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FAPI PET in musculoskeletal oncology: An update and future directions

Anja Dietze,[a,b] Daniel M. Aebersold,[b] Axel Rominger,[a] Constantin Lapa,[c] and Robert Seifert[a]

Fibroblast activation protein inhibitor (FAPI) imaging has become a promising approach in musculoskeletal oncology, with growing evidence supporting its application in both primary sarcomas and skeletal metastatic disease. Fibroblast activation protein (FAP) is expressed by cancer-associated fibroblasts and by tumor cells themselves in several sarcoma subtypes, while demonstrating limited expression in normal adult tissues. This biological profile has supported the development of radiolabeled FAP inhibitors, which provide high tumor-to-background contrast on PET imaging and enable theranostic applications with FAP-targeting radioligands. In sarcoma, available studies demonstrate higher FAPI uptake and improved lesion detection compared with [^{18}F]FDG PET across most histological subtypes, with particularly notable advantages in low- and intermediate-grade tumors. However, FAPI uptake varies according to histological subtype. In metastatic bone disease, FAPI PET detects more lesions than [^{18}F]FDG PET, particularly osteolytic and marrow-based metastases. The benefit is greatest in tumor entities with low [^{18}F]FDG uptake, though at the cost of reduced specificity, as benign skeletal and fibroinflammatory processes also take up the tracer. As FAPI and [^{18}F]FDG reflect different tumor biology with distinct strengths, their roles are increasingly regarded as complementary rather than competing. Beyond imaging, FAPI PET facilitates patient selection for FAP-targeted radioligand therapy, with early clinical experience demonstrating feasibility and encouraging preliminary evidence of disease control. Prospective studies are needed to define its clinical impact, establish standardized interpretation and response criteria, and determine the role of FAPI-based imaging and therapy in the management of musculoskeletal malignancies.

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Introduction

^{18}F-Fluorodeoxyglucose (FDG) remains the most widely utilized radiotracer in oncologic PET imaging. Its uptake is a reflection of cellular glucose metabolism, and is therefore not specific to malignancy, as benign metabolically active tissue also accumulates the tracer.[1] Physiological uptake is high in many tissues, and diffuse uptake in hematopoietic bone marrow can obscure skeletal and medullary disease.[2,3] Uptake in inflammatory and infectious tissue is a frequent source of false-positive findings.[1,4] Sensitivity is reduced in tumors with low glycolytic activity, including low-grade sarcomas, lobular breast carcinoma and mucinous gastrointestinal carcinomas, in which primary tumors and metastases may be underestimated.[5,6] Furthermore, FDG imaging requires fasting and adequate glycemic control.[7]

The limitations of glucose-based imaging have directed attention toward the tumor stroma as an alternative target. Solid tumors are composed not only of malignant cells but

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also of a supporting stroma in which cancer-associated fibroblasts are a principal cellular component, contributing to extracellular matrix remodeling, tumor invasion, angiogenesis, and immune modulation.[8] Fibroblast activation protein (FAP) is a type II transmembrane serine protease that is expressed on cancer-associated fibroblasts and is present in the stroma of more than ninety percent of epithelial malignancies, while its expression in normal adult tissue is low.[8,9] This restricted physiological expression, combined with its presence across many tumor types, identifies FAP as a target for tumor imaging.[10] Although initially characterized in epithelial malignancies, FAP expression has also been demonstrated in the stromal compartment of mesenchymal tumors, supporting its investigation in sarcomas and other musculoskeletal malignancies (Fig. 1).[11,12]

Radiolabeled FAP inhibitors (FAPI) were developed as small-molecule ligands binding FAP with high affinity, permitting PET imaging of FAP-expressing tissue.[10,13] They accumulate rapidly in tumor tissue and are cleared quickly from the circulation, producing high tumor-to-background ratios.[14] Physiological uptake is low in most normal organs, including bone marrow, brain, and myocardium, and no fasting or other patient preparation is required.[14,15] Because FAP is targeted by the same ligand class for imaging and for radioligand therapy, FAP-directed agents also provide a theranostic approach.[16]

FAPI PET has since been evaluated in a broad range of solid tumors, including lung cancer and lobular breast cancer.[17] Despite encouraging results in gastrointestinal (GI) malignancies, the application of FAPI PET in musculoskeletal oncology remains less established. This review summarizes the current oncologic applications of FAPI PET in musculoskeletal disease and outlines directions for future development.

