurrent/metastatic STS, offering higher accuracy in most STS types. FAPI-based radioligand therapy is a promising, safe treatment for challenging STS, with encouraging efficacy.

Keywords Soft tissue sarcoma · FAPI · [^{18}F]FDG · Theranostics · [^{177}Lu]Lu-FAPI · [^{68}Ga]Ga-FAPI

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Introduction

Soft tissue sarcomas (STSs) are rare and heterogeneous group of malignant tumors, originating from mesenchymal cells. According to the latest World Health Organization (WHO) classification they encompass over 70 different histologic subtypes, arising from mesenchymal tissues, including adipocytic, fibroblastic, vascular, pericytic, smooth muscle, skeletal muscle, peripheral nerve sheath, and tumors of uncertain differentiation [1]. The WHO classification of soft tissue and bone tumors advances sarcoma pathology by integrating molecular, histological, and immunohistochemical features to refine tumor categorization [1]. While relatively rare, with estimated incidence between 1.8 and 5 cases per 100,000 individuals annually, accounting for approximately 1 to 2% of all solid neoplasms, STS poses a significant therapeutic challenge due to its heterogeneity, aggressive behaviour, and complex anatomical locations [2].

Generally, these tumors are diagnosed at advanced clinical stages, resulting in a 5-year relative survival rate of 58% [2]. Survival rates vary by stage: 81% for localized STS versus 15% for those with distant metastases [3]. STS can arise in any anatomical location, primarily affecting the extremities (60%) and the retroperitoneum (15%) [2]. The most prevalent subtypes in adults include liposarcoma, leiomyosarcoma, angiosarcoma, undifferentiated pleomorphic sarcoma (UPS), rhabdomyosarcoma (RMS), and sarcomas of unspecified type [4]. Additionally, several rare subtypes such as alveolar soft part sarcoma (ASPS), clear cell sarcoma, dermatofibrosarcoma protuberans (DFSP), epithelioid hemangioendothelioma, gastrointestinal stromal tumors (GIST) and myxofibrosarcoma are noteworthy due to their unique characteristics [5].

Fibroblast Activation Protein (FAP) is a type II transmembrane serine protease predominantly expressed in cancer-associated fibroblasts (CAFs) within the stroma of epithelial cancers, including over 90% of sarcomas [6]. The high expression of FAP in STSs makes them suitable for targeting with FAPI positron emission tomography (PET) imaging, and in epithelial cancers, FAP is linked to proliferation, angiogenesis, migration, invasion, and poor prognosis [7]. Accurate imaging techniques are essential for the diagnosis and staging of these tumors to guide appropriate treatment. Traditional imaging modalities, including magnetic resonance imaging (MRI) and computed tomography (CT), provide essential information for initial diagnosis and surgical planning, but they lack specificity in differentiating benign from malignant lesions or assessing therapeutic response. In this context, molecular imaging with conventional PET/CT using [^{18}F]FDG has been widely employed for initial staging, restaging, and evaluating treatment response in STS. However, this modality lacks sensitivity for certain subtypes of sarcomas, particularly low-grade sarcomas, limiting its utility in the management of these tumors [8].

Given the critical need for improved diagnostic and therapeutic approaches, the recent development of [^{68}Ga]Ga-FAPI PET procedures offers a promising alternative. As mentioned earlier, [^{68}Ga]Ga-FAPI PET imaging leverages the high expression of FAP in CAFs, which modulate the tumor microenvironment (TME) thereby remodeling the extracellular matrix (ECM) [9]. Moreover, its negligible expression in most normal tissues results in high tumor-to-background ratio (TBR), making it an attractive potential target for diagnostic application [4]. Numerous studies have indicated the superiority of [^{68}Ga]Ga-FAPI PET/CT over [^{18}F]-FDG PET/CT imaging in lesion detectability, diagnosis, and staging [10–12].

In this systematic literature review, we aim to comprehensively investigate and evaluate the current evidence on the role of FAPI PET in the diagnosis, staging, and therapeutic management of STS.

Materials and Methods

Systematic Literature Search

For our systematic literature review, we adhered to the guidelines outlined in the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) statement of 2020 [13]. The first step involved defining a review question based on the PICO (Population, Intervention, Comparator, Outcomes) framework [13]. The question focuses on the diagnostic and theranostic yield (outcome) of FAP-guided PET imaging and therapy (intervention) in patients with STS (population) compared to [^{18}F]FDG PET/CT (comparator, if available). This predefined review question has guided the selection of eligibility criteria for including relevant studies in the systematic review.

The primary objective of this review was to map the existing knowledge on the role of FAPI in STS. We followed the most recent WHO classification of soft tissue and bone tumors as a reference for STS subtypes (Table 1) [1]. Only studies reporting on WHO-defined STS entities were considered, while non-STS tumors (e.g., osteosarcoma, Ewing sarcoma) were excluded. The search spanned from January 2014 to November 2024, encompassing a comprehensive examination of published manuscripts that investigated FAPI as a diagnostic and theranostic tool in STS. Two authors (M.A. and A.A.-I) have independently conducted thorough electronic searches across three databases, including PubMed, Scopus and Web of Science, between

Table 1 Who classification of malignant soft tissue sarcomas categorized by histologic subtypes [1]

Category	Tumor Type
Adipocytic Tumors	Well-differentiated liposarcoma (lipoma-like, sclerosing, inflammatory)
	Dedifferentiated liposarcoma
	Myxoid liposarcoma
	Pleomorphic liposarcoma
	Myxoid pleomorphic liposarcoma
Fibroblastic/Myofibroblastic Tumors	Malignant solitary fibrous tumor
	Fibrosarcoma NOS
	Myxofibrosarcoma
	Low-grade fibromyxoid sarcoma
	Sclerosing epithelioid fibrosarcoma
Fibrohistiocytic Tumors	Malignant tenosynovial giant cell tumor
Vascular Tumors	Epithelioid hemangioendothelioma
	Angiosarcoma
Pericytic (Perivascular) Tumors	Malignant glomus tumor
Smooth Muscle Tumors	Inflammatory leiomyosarcoma
	Leiomyosarcoma
Skeletal Muscle Tumors	Embryonal rhabdomyosarcoma
	Alveolar rhabdomyosarcoma
	Pleomorphic rhabdomyosarcoma
	Spindle cell/sclerosing rhabdomyosarcoma
	Ectomesenchymoma
Gastrointestinal Stromal Tumors	Gastrointestinal stromal tumors
Peripheral Nerve Sheath Tumors	Malignant peripheral nerve sheath tumor
	Melanotic malignant nerve sheath tumor
	Granular cell tumor (malignant)
	Malignant perineurioma
Tumors of Uncertain Differentiation	Phosphaturic mesenchymal tumor (malignant)
	NTRK-rearranged spindle cell neoplasm (emerging)
	Synovial sarcoma
	Epithelioid sarcoma (proximal and classic variant)
	Alveolar soft part sarcoma
	Clear cell sarcoma
	Extraskeletal myxoid chondrosarcoma
	Desmoplastic small round cell tumor
	Rhabdoid tumor
	Perivascular epithelioid tumor (malignant)
	Intimal sarcoma
	Ossifying fibromyxoid tumor (malignant)
	Myoepithelial carcinoma
	Undifferentiated sarcoma
	Spindle cell sarcoma (undifferentiated)
	Pleomorphic sarcoma (undifferentiated)
	Round cell sarcoma (undifferentiated)

August 15, 2024 and October15, 2024. A search algorithm based on the combined terms: [(Soft Tissue Sarcoma OR Sarcoma OR STS) AND ([^{68}Ga]Ga OR [^{18}F] OR [^{99m}Tc] OR [^{177}Lu]Lu OR [^{225}Ac]Ac OR [^{90}Y]) AND (Fibroblast Activation Protein Inhibitor OR FAPI OR FAP)] was employed, complemented by manual searches. Non-English studies were excluded during the initial screening phase to maintain linguistic consistency in data collection and analysis. Only studies involving human subjects were included, while duplicate studies, book chapters, conference papers, abstracts, seminars, or irrelevant articles were excluded. The full texts of potentially relevant studies were retrieved for detailed examination. A cross-reference search was conducted to ensure that all relevant studies were included. The retrieved data was loaded into Microsoft Excel Professional Plus 2021 software. This software was utilized to organize, sort, screen, and filter the retrieved data, thereby facilitating a systematic and efficient data management process.

Assessment of Methodological Quality

Next, the methodological quality of the included articles discussing diagnostic utility of FAPI in STS was independently assessed for risk of bias and methodological application using the standardized Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) protocol [14]. Other original articles investigating the potential theranostic applications of FAPI in STS were systematically evaluated using the Risk of Bias In Non-randomized Studies—of Interventions (ROBINS-I) tool [15]. This tool is specifically designed to assess the risk of bias in non-randomized studies, which are critical for understanding the effectiveness and safety of interventions [16]. These scores were then documented and organized in a table for all the studies included in the analysis. For single reported cases, we implemented an adapted CAse REport (CARE) guideline criteria to assess the reliability of the information presented [17]. A set of 13 criteria outlined in the CARE checklist were utilized for this evaluation [17]. High-quality papers should fulfill a minimum of 10 criteria, while low-quality papers should address no more than 4. Papers of intermediate quality should meet a range of 5–9 criteria [17]. For each article, information such as the year of publication, first author, country of origin, study design, objectives, study population characteristics, adopted radiotracer with specific FAPI variant, and main findings were extracted, including tumor subtype, SUV_{max} within primary and metastatic lesions, TBR, and response to therapy were extracted. Finally, although two authors conducted the searches and quality ratings individually, they resolved any discrepancies through conversation and agreement.

Results

Search Results

Following the comprehensive computerized search and cross-checking of reference lists, a total of 46 papers, 32 from PubMed, 9 from Scopus and 5 from Web of Science were identified. After excluding duplicates and applying eligbiltiy criteria, only 36 papers were deemed eligible for inclusion in the systematic review (Fig. 1). Information regarding study details including authors, publication year, study design, patient characteristics, STS subtype and type of specific FAPI variant used for diagnostic and therapeutic purposes is detailed in Supplementary Table 1.

Assessment of Methodological Quality and Risk of Bias

The majority of the incorporated diagnostic studies were case reports (Supplementary Table 2). Among the studies, 2 were rated as Low Quality due to significant deficiencies in reporting essential components such as the abstract, introduction, clinical findings, and informed consent [18, 19]. In contrast, 2 studies were rated as High Quality [20, 21]. The remainder of the case reports were classified as Intermediate Quality while these reports generally provided more comprehensive details regarding patient information, diagnostic assessments, and therapeutic interventions, they still lacked certain critical elements that would enhance their overall quality and reliability [22–38].

The assessment of the risk of bias and applicability concerns in the studies using the QUADAS-2 tool revealed several trends regarding methodological quality across the included research, in which the overall risk of bias is rated as low in four studies indicating robust methodologies [8, 39–41]. In contrast, Koerber et al. presents significant concerns [42], while the study by Watanabe et al. [43], showed moderate risk, warranting further consideration in the context of its applicability (Fig. 2).

With regard to the assessment of the risk of bias across the studies using the ROBINS-I tool, only five studies were found to be eligible for evaluation (Fig. 3), as they implemented FAPI for therapy as well as post therapy imaging. The overall risk of bias varied from moderate to serious. Banihashemian et al. demonstrated a moderate overall risk of bias, with serious concerns related to confounding and moderate risks in participant selection and outcome reporting [44]. Moreover,three studies also exhibited a moderate overall risk of bias, primarily due to moderate confounding, suggesting a more acceptable level of adjustment for confounders compared to the other studies [45–47]. The most prominent concern across all of the included studies was bias due to confounding. This was classified as serious in Fendler et al., indicating insufficient control for variables that could significantly influence outcomes [48].

Systematic Review

The present systematic review includes 36 studies satisfying the inclusion criteria [8, 18–52]. These studies involved a total of 316 STS patients with an average age of approximately 53.5 years. Male to female ratio ≈1.34:1. All the studies were conducted as monocentric**.** The chosen studies were published by Chinese (21/36), German (9/36), Turkish

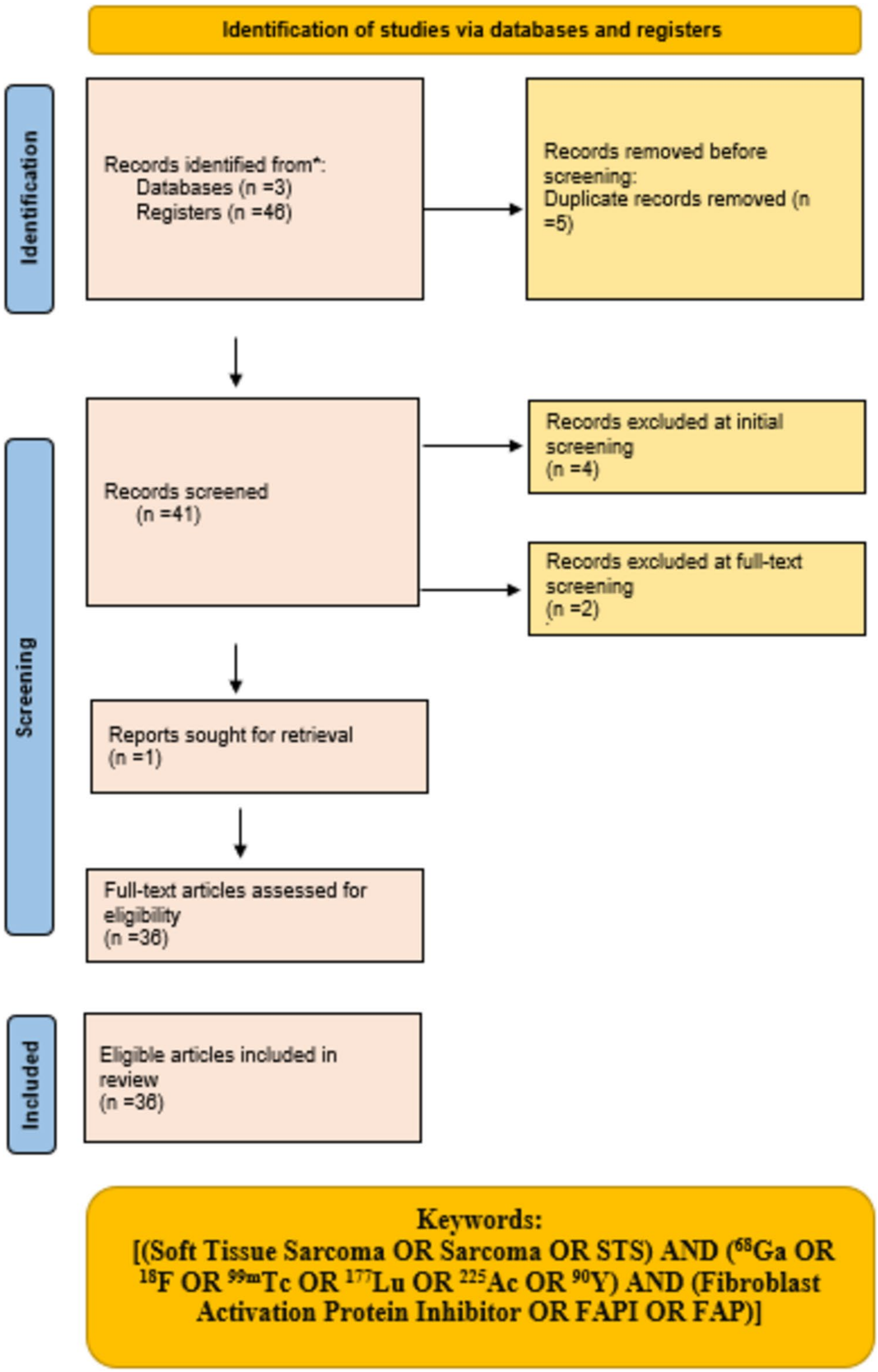

Fig. 1 Study flow diagram of study selection process illustrates the systematic identification and screening of studies according to Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines

(2/36), Iranian (3/36) and Japanese (1/36) groups during the years 2020 and 2024.

Of these, 12 studies were original research [8, 39–48, 51]. The predominant method used in these studies was a prospective analysis, with only four studies utilizing a retrospective approach [42, 45, 46, 51]. The remaining 24 studies (68.5%) were documented as case reports [18–38, 49, 50, 52]. Among all studies, 28 studies focused on diagnostic utility of FAPI [8, 18–43, 51], while only 8 studies explored theranostic applications [44–50, 52].