FAPI PET in sarcoma imaging

Sarcomas are a heterogeneous group of mesenchymal malignancies comprising more than 100 histological subtypes and arising in both soft tissue and bone.[18] They are rare, and metastatic disease is associated with a poor prognosis, with reported median overall survival estimates of 12 to 18 months.[19,20] Therapeutic options in advanced disease are limited, placing considerable importance on accurate early detection and staging to separate localized from metastatic disease and guide treatment with curative or palliative intent.

Cross-sectional imaging, particularly magnetic resonance imaging (MRI), remains the primary means of assessing the local extent of the primary tumor because of its high tissue contrast. For whole-body staging and restaging, FDG PET/CT is widely used and additionally contributes to grading, biopsy guidance, and evaluation of treatment response.[21] Its diagnostic performance is greatest in high-grade tumors, in which elevated glucose metabolism produces reliable uptake, and FDG uptake intensity correlates with histological grade.[22] This dependence on glucose metabolism, however, constrains its performance across the wider spectrum of sarcoma subtypes. Well-differentiated, low-grade, and several myxoid tumors often show low glycolytic activity and

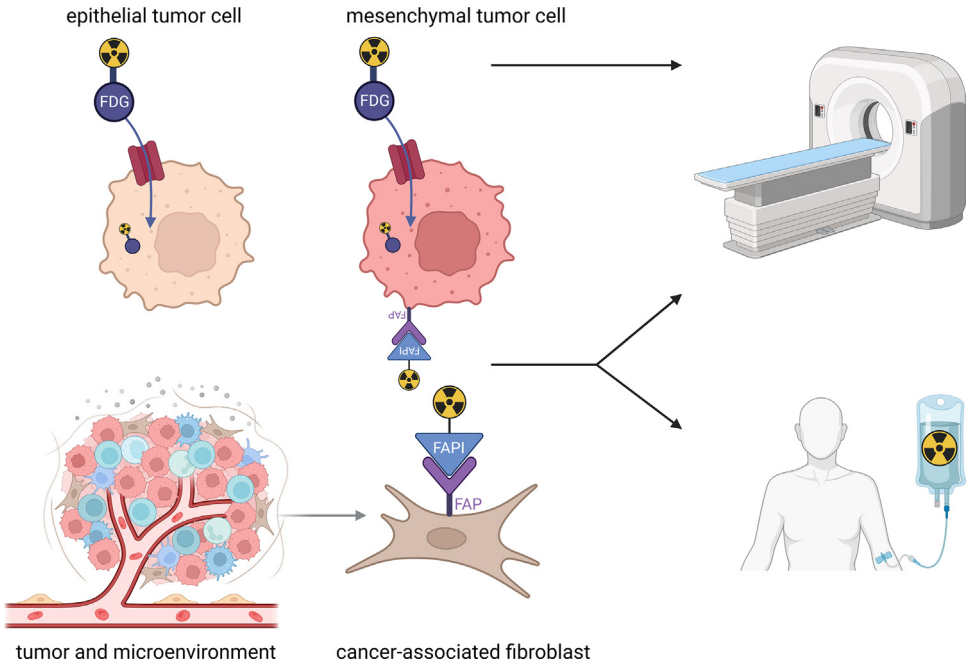


Fig. 1 Comparison of the biological targets and clinical applications of FDG and radiolabeled FAPI. FDG is taken up by epithelial and mesenchymal tumor cells via glucose transporters. Radiolabeled FAPI (FAP inhibitor) binds fibroblast activation protein (FAP) expressed by cancer-associated fibroblasts and many mesenchymal tumor cells. While FDG is used exclusively for PET imaging, FAPI can be used for both PET imaging and radioligand therapy. FDG: ^{18}F-Fluorodeoxyglucose; FAP: fibroblast activation protein; FAPI: fibroblast activation protein inhibitor. Created in https://BioRender.com.

correspondingly low FDG uptake, reducing sensitivity in precisely the subtypes where imaging is most challenging.[3,23] Restaging is further complicated by post-surgical and post-radiotherapy inflammation, which can increase FDG uptake and mimic or obscure residual disease.[3]