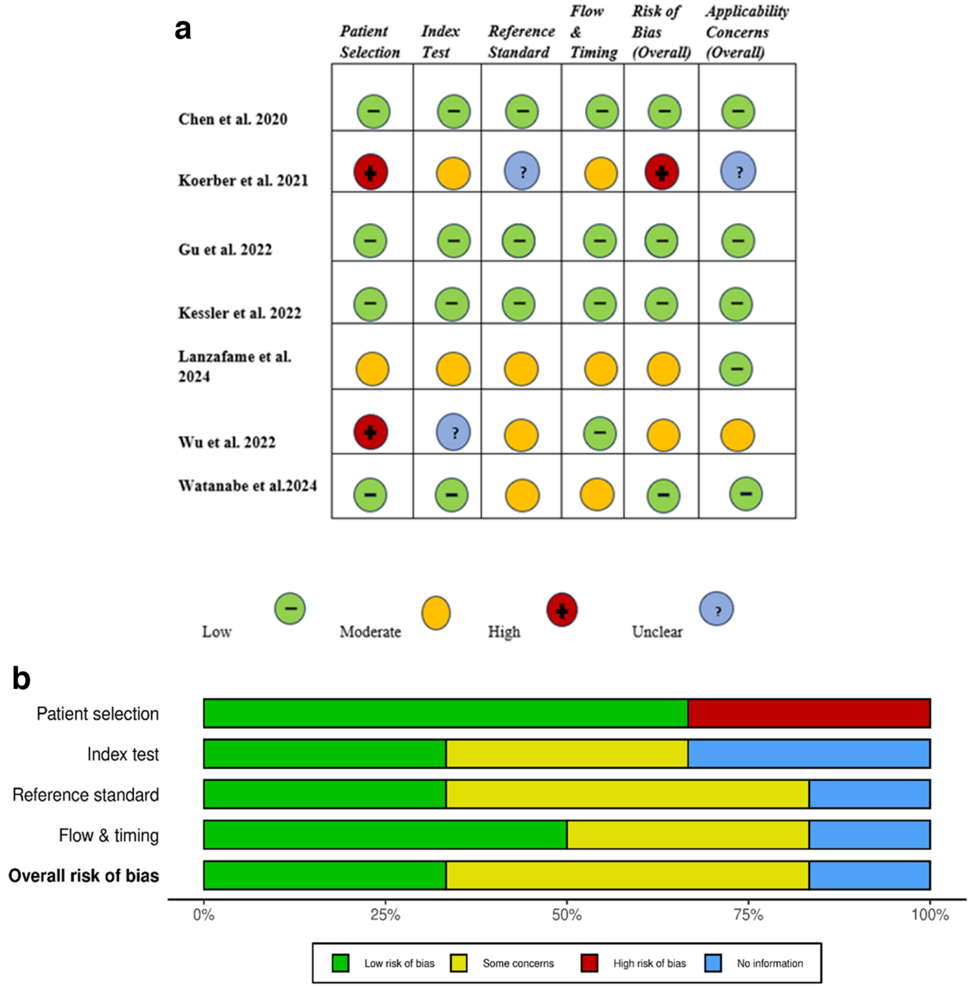

Fig. 2 Assessment of bias risk using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) protocol for diagnostic studies incorporated in the systematic review. (**a**) Individual study risk of bias assessment across four domains: Patient, Index Test, Reference Standard (histopathology confirmation), and Flow & Timing (time interval between tests). (**b**) Domain-specific risk summary. Bar graph illustrating the proportion of studies rated as Low risk, Some concerns, or High risk across four QUADAS-2 domains

Sporadic Reported Cases of Diagnostic FAPI Utility in STS

Recently published case studies have increasingly focused on imaging techniques for diagnosing and monitoring STS, particularly comparing the efficacy of FAPI PET imaging to [^{18}F]FDG PET/CT, given its specificity for targeting activated fibroblasts commonly associated with TME of various STS subtypes.

Vascular Tumors

Two cases of cardiac angiosarcoma were reported, comparing the imaging results of [^{68}Ga]Ga-FAPI PET/CT and [^{18}F]FDG PET/CT. The first case by Zhao et al. suggested that ^{68}Ga-FAPI PET/CT may outperform [^{18}F]FDG PET/CT in detecting cardiac angiosarcoma as it revealed a significant focus of uptake in the right atrium, with a maximum standardized uptake value (SUV$_{max}$) of 5.5 and estimated TBR: 1.6, while [^{18}F]FDG PET/CT failed to show any activity within the mass [18]. Conversely, the second case of cardiac angiosarcoma by Xu et al. showed that while [^{18}F]FDG PET/CT detected increased tracer uptake in the right atrial mass, [^{68}Ga]Ga-FAPI-04 PET/CT showed unevenly increased uptake in the thickened pericardium but not in the mass itself. The latter case concluded that FAPI PET was not superior to [^{18}F]FDG PET in visualizing cardiac angiosarcoma, though it provided valuable information regarding pericardial infiltration by the mass [21].

In bilateral mammary angiosarcoma, Qiu et al. reported a 30-year-old female. Initial [^{18}F]FDG PET/CT imaging showed minimal uptake in the breast lesions (SUVmax 2.5). In contrast, [^{68}Ga]Ga-FAPI PET/CT performed the following day revealed intense tumor visualization (SUV$_{max}$: 6.9, TBR: 4.3) and additional focal uptake in the left nipple (SUV$_{max}$: 8.4). Histopathologic analysis after bilateral mastectomy confirmed well-differentiated angiosarcoma with negative sentinel lymph node biopsy [31].

In contrast, Tatar et al. reported a case of gastric Kaposi sarcoma (KS) with metastases to lymph nodes and the liver, comparing the efficacy of [^{18}F]FDG PET/CT and [^{68}Ga]Ga-FAPI

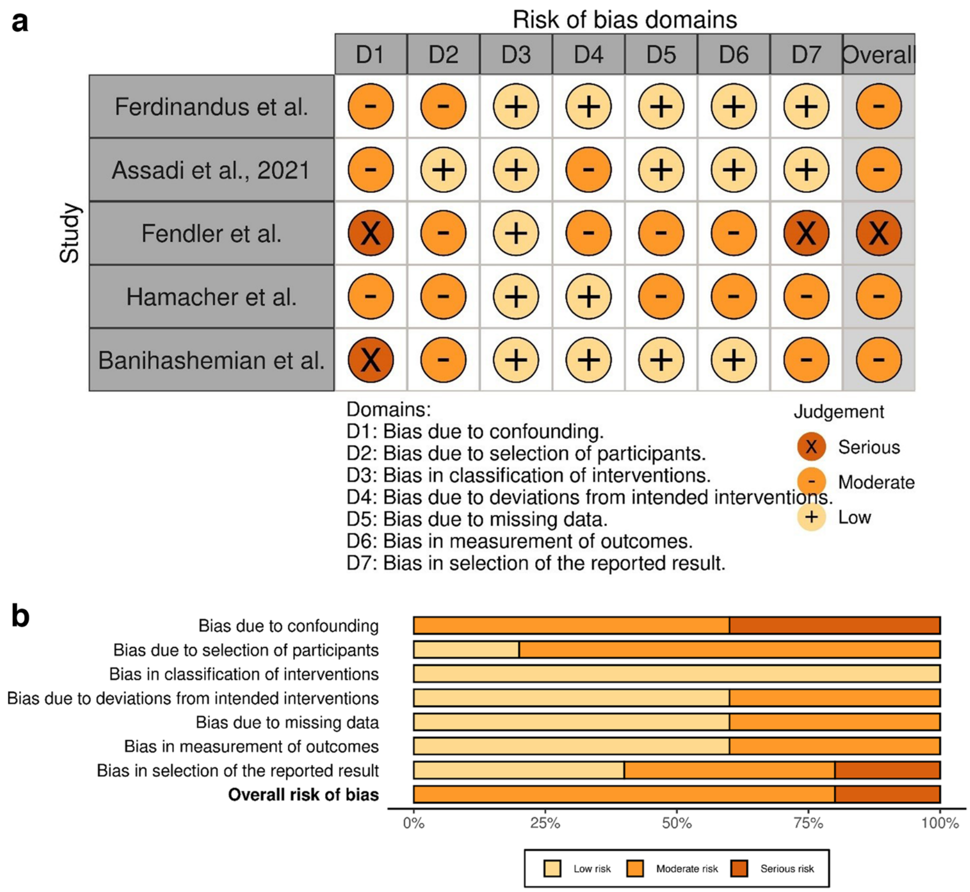

Fig. 3 Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) assessment for FAPI theranostic studies. (**a**) Domain evaluation: D1 (Confounding—prior treatments), D2 (Participant selection—eligibility criteria), D3 (Intervention classification—FAPI dosing consistency), D4 (Intervention deviations—protocol adherence), D5 (Missing data—dropout rates), D6 (Outcome measurement—RECIST standardization), D7 (Selective reporting—outcome completeness). (**b**) Risk distribution proportion

PET/CT in imaging both primary and metastatic sites. The primary gastric tumor demonstrated higher uptake with FAPI (SUV_{max}: 14) compared to FDG (SUV_{max}: 10). However, [^{18}F]FDG PET/CT outperformed [^{68}Ga]Ga-FAPI PET/CT in detecting metastatic spread, particularly in the liver and lymph nodes, where SUV_{max} reached 31 in the former, contrasting sharply with a lower FAPI SUV_{max} of 8.4. Histopathological analysis confirmed KS with human herpesvirus-8 (HHV-8) positivity, showing gastric involvement and widespread lymphadenopathy. The findings suggest that [^{18}F]FDG PET/CT remains a more reliable imaging modality for determining the overall extent of KS, particularly for identifying metastases [32].

Dong et al. presented a case of high-grade intimal sarcoma in the pulmonary artery of a 65 aged male, illustrating the diagnostic advantage of [^{68}Ga]Ga-FAPI PET/CT over [^{18}F]FDG PET/CT, providing superior delineation of the lesion aided by the low background uptake in surrounding vascular structures, which allowed for more precise visualization compared to [^{18}F]FDG PET/CT. Histopathologic analysis following surgical resection confirmed the diagnosis. This case underscores the potential utility of [^{68}Ga]Ga-FAPI-04 PET/CT in differentiating malignant intravascular lesions from thromboembolic and benign vascular conditions [24].