These limitations have directed interest toward the tumor stroma as an alternative imaging target. In epithelial malignancies, FAP expression is primarily associated with cancer-associated fibroblasts within the tumor microenvironment, with limited expression in most normal adult tissues.[9] Sarcomas are distinct from epithelial malignancies in this regard. Owing to their mesenchymal origin, FAP expression extends beyond stromal fibroblasts to the sarcoma cells themselves, resulting in target expression across both compartments.[11,12] Subtype-specific FAP expression has been documented in several sarcomas, including osteosarcoma, myofibroblastic sarcoma, and undifferentiated pleomorphic sarcoma.[12] This dual-compartment expression, combined with the low physiological background of FAP-directed tracers and their independence from glucose metabolism, provides a strong biological rationale for FAPI PET in sarcoma and has made it one of the most actively investigated applications of this tracer class outside epithelial cancer. Notably, this research has focused largely on soft tissue sarcomas, whereas data in primary bone sarcomas remain limited.

Tracer uptake and target expression

Consistent with this biological rationale, FAPI PET produces higher tumor uptake and superior tumor-to-background contrast than FDG PET across most sarcoma subtypes. In a prospective cohort of 200 patients with bone and soft-tissue sarcoma, mean SUVmax and the tumor-to-liver ratio were higher for [^{68}Ga]Ga-FAPI-46 than for FDG in nearly all subentities examined.[24] Comparable findings have been reported across further sarcoma cohorts, including in recurrent soft-tissue sarcoma, with consistently higher SUVmax, SULpeak, SUVmean, and tumor-to-background ratios for FAPI.[25-27] This advantage derives largely from the low physiological uptake of FAPI in normal organs, including the liver and blood pool, against which lesions are more readily distinguished than with FDG.[14,25] The performance of FAPI PET across different sarcoma subtypes is detailed in the following sections.

Importantly, the elevated FAPI signal reflects the intended molecular target rather than nonspecific accumulation. FAPI uptake intensity correlates moderately with histopathological FAP expression measured by immunohistochemistry in sarcoma,[24,28] indicating that the contrast on FAPI PET is a direct consequence of target expression in the tumor and its associated stroma.

FAPI uptake depending on tumor grade and histological subtype

Whereas FDG uptake in sarcoma rises with histological grade, FAPI uptake follows a different pattern. Intense FAPI uptake occurs across all grades, including in high-grade tumors,[25] but its advantage over FDG is greatest in low-grade and intermediate or unclassifiable sarcomas, in which glycolytic activity is frequently low. In a prospective cohort of 200 patients, FAPI uptake significantly exceeded FDG uptake in low-grade (mean SUVmax 10.4 versus 7.0) and intermediate-grade tumors (22.3 versus 8.5), with correspondingly higher detection rates and accuracy in these subgroups.[24] In recurrent soft-tissue sarcoma, [^{68}Ga]Ga-DOTA-FAPI-04 uptake surpassed FDG uptake in both low-grade and high-grade disease and was higher in low-grade than in high-grade tumors, the reverse of the pattern shown by FDG.[26] Across histological subgroups, [^{68}Ga]Ga-FAPI-04-derived SUVmax, SULpeak, and SUVmean did not differ significantly by grade, whereas for FDG both SULpeak and SUVmean varied significantly with grade.[27] This apparent grade independence, however, may also represent a limitation. Because FDG uptake correlates with histological grade, it provides prognostic information that FAPI uptake, lacking a similar grade association, does not.[24,27]

FAPI uptake is strongly dependent on the histological subtype (Fig. 2). The highest uptake has been observed in

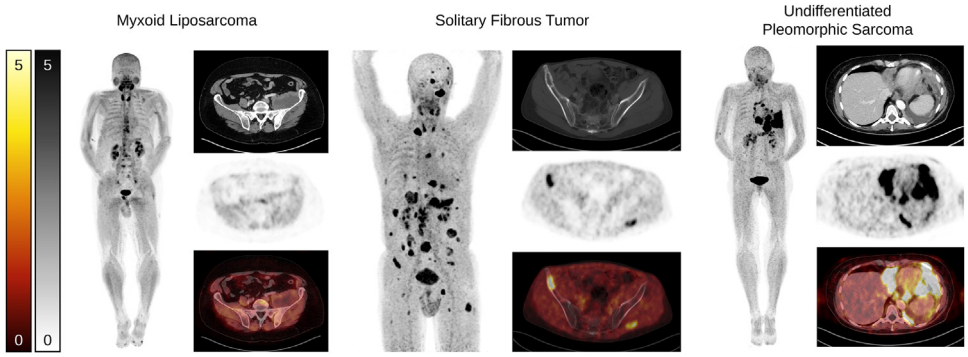


Fig. 2 FAPI uptake in different histological subtypes of sarcoma. Representative [^{68}Ga]Ga-LNTH-1363S PET/CT maximum intensity projection (MIP) and axial images from (A) a 57-year-old man with suspected recurrent myxoid liposarcoma undergoing staging, (B) a 69-year-old man with advanced solitary fibrous tumor (SFT) undergoing FAP-directed PET for radioligand therapy (RPT) assessment (SUVmax 26.4), and (C) a 66-year-old woman with advanced undifferentiated pleomorphic sarcoma (UPS) undergoing FAP-directed PET for RPT assessment (SUVmax 18.8).

solitary fibrous tumor, undifferentiated pleomorphic sarcoma, and leiomyosarcoma, with solitary fibrous tumor reaching mean SUVmax values roughly twice the average across subtypes.[24] Myxoid liposarcoma, which showed the lowest absolute [^{68}Ga]Ga-FAPI-46 uptake, still exceeded its correspondingly low FDG uptake.[24] Intense FAPI uptake has also been described in a range of less common entities, including epithelioid hemangioendothelioma, alveolar soft part sarcoma, and dermatofibrosarcoma protuberans, in several of which uptake exceeded that of FDG.[29] In recurrent soft-tissue sarcoma, [^{68}Ga]Ga-DOTA-FAPI-04 demonstrated significantly higher uptake than FDG in liposarcoma and malignant solitary fibrous tumor, whereas higher FDG uptake was observed in undifferentiated pleomorphic sarcoma and rhabdomyosarcoma.[26] Lower FAPI than FDG uptake has also been reported in synovial sarcoma, indicating that FAPI sensitivity is not uniform across all subtypes and cannot be assumed in every histology.[27] This heterogeneity in relative FAPI and FDG uptake appears to extend beyond musculoskeletal sarcomas, with FAPI uptake reported to exceed that of FDG in gastrointestinal stromal tumors and angiosarcoma, and FDG uptake appearing higher in Kaposi sarcoma and follicular dendritic cell sarcoma.[29]

Lesion detection and metastatic staging

Across several studies, FAPI PET identified more lesions than FDG PET in sarcoma. In recurrent soft-tissue sarcoma, [^{68}Ga]Ga-DOTA-FAPI-04 identified 275 lesions compared with 186 for FDG, with higher sensitivity, specificity, predictive values, and accuracy.[26] The advantage was distributed across patients, with upstaging in 4/45 (8.9%). In a mixed sarcoma population, [^{68}Ga]Ga-FAPI-04 likewise detected more true-positive lesions and achieved higher lesion-based sensitivity and accuracy than FDG.[27] This advantage was most pronounced in low-grade and intermediate tumors, while [^{68}Ga]Ga-FAPI-46 and FDG performed similarly in high-grade disease.[24] The improvement was largely lesion-based rather than patient-based, as additional [^{68}Ga]Ga-FAPI-04-positive lesions frequently occurred in patients already correctly identified by FDG.[27] It should be noted that these findings derive largely from cohorts that, while predominantly musculoskeletal, also include retroperitoneal and visceral primaries and are not stratified by anatomical site.

The relative performance of the two tracers appears to depend on lesion site. FAPI PET shows a consistent advantage for liver metastases, attributable to its low hepatic background, with more hepatic lesions detected than by FDG PET in recurrent soft-tissue sarcoma and in a further prospective sarcoma trial.[26,28] Higher osseous detection with FAPI PET has likewise been reported.[27,30] Performance in the lung is less consistent. [^{68}Ga]Ga-FAPI-04 PET detected more pulmonary lesions than [^{18}F]FDG PET in one series,[27] whereas in recurrent soft-tissue sarcoma [^{68}Ga]Ga-DOTA-FAPI-04 PET failed to detect 7 of 29 confirmed lung metastases,[26] a discrepancy that might reflect declining FAP expression as pulmonary metastases progress.[31] FDG PET showed higher nodal detection than FAPI PET in sarcoma series,[27,30] but this did not reach significance in one study.[30] Part of the additional FDG signal reflected uptake in reactive and inflammatory lymph nodes confirmed to be benign.[27] A meta-analysis could not establish a nodal difference between the two tracers in sarcoma.[32] FAPI, with its low uptake in reactive lymph nodes, may improve the specificity of nodal assessment.[27] Still, FAP-targeted imaging has its own limitations, as FAP is also upregulated in wound healing and fibrosis, including at post-surgical and post-radiotherapy sites.[33]