Fibroblastic/Myofibroblastic Tumors

In 2022, two case studies have explored the utility of [^{68}Ga]Ga-FAPI PET/CT in diagnosing DFSP, a rare soft tissue sarcoma; and both indicate that [^{68}Ga]Ga-FAPI PET/CT may provide excellent diagnostic performance in detecting DFSP and its recurrences. In Yang et al.'s case, a 47-year-old woman presented with slow-growing, painless masses in her right hip. Pelvic CT identified three subcutaneous masses in the right groin, suggestive of malignancy with SUVmax of 29.4 in a medium-sized mass. Biopsy confirmed the presence of fusiform tumor cells, leading to a diagnosis of DFSP with sarcomatous transformation. Histological analysis showed uniform spindle cells and specific immunohistochemical markers (Vim+, CD34−, Bcl-2+, CD99+, Ki-67+at 50%) [35]. Similarly, Wu et al. presented a case of a 45-year-old male with recurrent dermatofibrosarcoma protuberans, initially treated with surgical excision from his back. Upon recurrence, the patient was evaluated with both ^{18}F-FDG PET/CT and [^{68}Ga]Ga-FAPI PET/CT. The [^{68}Ga]Ga-FAPI PET/CT scan revealed two lesions one at the original tumor site on the back and another on the left upper arm, with significantly higher FAPI uptake (SUVmax 7.2) compared to [^{18}F]FDG uptake (SUVmax 1.9) in the back lesion Both cases are suggesting enhanced sensitivity of [^{68}Ga]Ga-FAPI PET/CT for this sarcoma type [34].

Similarly, in a case of a slow-growing epithelioid inflammatory myofibroblastic sarcoma, [^{68}Ga]Ga-FAPI PET/CT showed high uptake (SUV_{max}:14.5) in a primary left thigh mass, aiding in diagnosis and guiding successful surgical resection [22]. Additionally, a case presented by Liu et al. involving a 20-year-old male with a slow-growing mass in the left thigh with intense FAPI uptake (SUV_{max}:14.5), indicating potential malignancy [27]. Histopathology confirmed epithelioid inflammatory myofibroblastic sarcoma (EIMS), a rare and aggressive STS. However, the previous studies lack a direct comparison with FDG, leaving its utility as an area warranting further research.

Smooth Muscle Tumors

Guzel et al. demonstrated greater FAPI uptake (SUV_{max}:17.7) versus FDG (SUV_{max}:4.3) in a 56-year-old woman with abdominal leiomyosarcoma. Histopathology confirmed leiomyosarcoma with a high Ki-67 proliferative index (85–90%) [26].

Skeletal Muscle Tumors

Wu et al. reported the first application of [^{68}Ga]Ga-FAPI PET/CT imaging in a 48-year-old male patient with rhabdomyosarcoma. MRI had identified a suspicious mass in the right thigh, raising concern for malignancy. [^{68}Ga]Ga-FAPI PET/CT was performed for staging and demonstrated multiple FAPI-avid lesions in the right thigh, skin, lungs, mediastinal lymph nodes, and left femur. Incisional biopsy of the thigh mass confirmed pleomorphic rhabdomyosarcoma, and histopathological analysis of a pulmonary lesion verified metastatic disease from the primary tumor [33].

Gastrointestinal Stromal Tumors (GIST)

Two reported cases demonstrated that [^{68}Ga]Ga-FAPI-04 PET/CT outperforms [1^{8}F]FDG PET/CT in the detection of gastrointestinal stromal tumors (GISTs). In both instances, FAPI imaging provided superior tumor-to-background contrast and revealed a greater number of primary and metastatic lesions, particularly in non-FDG-avid sites. Qiu et al. described a 67-year-old man presenting with epigastric discomfort and anorexia lasting over two months. [1^{8}F]FDG PET/CT showed no abnormal uptake throughout the gastrointestinal tract. The patient was enrolled in a [^{68}Ga]Ga-FAPI PET/CT clinical trial, which revealed nodular thickening with increased tracer uptake in the greater curvature of the stomach. Histopathology confirmed a diagnosis of gastric stromal tumor [30]. Similarly, Zhang et al. reported a 65-year-old man with progressive abdominal bloating initially diagnosed with gastric carcinoma with hepatic metastases on CT. [^{68}Ga]Ga-FAPI PET/CT demonstrated higher tumor-to-background contrast and detected additional metastatic sites compared to [1^{8}F]FDG PET/CT. Subsequent endoscopic and histological evaluation confirmed a diagnosis of malignant GIST [38].

Tumors of Uncertain Differentiation

Eight case reports with biopsy-proven various STS subtypes suggest superiority of FAPI over FDG. Yang et al. described a nasal cavity chondrosarcoma with intense FAPI uptake (SUVmax 6.8) in a 54-year-old male patient with a large, polypoid mass filling the nasal cavity. Imaging revealed a single lesion with significant tracer uptake and associated bony destruction of the nasal septum, indicative of malignancy [36]. Moreover, case of a 47-year-old man with ASPS, in which [^{68}Ga]Ga-FAPI-04 PET/CT identified multiple lesions, including scalp lesions (SUVmax: 9.3), lung (SUVmax:7.3), lymph nodes (SUVmax:6.5), liver (SUVmax:12.7), and bone (SUVmax:4.8). In contrast, [^{18}F]FDG PET/CT showed lower uptake with SUVmax values of the previous lesions respectively: 2.1, 3.0, 4.0, 4.0 and 4.8, resulting in missed detections, particularly in the scalp due to low radiotracer accumulation and interference from high brain glucose metabolism [19]. Zhang et al. investigated the efficacy of [^{68}Ga]Ga-FAPI versus [^{18}F]FDG PET/CT in assessing recurrent undifferentiated pleomorphic sarcoma (UPS) in a rare location; the colon mesentery. In a clinical case, a 56-year-old woman with recurrent UPS underwent both imaging modalities. The SUVmax values obtained were significantly higher for FAPI compared to FDG, indicating superior tracer uptake (26.8 vs 18.5). Similarly, other metastatic sites showed enhanced uptake of FAPI. This pattern of increased uptake suggests that [^{68}Ga]Ga-FAPI PET/CT may offer improved sensitivity and specificity for detecting recurrent UPS and its metastases compared to traditional [^{18}F]FDG PET/CT [37]. Lastly, another report by Dong et al. of a patient with a known history of Peutz-Jeghers syndrome and primary duodenal clear cell sarcoma, suggested that [^{68}Ga]Ga-FAPI PET/CT provides better delineation of peritoneal carcinomatosis compared to [^{18}F]FDG PET/CT. Both imaging modalities detected significant activity in the duodenal tumor; however, FAPI uptake was significantly higher in peritoneal implants, allowing for clearer visualization. In contrast, the gastrointestinal polyps associated with Peutz-Jeghers syndrome were hypermetabolic (SUVmax:13.9) yet no FAPI uptake within [25].

Likewise, a 48-year-old patient diagnosed with a rare malignancy, classified as an isolated nodal-type FDCS, which constitutes approximately 0.4% of all STS variants,

[^{18}F]FDG PET/CT and [^{68}Ga]Ga-FAPI PET/CT were used for imaging comparison, with [^{18}F]FDG PET/CT yielding a higher SUVmax than [^{68}Ga]Ga-FAPI PET/CT. Specifically, the [^{18}F]FDG SUVmax was (5.5) compared to the lower FAPI SUVmax of (1.9). Additionally, the TBR demonstrated greater pronounced contrast with FDG (5.5) than with FAPI (2.6), reflecting a higher affinity of [^{18}F]FDG for this sarcoma subtype. The tumor exhibited positive immunohistochemical markers including CD23, CD35, D2-40, S100, CD1a, Langerin, LCA, CD68, and a Ki-67 proliferation index of 40%. FDCS, a rare malignancy comprising 0.4% of soft tissue sarcomas, often presents with isolated nodal or extranodal disease. While [^{18}F]FDG PET/CT effectively evaluates systemic involvement and therapy response, low [^{68}Ga]Ga-FAPI I uptake in this case suggests limited applicability of [^{68}Ga]Ga-FAPI PET/CT for FDCS [20].

In an unusual and remarkable finding revealing the unique diagnostic potential of [^{68}Ga]Ga-FAPI PET/CT in discerning the true extent of disease in STS, a case of a 67-year-old woman with history of right chest pain with an initial biopsy suggesting spindle cell tumor in a pleural lesion. While an [^{18}F]FDG PET/CT scan showed multiple [^{18}F]FDG-avid lesions, including a right pleural mass (SUVmax up to 16.2) and mediastinal lymph nodes, the use of [^{68}Ga]Ga-FAPI PET/CT highlighted a striking difference with intense FAPI avidity in the pleural masses (SUVmax:16.7) but no uptake in the mediastinal lymph nodes. This was confirmed by CT-guided biopsy from pleura as G2 spindle cell sarcoma. After one cycle of chemotherapy (doxorubicin and dacarbazine), the pleural lesions progressed while the mediastinal lymph nodes showed interval size regression from 1.4 × 0.9 cm to 0.5 × 0.4 cm, indicating that these lymph nodes responded differently to treatment compared to the primary lesion, suggesting they were primarily not metastatic. Despite the potential of [^{68}Ga]Ga-FAPI PET for downstaging, the patient died from rapid disease progression about half a month later, which further supports this assumption [23].