Clinical implications

A small number of studies have examined the impact of FAPI PET on clinical management in sarcoma. In a large prospective cohort of mixed sarcoma subtypes, [^{68}Ga]Ga-FAPI-46 PET altered the planned management in approximately one-fifth of patients, most often by redirecting patients from surveillance to systemic treatment.[24] Upstaging relative to FDG has been reported in 8.9% of patients in one cohort and 18.6% in another.[26,28] Its diagnostic value appears to lie in improved lesion detection rather than in characterization of tumor grade, and the two tracers provide partly non-overlapping information.[30] The SNMMI Procedure Standard and EANM Practice Guideline for FAPI PET is more measured, noting that in sarcomas, high FAPI uptake so far has not translated into improved staging relative to FDG, and that its role may be confined to sarcomas with low FDG avidity and high FAP expression, such as solitary fibrous tumor, and to the selection of patients for radioligand therapy.[34]

The shared molecular target of FAPI imaging and FAP-directed radioligand therapy provides a theranostic framework, and FAPI PET has been used to select sarcoma patients for such treatment, an application examined in its own dedicated section below.

FAPI PET in metastatic bone disease

Beyond primary tumors, metastatic bone disease has attracted considerable attention in musculoskeletal FAPI imaging. Skeletal metastases arise predominantly from epithelial malignancies, in which FAP is expressed by reactive stromal fibroblasts rather than by the malignant cells themselves.[8,9] Bone is among the most frequent sites of distant spread in solid malignancy. Approximately five percent of patients have skeletal involvement already at primary diagnosis, with the highest cumulative incidence observed in breast, prostate and lung cancer.[35,36] Some tumors that commonly metastasize to bone, such as lobular breast and renal cell carcinoma, show weak FDG uptake, limiting the sensitivity of metabolic imaging. Skeletal metastases cause bone pain, pathological fracture, spinal cord compression and hypercalcemia.[37,38] These events impair quality of life and are associated with shortened survival.[36,39] Accurate detection therefore influences initial staging, restaging, treatment planning, treatment monitoring and survival prediction.[40]

Bone scintigraphy with technetium-99 m labeled diphosphonates and FDG PET/CT are both established options for skeletal staging.[41] CT and MRI provide structural information, but atypical metastases and benign osseous lesions frequently share morphological features, which limits confident differentiation.[42] Diphosphonate uptake reflects osteoblastic activity and regional blood flow rather than tumor tissue itself, so sensitivity is high in advanced osteoblastic disease but limited in early and predominantly lytic lesions.[41] FDG PET/CT detects more skeletal lesions than bone scintigraphy overall and is sensitive in osteolytic, mixed and marrow-based disease.[43,44] However, glycolytic activity is lower in osteoblastic metastases, with correspondingly reduced FDG uptake.[45,46] Physiological and reactive uptake in hematopoietic marrow, including after administration of hematopoietic growth factors, can obscure medullary deposits.[47,48]

These limitations highlight the potential value of imaging targets beyond bone remodeling and glycolysis. Cancer-associated fibroblasts are integral components of the bone metastatic niche, where they coordinate interactions between tumor cells and the bone matrix and contribute to the establishment of skeletal metastases.[49,50] As physiological FAP expression in normal bone and marrow is low,[14,15] FAPI PET may offer improved lesion-to-background contrast for detecting skeletal metastatic disease.

Detection of skeletal metastases

FAPI PET/CT has been shown across series to detect more skeletal metastases than FDG PET/CT. In the largest single cohort reported to date, comprising 293 patients of whom 48 had bone metastases, [^{68}Ga]Ga-DOTA-FAPI-04 identified all 376 metastatic lesions against 228 with FDG, corresponding to lesion-based sensitivities of 100 and 60.6 percent.[51] Comparable differences have been observed in smaller series, with lesion-based sensitivities of 100 against 81.7 percent in 109 lesions using [^{68}Ga]Ga-DOTA-FAPI-04,[52] and visualization of 767 of 827 lesions with [^{68}Ga]Ga-FAPI-04 against 678 with FDG.[53] The only prospective series, conducted in lung cancer with partial histopathological confirmation, used Al[^{18}F]F-NOTA-FAPI-04 and reported bone metastasis sensitivities of 99 and 89 percent.[54] Pooled analyses show the same advantage. Lesion-based detection was 1.00 for FAPI against 0.71 for FDG across nine studies and 2496 lesions,[55] and 0.95 against 0.65 in gastric cancer.[56]

The magnitude of this difference depends on the level at which detection is assessed. In the same cohorts in which lesion-based differences were large, patient-based differences were considerably smaller and did not reach statistical significance. Patient-based accuracy in the largest cohort was 99.3 percent for FAPI against 97.6 percent for FDG, a difference that was not significant, whereas the lesion-based numbers were 97.6 percent against 75.8 percent.[51] The same pattern was seen in a smaller series.[52] This has been attributed to the multiplicity of skeletal deposits, since patients harboring several metastases remain correctly classified even when individual lesions are not detected.[51]

Pooled analyses have reached conflicting conclusions. One found a significantly higher detection with FAPI at both levels, with detection rates of 0.99 for FAPI against 0.79 for FDG across patients and 1.00 against 0.71 across lesions.[55] A gastric cancer analysis found a lesion-based advantage but a marginally lower patient-based sensitivity for FAPI, at 0.93 against 1.00.[56] A third analysis, using positivity rate, found no significant difference, at 0.73 against 0.57.[57] This likely reflects differences in the endpoints used and the studies included.

Factors influencing tracer performance

The additional lesions detected with FAPI are not evenly distributed across the skeleton. In the largest cohort, FDG detected 48.9 percent of thoracic and 56.4 percent of spinal metastases, but all lesions in the extremities. [^{68}Ga]Ga-DOTA-FAPI-04 detected all lesions irrespective of site.[51] A smaller series showed the same pattern, with FDG detecting 50 percent of cranial and 74 percent of rib metastases against 100 percent for [^{68}Ga]Ga-DOTA-FAPI-04.[52] The low cranial detection was attributed to physiological uptake of the adjacent brain. The lesions escaping detection appear to be small: those missed by FDG in the prospective series measured 7.9 mm on average.[54]

One potential advantage of FAPI is low background activity in the skeleton. In one series, median SUVmax differed modestly between the tracers, at 6.15 for [^{68}Ga]Ga-FAPI-04 against 5.2 for FDG, whereas the corresponding tumor-to-background ratios were 9.2 and 2.55.[53] A similar difference in ratio, 8.6 against 4.3, was found prospectively.[54] This was not consistent across studies, however, as a gastric cancer meta-analysis found that neither SUVmax nor tumor-to-background ratio differed significantly between the tracers.[56]

Lesion morphology is of particular interest, since bone scintigraphy is insensitive in lytic disease and FDG uptake is reduced in osteoblastic metastases.[58] Higher FAPI uptake in osteolytic, medullary and mixed lesions has been reported across several series.[52-54] In sclerotic lesions the uptake data remain mixed. Two series reported markedly higher FAPI SUVmax in sclerotic lesions, with values for FAPI against FDG of 10.52 against 4.45 and 7.7 against 3.7.[51,52] A third study found no significant difference, with a FAPI SUVmax of 4.20 against 4.60 for FDG.[53] Detection nonetheless appears less affected, since lesions identified with FAPI alone were predominantly sclerotic in one cohort.[59] Whether FAPI offers a consistent advantage over FDG in sclerotic metastases thus remains to be established.

Performance may likewise differ according to the primary tumor (Fig. 3). FAPI uptake in bone metastases has been reported to be higher in metastases from breast and lung cancer than from gastrointestinal or neuroendocrine prostate carcinoma.[53] A significant advantage over FDG was found in lung, thyroid and liver cancer in one series,[52] and in lung and gastric cancer in another.[51] The strongest evidence has been reported in invasive lobular breast carcinoma, in which 473 bone metastases were detected with [^{68}Ga]Ga-FAPI-04 against 264 with