Labelled with [^{18}F], Ni et al. recently documented a case study of an 18-year-old woman with recurrent synovial sarcoma implying for the value of [^{18}F]FAPI PET/CT imaging in evaluating primary and metastatic lesions, with SUVmax values of 6.5 in the calf mass and 9.6 in a thoracic metastasis [29].

Lastly, a case of desmoplastic small round cell tumor (DSRCT), a rare and highly aggressive soft tissue sarcoma that predominantly arises in the serosal surfaces of the abdominal and pelvic peritoneum, in a young patient (19 years old) who was enrolled in a clinical trial assessing [^{68}Ga]Ga-FAPI PET/CT imaging. Imaging demonstrated increased FAPI uptake in the pelvic cavity (SUVmax 7.9) and lower abdomen (SUVmax 6.8), correlating with the identified masses and peritoneal thickening, thereby supporting the DSRCT diagnosis. Following imaging, treatment with [^{177}Lu]Lu-FAP2286 (7.4 GBq) resulted in stable disease, and the patient remains under observation [28].

Original Studies: FAPI Diagnostic utility in STS

Diagnostic Accuracy in Primary and Metastatic STS

Chen et al. was the first to conduct a retrospective study in 2020 to evaluate the usefulness of FAPI.

for the diagnosis of primary and metastatic lesions in various types of cancer and included 2 cases of STSs among them, comprising hemangiosarcoma and liposarcoma. The specific labelled FAPI variant applied in the study was FAPI-04 and results were compared with [^{18}F]FDG PET/CT. Notably, the median SUV for [^{18}F]FDG was 9.18, with a range of 8.05–11.59, as compared to [^{68}Ga]Ga-FAPI which demonstrated a higher median SUV of 13.61 and a broader range of 8.59–35.39, suggesting enhanced sensitivity and specificity for detecting FAP-expressing tumors. Although the p-value of 0.109 indicates no statistically significant difference in SUV between the two modalities, the higher SUV values associated with FAPI underscore its potential as a promising diagnostic and theranostic tool in the evaluation of sarcomas [39].

FAPI Uptake Metrics in STS

A cohort study by Koerber et al. included 13 patients with various types of soft tissue sarcoma (STS), consisting of liposarcomas, undifferentiated pleomorphic sarcomas (UPS), and leiomyosarcomas. Amongst all participated patients, a significant proportion (53.3%) were presented with metastatic disease, with local relapse suspected in three cases. The majority of patients (80%) were diagnosed with low-grade sarcoma, with grading information missing for three individuals. The imaging results with [^{68}Ga]Ga-FAPI PET/CT revealed very low background activity observed in normal organs, such as blood pool (SUV_{max} 2.00, SUVmean 1.34) and liver parenchyma (SUV_{max} 1.48, SUVmean 0.86). Thus, [^{68}Ga]Ga-FAPI PET/CT successfully detected four primary tumors with a median SUV_{max} of 7.16 and SUVmean of 3.27, alongside three local relapses characterized by higher uptake values (median SUV_{max} 11.47, SUVmean 7.03). For metastatic lesions, the median SUV_{max} and SUVmean were 6.29 and 3.01, respectively, with the highest uptake seen in lung metastases (median SUV_{max} 37.35, SUVmean 19.44). Notably, histological subgroup analysis indicated that liposarcomas exhibited the highest uptake (median SUV_{max} 14.19, SUVmean 8.90), and [^{68}Ga]

Ga-FAPI uptake was significantly elevated in high-grade sarcomas compared to low-grade disease (median SUV_{max}: 30.21 vs. 6.35; median SUVmean: 16.49 vs. 2.90). These findings underscore the potential clinical application of [^{68}Ga]Ga-FAPI PET/CT in identifying sarcomas and their metastases, as the analysis confirmed promising intratumoral uptake, particularly for liposarcoma, and suggests that this imaging modality could enhance diagnostic accuracy and inform therapeutic strategies [42].

Diagnostic Accuracy in Recurrent STS

One pivotal prospective study by Gu et al. implementing a head-to-head comparison of [^{68}Ga]Ga-FAPI and [^{18}F]FDG PET/CT for detecting recurrent STS in 45 patients with various STS subtypes as listed in Table 2. A key strength of this study is its systematic comparison of two radiotracers in the same cohort, allowing for direct evaluation of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy. [^{68}Ga]Ga-FAPI PET/CT identified 48% more recurrent lesions (275 vs. 186) than [^{18}F]FDG PET/CT, a significant improvement ($p<0.001$). The sensitivity, specificity, PPV, NPV, and accuracy of [^{68}Ga]Ga-FAPI were all significantly higher compared to [^{18}F]FDG PET/CT ($p<0.001$)[8]. On a subtype level, [^{68}Ga]Ga-FAPI PET/CT exhibited superior performance in detecting recurrences of liposarcoma, malignant solitary fibrous tumor, and interdigitating dendritic cell sarcoma (IDCS), showing significantly higher SUV_{max} and TBR values than [^{18}F]FDG PET/CT ($p=0.011$, $p<0.001$, respectively). This improved detection in specific subtypes highlights the ability of FAPI to target the tumor stroma and FAP-rich environment. In contrast, [^{18}F]FDG PET/CT outperformed [^{68}Ga]Ga-FAPI PET/CT in UPS and RMS, with significantly higher SUV_{max} and TBR values ($p=0.003$, $p<0.001$, respectively), reflecting the strong metabolic activity of these tumor types, which favors FDG uptake. Furthermore, tissue-specific comparisons revealed that [^{68}Ga]Ga-FAPI PET/CT was superior in detecting metastases in soft tissues, liver, and bone, while [^{18}F]FDG performed better for lymph node metastases (SUVmax = 8.57 vs. 6.26, $p=0.006$; TBR = 11.71 vs. 8.08, $p=0.011$). Another interesting observation was the tracer performance in different tumor grades [^{68}Ga]Ga-FAPI PET/CT demonstrated higher uptake in low-grade STS ($p<0.001$) compared to [^{18}F]FDG PET/CT, while [^{18}F]FDG PET/CT had greater uptake in high-grade tumors ($p<0.001$), suggesting distinct biological features being targeted by the two tracers. The ability of [^{68}Ga]Ga-FAPI PET/CT to detect low-grade tumors provides a diagnostic advantage in situations where [^{18}F]FDG PET/CT, which primarily targets high metabolic activity, may be less effective. So this study provided compelling evidence supporting the use of [^{68}Ga]Ga-FAPI PET/CT as an advanced imaging modality for the detection of recurrent, particularly in low-grade STS [8].

Correlation with FAP Immunostain

Kessler et al. conducted a prospective trial to assess the correlation between FAPI uptake intensity and histopathological FAP expression in 47 patients with bone or soft tissue sarcomas, among which STS accounted for 27 cases (57.4%), predominantly comprising individuals with UPS and leiomyosarcoma. The results confirmed a significant association between FAPI uptake and histopathological FAP expression (Spearman's $r=0.43$, $p=0.03$). Additionally, [^{68}Ga]Ga-FAPI PET/CT showed high diagnostic accuracy with a PPV of 1.00 on a per-patient basis and 0.97 on a per-region basis. Sensitivity was also high, with 96% on a per-patient basis and 94% on a per-region basis, indicating the solid performance of [^{68}Ga]Ga-FAPI PET/CT in detecting sarcomas. Importantly, in 18.6% of patients, [^{68}Ga]Ga-FAPI PET/CT led to upstaging compared to ^{18}F-FDG PET/CT, highlighting its potential in providing more accurate staging information. However, there was no significant difference in uptake between low- and high-grade sarcomas [40].

Diagnostic Accuracy in Staging and Restaging of STS

In relation to GISTs, being classified as a type of STS, Wu et al. retrospectively compared [^{18}F]FAPI PET/CT with [^{18}F]FDG PET/CT in 35 patients with recurrent or metastatic GIST, assessing 106 lesions. [^{68}Ga]Ga-FAPI PET/CT detected 35.8% more lesions than [^{18}F]FDG PET/CT,

Table 2 RECIST Response and Subtype Distribution of Soft Tissue Sarcoma (STS) Patients[33]

RECIST Response	Number of Patients	Percentage (%)
PR (Partial Response)	10: leiomyosarcoma (2), alveolar soft sarcoma (1), thyroid sarcoma (1), rhabdomyosarcoma (1), solitary fibrous tumor (1), unspecified type (1), other (3)	23.30%
SD (Stable Disease)	16: fibrosarcoma (1), fibrous spindle cell soft tissue sarcoma (1), spindle cell sarcoma (1), desmoplastic small round cell tumor (1), unspecified type (6), solitary fibrous tumor (6)	37.20%
PD (Progressive Disease)	10: chondroma (1), conventional chondrosarcoma (1), pleomorphic cell sarcoma (1), unspecified type (5), solitary fibrous tumor (2)	23.30%
Total	43	100%

especially in liver and peritoneal metastases. The overall detection rate was significantly higher for FAPI (80.2% vs. 53.8%, $p<0.001$), with a notably higher TBR and SUV_{max} for liver metastases. Unlike FDG, FAPI uptake was independent of tumor size, gene mutation, targeted therapy, or enhancement [51].

Lanzafame et al. performed a recent prospective observational study, evaluating the diagnostic performance of [^{68}Ga]Ga-FAPI PET/CT in STS, comparing it with [^{18}F]FDG PET/CT for staging and restaging purposes. Among the 200 patients enrolled, 135 (67%) had STS. [^{68}Ga]Ga-FAPI PET/CT demonstrated higher uptake (mean SUVmax 10.4 ± 8.5 vs. 7.0 ± 4.5, $p=0.01$) in low-grade STS and greater accuracy (92.2% vs. 80.0%) compared to [^{18}F]FDG PET/CT. Additionally, 45% of patients with metastatic STS were eligible for FAPI-RLT defined by an SUVmax greater than 10. While higher-grade STS exhibited no significant difference in SUVmax between [^{68}Ga]Ga-FAPI and [^{18}F]FDG PET/CT, [^{68}Ga]Ga-FAPI PET/CT altered clinical management in 20% of all included patients. The findings indicate that [^{68}Ga]Ga-FAPI PET/CT provides superior detection rates and accuracy for low-grade sarcomas, potentially aiding in better treatment planning and identification of candidates for FAP-RPT [41].

Watanabe et al. included a 62-year-old male with GIST who underwent [^{68}Ga]Ga-FAPI-FAPI-46 PET/CT in their cohort study of 232 patients. [^{68}Ga]Ga-FAPI PET/CT plus CE-CT had the highest detection rate (91.2%), surpassing [^{18}F]FDG PET/CT plus CE-CT (82.5%, $p<0.0001$) and CE-CT alone (60.2%, $p<0.0001$). [^{68}Ga]Ga-FAPI PET/CT outperformed in detecting primary lesions (95.6% vs. 87.9% vs. 78.6%) and metastases, including nodal (93.2%), liver (95.3%), and other visceral (91.6%) ($p\leq0.0002$) [43].

Theranostic Applications of FAPI in STS

Eight studies investigated the utility of FAPI PET/CT in assessing therapeutic eligibility for FAPI RLT in STS. The overall response and outcome are summarized in Table 2.

Fibroblastic/Myofibroblastic Tumors

Kratochwil et al. were the pioneers in investigating FAPI-RLT for the treatment of STS, as in 2021 they targeted a patient with progressive lung metastatic fibrous spindle cell soft tissue sarcoma, who had previously undergone resection and radiotherapy but was deemed unsuitable for standard chemotherapy. The quinoline-based FAPI-46 was labelled with [^{153}Sm]Sm (half-life: 46.3 h) due to its short biological half-life, with emission scans at 44 h post-injection demonstrating effective tumor targeting and rapid clearance from normal organs. The patient was administered three cycles of therapy comprising a cumulative dose of 20 GBq of [^{153}Sm]Sm-FAPI-46 and 8 GBq of [^{90}Y]Y-FAPI-46, which was well tolerated and resulted in stable disease (SD) for 8 months interval. The subsequent treatment of the patient with pembrolizumab, enhanced with oncolytic parvovirus and nab-paclitaxel, although progression occurred after only 3 months; and the attribution of the clinical activity of [^{90}Y]Y-/[^{153}Sm]Sm-FAPI-46 to FAP expression in CAFs in STS, potentially acting as a"can opener"for subsequent immunotherapy; indicating effective targeting of the therapy (Fig. 4) [50].

Yang et al. described a 57-year-old woman with a malignant SFT of the parietal bone, initially treated with surgical resection. Two years later, renal metastases were confirmed, and she underwent chemotherapy with temozolomide and bevacizumab. Due to disease progression detected on [^{18}F]FDG PET/CT, she received [^{177}Lu]Lu-FAP-2286 therapy. Baseline [^{68}Ga]Ga-FAP-2286 PET/CT showed multiple metastases with high FAP expression (SUVmax up to 24.1). Twelve weeks post-treatment, follow-up imaging demonstrated a partial response with reduced lesion size and SUVmax. No adverse effects were observed [52].

Smooth Muscle Tumors

Banihashemian et al. detailed the first clinical experience, aiming for therapy to a 67-year-old male patient with unresectable metastatic mediastinal high-grade leiomyosarcoma. After an unsuccessful surgical intervention and standard chemotherapy, the patient was enrolled in a clinical trial for [^{177}Lu]Lu-FAPI therapy, receiving a total of four treatment cycles. Initial imaging using [^{68}Ga]Ga-FAPI PET/CT revealed significant FAPI localization in the primary tumor and metastatic lesions. Following the first cycle, there was a notable reduction in tumor size and no adverse events were reported, encouraging to complete four treatment cycles, although the mediastinal mass had reduced in size, there was an increase in SUVmax to 29.4, with dimensions of $53\times75\times97$ mm (compared to a previous SUVmax of 15.4 and size of $81\times113\times130$ mm). Additionally, newly seen right lower lip FAPI-avid lesion, which was pathologically confirmed as leiomyosarcoma. These findings suggest PD. The patient received a total cumulative dose of 23 GBq of [^{177}Lu]Lu-FAPI over four cycles, with specific doses of 4.4 GBq (120 mCi) for the first cycle and 5.5 GBq for the second cycle, followed by two additional cycles administered every six weeks (Fig. 5) [49].

Skeletal Muscle Tumors

Assadi et al. conducted a preliminary study, including 18 patients with different cancer subtypes who underwent

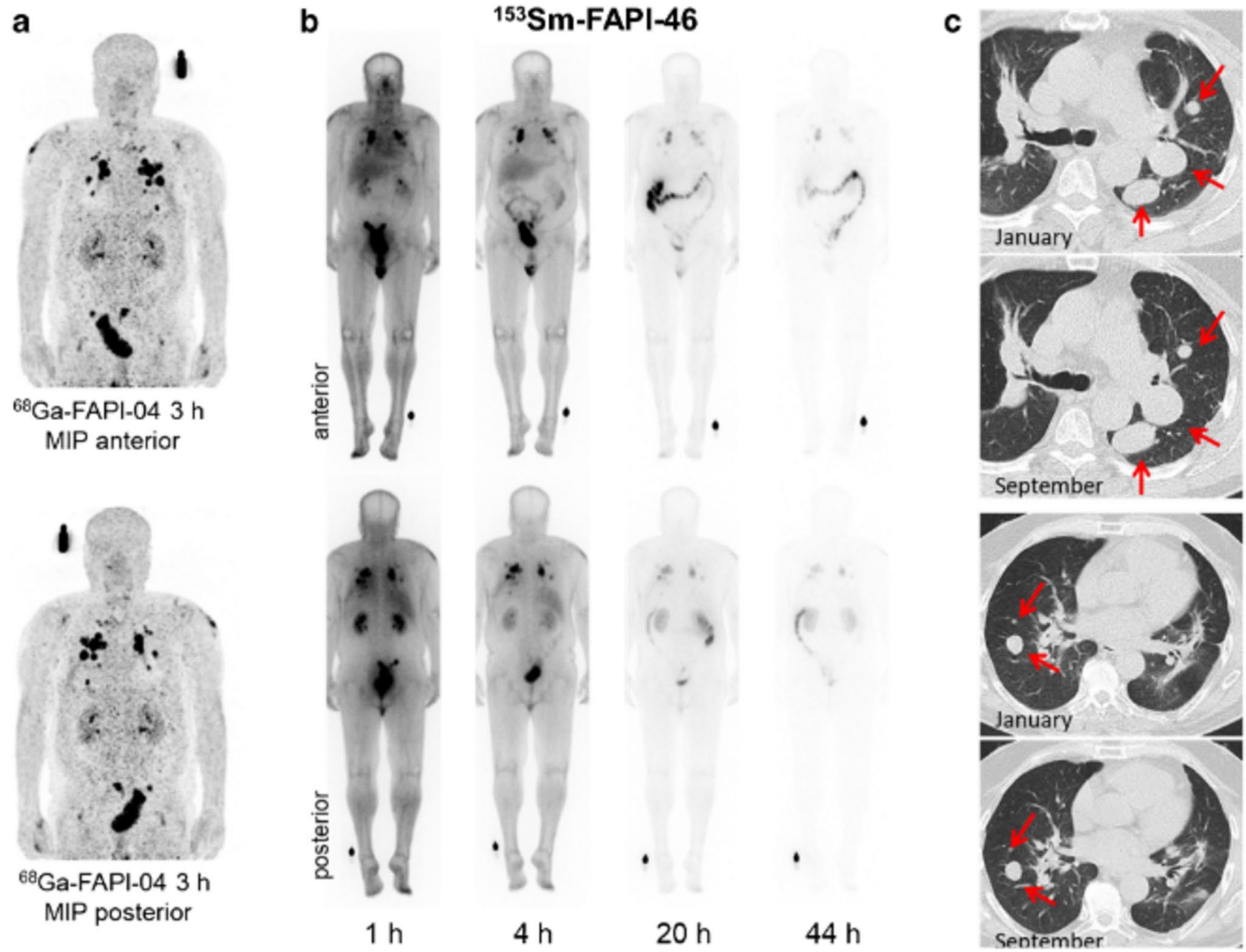

Fig. 4 Anterior (upper plane) and posterior (lower plane) views of a patient with progressive treatment-refractory lung metastatic fibrous spindle cell soft tissue sarcoma, illustrating the therapeutic potential of FAPI-RLT (**a**) ^{153}Sm-FAPI-46 imaging demonstrates avid lung meatastatic lesions, indicating effective tumor localization.(**b**) Emission scans obtained during therapy with ^{153}Sm, showing tumor-targeting sustained for up to 44 h post-injection, alongside rapid clearance from normal organs. (**c**) Follow up scan after three cycles with 20 GBq of ^{153}Sm-FAPI-46 and 8 GBq of^{90}Y-FAPI-46 cumulative dose, exhibiting SD for 8 months (from Jan. to Sep). Adapted with permission from reference [50], under creative commons license (CC BY 4.0)

evaluation with FAPI-based PET imaging and FAPI RLT using [^{177}Lu]Lu-FAPI. Among them, a pediatric patient with rhabdomyosarcoma received a fixed dose of 1.85 GBq per cycle across four treatment cycles with no reported toxicity. The specific response and outcome were not available [45].

Tumors of Uncertain Differentiation

Assadi et al. also explored FAPI RLT utility in a 28-year-old male diagnosed with DSRCT, who had a prior history of abdominal surgery and chemotherapy. The patient underwent both [^{18}F]FDG PET/CT and [^{68}Ga]Ga-FAPI PET/CT for lesion assessment. [^{18}F]FDG PET detected metastases in the right paracardiac lymph node, abdomen, pelvis, liver, and right hemiscrotum. FAPI PET showed a similar distribution with higher SUVmax but identified an additional posterior abdominal lesion missed on ^{18}F-FDG PET/CT, while the mediastinal lesion was better visualized on [^{18}F]FDG PET/CT. This patient underwent two cycles of PTRT with a total administered activity of 6.6 GBq. Post-therapy scintigraphy after the first cycle confirmed radiotracer uptake in the metastatic lesions. Following the second cycle, a reduction in uptake was observed in the left pelvic lymph node, although the overall disease status remained stable. Evaluated response according to RECIST 1.1, indicated stable disease (SD). No significant adverse effects or toxicities were reported [45].

Basket Studies

Ferdinandus et al. reported their initial clinical experience with [^{90}Y]Y-FAPI-46) as a RLT administered to nine

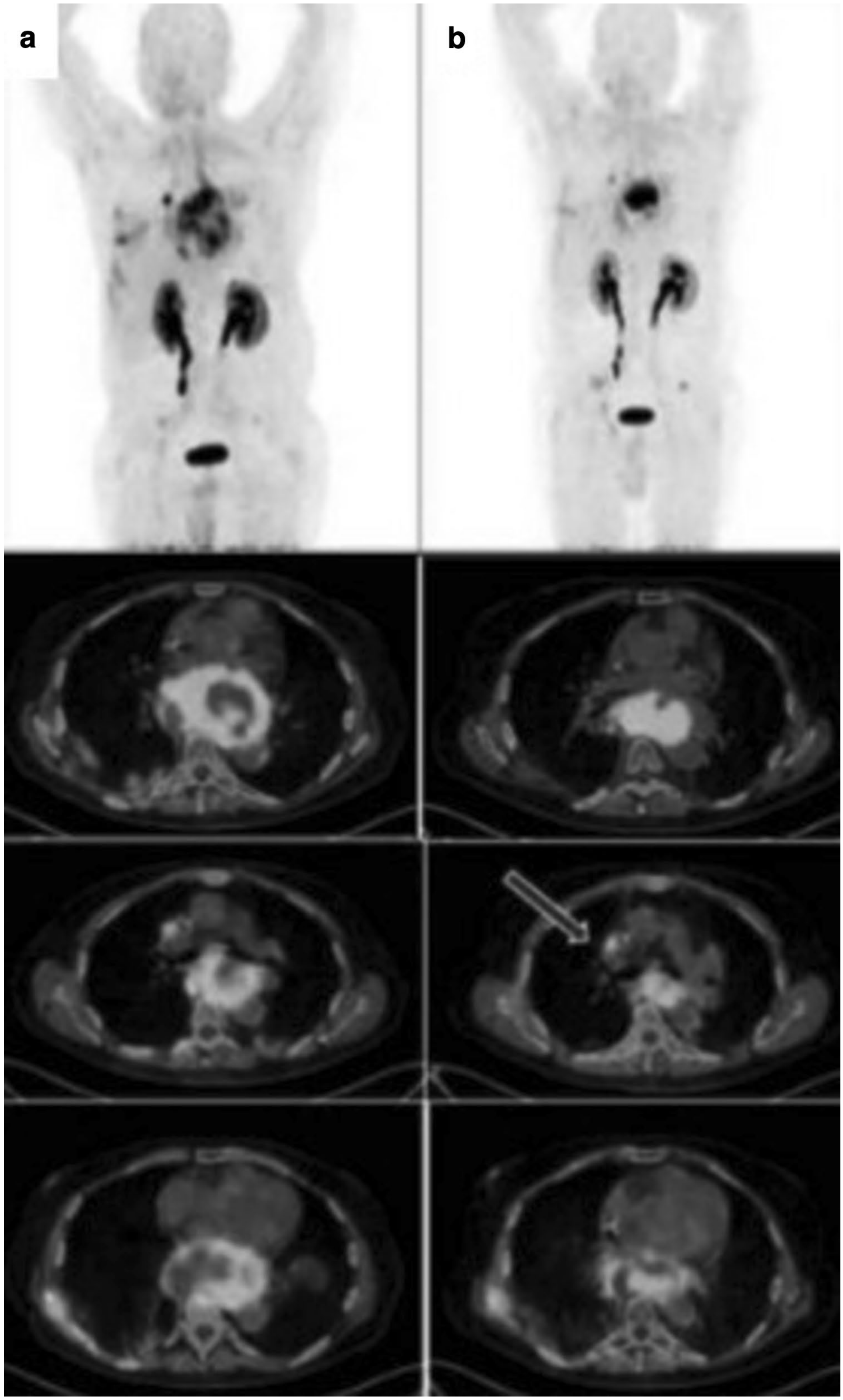

Fig. 5 Comparison of ^{68}Ga-FAPI PET/CT imaging before and after four cycles of [^{177}Lu]Lu-FAPI therapy in a patient with metastatic mediastinal leiomyosarcoma, Panel A: Baseline ^{68}Ga-FAPI PET/CT showing intense FAPI uptake in the mediastinal primary tumor (indicated by the dashed arrow) and metastatic sites before initiation of therapy. Panel B: Post-therapy ^{68}Ga-FAPI PET/CT after four cycles of [^{177}Lu]Lu-FAPI. Despite a reduction in the size of the primary mediastinal mass, an increase in SUVmax to 29.4 is observed (previous SUVmax was 15.4). A newly detected FAPI-avid lesion in the right lower lobe is marked by a solid arrow, pathologically confirmed as metastatic leiomyosarcoma, indicating disease progression. The patient received a cumulative dose of 23 GBq of [^{177}Lu]Lu-FAPI over four cycles, with no adverse events reported. These imaging findings demonstrate the partial response in terms of size reduction but highlight the need for monitoring SUVmax increases and new lesions as markers of disease activity. Adapted with permission from reference [49], under creative commons license (CC BY-NC-SA 4.0)

patients with advanced solid tumors. This cohort included five patients with metastatic STS with a median age of 61 years, encompassing various subtypes such as chordoma, fibrosarcoma, gastrointestinal neuroectodermal tumor (GNET), chondrosarcoma, and spindle cell sarcoma. These patients had exhausted all standard treatment options, and the most prevalent Eastern Cooperative Oncology Group (ECOG) performance score was two or higher. Selection was based on high FAP expression (SUVmax ≥ 10 in > 50% of lesions), patients received a median dose of 3.8 GBq for the first cycle, with adequate tumor uptake confirmed in 78% of cases. The therapy was well tolerated, with hematologic grade 3/4 toxicities occurring in 44% of patients, primarily thrombocytopenia, possibly related to either tumor progression or initiation of concomitant other systemic therapy and no acute toxicities attributed to the treatment, suggesting potential clinical applicability. responses varied across different tumor subtypes. According to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, two patients, one with fibrosarcoma and another with spindle cell sarcoma, experienced SD. In contrast, two other patients with chondroma and chondrosarcoma showed progressive disease (PD), although both patient groups reported no adverse effects. Unfortunately, the chondroma patient died 62 days post-therapy, and the outcome of the chondrosarcoma patient remains unclear due to a lack of follow-up. Overall, FAPI- RLT demonstrated a favorable safety profile, though efficacy was inconsistent across the different sarcoma subtypes [46].

Fendler et al. conducted a prospective observational study to evaluate [^{90}Y]Y-FAPI-46 RLT in 16 patients with metastatic STS who had exhausted standard treatments and exhibited high FAP expression (SUVmax ≥ 10 in > 50% of the tumor). ECOG performance status was ≥ 2 in 38% of cases. Among 12 evaluable patients, partial response (PR) was observed in 8% (1/12), stable disease (SD) in 50% (6/12), and progressive disease (PD) in 42% (5/12). High FAP expression (SUVmax > 20) was most common in solitary fibrous tumors (SFT). Median progression-free survival (PFS) was 3.4 months, and median overall survival (OS) was 10.0 months, with longer OS in RECIST responders. Grade 3/4 adverse events occurred in 38%, mainly thrombocytopenia and anemia [48].

Another preliminary study by Hamacher et al. explored [^{90}Y]Y-FAPI-46 RLT in patients with advanced STS demonstrated promising results, particularly in SFT cases. Among 16 STS patients, 9 had SFT, all exhibiting high FAP expression (SUVmax > 20). All patients had advanced-stage disease, with multiple organ involvement and an ECOG performance status of ≥ 2 in 38% of cases. Up to four cycles of [^{90}Y]Y-FAPI-46 were administered, with 12 patients evaluable for response. Disease control by RECIST criteria was observed in 7 of 12 patients (58%), including 1 (8%) PR and 6 (50%) SD, while 5 (42%) had PD. PERCIST response was noted in 7 of 12 patients (58%). Median SUVmax was highest in SFT (max 29.1, mean 15.7) [47].

Subsequently, Banihashemian et al. conducted a prospective clinical study, demonstrating that FAP is highly expressed in the stroma of many cancers, making it an attractive target for imaging and therapy. They prospectively assessed 21 patients with advanced solid tumors, of whom 6 were initially identified as having metastatic sarcomas. These included patients with leiomyosarcoma, metastatic sarcoma from thyroid, alveolar soft part sarcoma, and pleomorphic cell sarcoma, with a median age of 60.5 years. [^{68}Ga]Ga-FAPI PET/CT was employed to determine eligibility for FAPI RLT. Patients received a radiolabeled dose of [^{177}Lu]Lu FAPI-2286 at 4 MBq/kg. Among STS patients, responses varied as follows: PR for mediastinal leiomyosarcoma, thyroid sarcoma and alveolar soft sarcoma, whereas PD is gained in pleomorphic cell sarcoma. Importantly, no adverse events were detected, and all patients remained alive with an average survival period of 7.8 ± 0.9 months from the initiation of RLT [44].

Discussion

This study provides the first systematic review of FAPI yield from diagnostic and theranostic perspectives in STS. Our findings demonstrate that FAPI-based imaging offers a reasonable promising alternative to [^{18}F]FDG PET/CTin STS across multiple documented studies, revealing reliable tumor targeting and increased uptake in both primary and metastatic lesions. The results from multiple studies confirm that FAPI-targeted radiotracers, specifically [^{68}Ga]Ga; demonstrated high tumor uptake in primary and metastatic lesions, with strong tumor-to-background contrast. Moreover, FAPI-based radionuclide therapy has shown varying degrees of efficacy, including SD and PR in certain STS subtypes. However, disease progression in some patients suggests that further clinical trials are needed to refine and optimize therapeutic outcomes [45–48].

Our systematic review reveals that [^{68}Ga]Ga-FAPI PET/CT consistently exhibits high SUVmax and TBR values across a broad spectrum of STS subtypes, reflecting a favorable uptake profile. In most comparative studies, these metrics surpassed those obtained from [1^{8}F]FDG PET/CT, highlighting the superior sensitivity achievable with FAPI-based imaging [19, 23, 25, 26, 33, 38]. The underlying mechanism of this enhanced performance lies in FAPI's dual targeting capability: uptake occurs not only within sarcoma tumor cells but also in the abundant population of cancer-associated fibroblasts (CAFs) embedded in the tumor stroma [4]. This dual pathway provides a more comprehensive and biologically relevant depiction of the tumor microenvironment, in contrast to [^{18}F]FDG, which is limited to detecting increased glucose metabolism and is known for variable uptake in sarcomas—particularly those that are low grade or exhibit slow proliferation.

This biologic and imaging advantage is a key reason why FAPI PET/CT is emerging as a promising imaging biomarker in STS. Its ability to produce high tumor-to-background contrast enhances diagnostic accuracy, particularly in challenging clinical scenarios. Notably, recent basket trials have demonstrated the diagnostic reliability of FAPI PET/CT not only in the context of initial staging but also in restaging—where conventional modalities such as MRI often fall short [8, 39–43, 51]. In cases of suspected recurrence, MRI may lack sufficient specificity or fail to delineate lesions accurately, thereby potentially leading to suboptimal therapeutic decision-making [53]. FAPI PET/CT, by contrast, offers an imaging profile well-suited to overcoming these limitations.

This diagnostic advantage naturally extends into the therapeutic domain, where FAPI-based radioligand therapy is emerging as a promising approach in the management of metastatic STS, offering targeted treatment options for patients with high FAP expression. When all other therapeutic options have been exhausted, the primary objective of a novel therapy is to achieve disease control. Hence, the utility of FAPI RLT, demonstrates a promising approach for patients with advanced or metastatic STS who have no further treatment options available through conventional therapies. Studies using radiolabeled FAPI agents, such as [^{153}Sm]Sm-FAPI-46, [^{90}Y]Y-FAPI-46, and [^{177}Lu]Lu-FAPI-46, showed favorable safety profiles with tolerability across patient cohorts [44–48]. Despite documented hematologic toxicity in some cases, it was attributed to systemic treatment rather than RLT. However, the variability in treatment responses, ranging from stable disease to progressive disease, urges further research to improve patient selection, dosing protocols, and long-term outcomes [54].

An essential aspect of FAPI-based imaging and therapy is the selection and labeling of different FAPI variants, each with distinct pharmacokinetics, biodistribution profiles, and tumor retention, influencing their utility in both diagnostic and theranostic applications. Various FAPI derivatives, such as FAPI-04, FAPI-46, and FAPI-2286, have been developed; however, there is currently no available study comparing the differences among these variants [54].

This systematic review is subject to several limitations inherent to the current body of literature. First, the majority of included studies are case reports or small case series, limiting both generalizability and statistical robustness. Second, the absence of long-term follow-up data and the lack of prospective, randomized, multicenter trials restrict the ability to draw definitive conclusions regarding the broader clinical utility of FAPI PET/CT. Third, inconsistencies across studies—particularly regarding imaging protocols, diagnostic sensitivity and specificity, and clinical outcomes—impede a comprehensive assessment of diagnostic accuracy. Furthermore, several challenges must be addressed before FAPI PET/CT can be fully integrated into routine clinical practice. As highlighted by Al-Ibraheem, FAPI uptake is not entirely tumor-specific and may occur in benign conditions such as fibrosis, scar tissue, and inflammatory processes [55]. This underscores the need for cautious interpretation of FAPI PET/CT findings, especially when differentiating malignant lesions from benign or reactive changes.

Conclusion

STS poses significant challenges in diagnosis and treatment due to their variable growth and extensive overlap between benign and malignant presentations. The integration of [^{68}Ga]Ga-FAPI PET/CT into clinical practice could significantly enhance diagnostic precision providing enhanced sensitivity and specificity for detecting primary and secondary lesions in various subtypes of STS, particularly low-grade sarcomas, and replace standard imaging modalities like [^{18}F]FDG PET/CT. Prospective, multi-center studies which explore sensitivity, specificity and accuracy as well as management impact comparing FAPI PET and [^{18}F]FDG PET are required to fully define the clinical role of FAPI PET in these cancer types. For theranostics, FAPI-based RLT offers a potential treatment option for difficult-to-treat STS cases. Nonetheless, future studies should prioritize larger clinical trials to validate FAPI's diagnostic and therapeutic efficacy. This includes investigating FAPI overexpression in CAFs within STS to improve its application in imaging techniques and therapeutic interventions. Additionally, research should explore combinational strategies, such as integrating FAPI with immunotherapies or chemotherapy, and assess long-term outcomes.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13139-025-00936-y.

Author Contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Marwah Abdulrahman and Akram Al-Ibraheem. The first draft of the manuscript was written by Marwah Abdulrahman and revised by Ahmed Saad Abdlkadir. All authors read and approved the final manuscript.

Funding The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Data Availability Data is available from the corresponding author upon reasonable request.

Declarations

Ethics Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Declaration of Generative AI in Scientific Writing Authors did not use generative AI in writing.

Informed Consent Not applicable.

Competing interests Akram Al-Ibraheem is an editorial board member while conducting this study. All other authors have no competing interests.

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