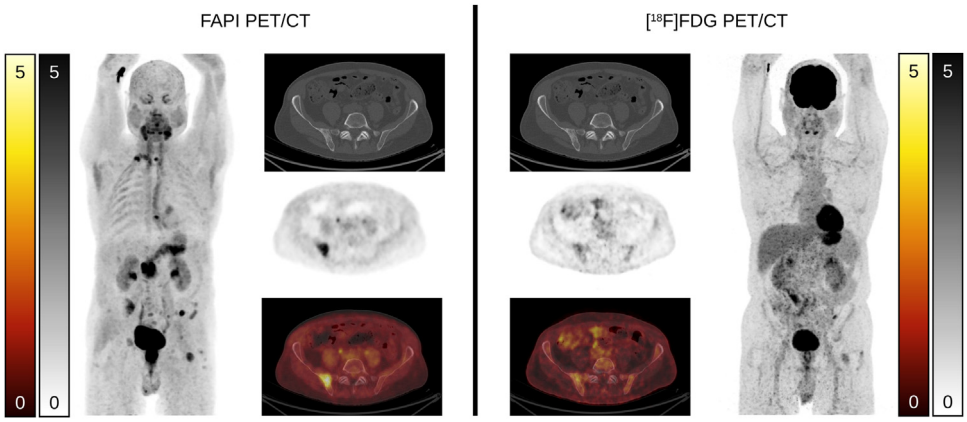


Fig. 3 Representative FAPI and [^{18}F]-FDG PET/CT of a sclerotic osseous metastasis in a patient with rectal adenocarcinoma. A 61-year-old man with high-grade (G3), microsatellite stable (MSS) signet ring cell rectal adenocarcinoma. Maximum intensity projection (MIP) and axial PET/CT images of [^{68}Ga]Ga-LNTH-1363S PET/CT (left) and [^{18}F]-FDG PET/CT (right) are provided. SUVmax: 5.1 ([^{68}Ga]Ga-LNTH-1363S) and 3.8 ([^{18}F]-FDG).

FDG, with mean uptake of 19.1 against 5.3.[60] FAPI is therefore of particular interest in primaries with low FDG avidity.

Clinical relevance

The clinical consequence of the additional bone lesions detected with FAPI appears to depend on the setting. In metastatic disease, a greater number of bone metastases identified on FAPI PET did not alter staging or subsequent treatment,[61] consistent with the observation that patients harboring multiple metastases remain correctly classified irrespective of the number of individual lesions detected.[51] At initial staging the difference may be more consequential. In the prospective lung cancer series, TNM stage assigned on imaging matched the reference standard in 88 percent of patients with Al[^{18}F]F-NOTA-FAPI-04 against 69 percent with FDG, although most of the discrepancy arose from nodal rather than skeletal findings.[54] The clinical relevance of improved skeletal lesion detection may be greatest in oligometastatic disease, where accurate assessment of the number and distribution of metastases can influence both diagnostic classification and treatment strategy.[62] Metastasis-directed therapy has been shown to improve outcomes in selected patients with oligometastatic disease and is increasingly incorporated into multidisciplinary management.[63] In this context, additional osseous lesions detected by FAPI PET may refine the selection of patients for MDT by more accurately defining the extent of metastatic disease, although whether this changes outcomes remains to be established.

FAPI uptake may also carry prognostic information independent of lesion count. In a retrospective cohort of 75 patients with various primary tumors, a bone-lesion SUVmax exceeding 7.7 was associated with shorter median overall survival, 32 versus 45 months ($p = 0.002$), and remained an independent predictor on multivariate analysis. Notably, FDG SUVmax was not prognostic in the same patients.[59] However, this single-cohort finding requires confirmation. The clinical consequence of FAPI compared with FDG in metastatic bone disease, whether in terms of lesion detection or uptake intensity, thus remains to be determined. On current evidence, FAPI PET is most likely to add value in patients whose primary tumor shows low FDG avidity, such as lobular breast, renal cell carcinoma, signet-ring-cell gastric carcinoma and thyroid cancer, and in predominantly sclerotic or marrow-based disease, where metabolic imaging is least reliable.

Specificity and interpretive pitfalls

The improved bone lesion detection by FAPI comes partly at the expense of specificity. FAP is expressed not only by cancer-associated fibroblasts but also by normal activated fibroblasts involved in wound healing and tissue repair,[64] so benign skeletal processes may accumulate the tracer. Degenerative osteophytes, osteoarthritis, fractures, fibrous dysplasia and Schmorl nodes have all been reported as false-positive findings.[33,51,52] In the largest cohort, 15 benign lesions were falsely classified as metastatic with [^{68}Ga]Ga-DOTA-FAPI-04 against 2 with FDG, giving lesion-based specificities of 93.8 and 99.2 percent.[51] A smaller series similarly reported more false-positive lesions with [^{68}Ga]Ga-DOTA-FAPI-04 than FDG, with 10 versus 5 lesions, respectively.[52] Pooled data likewise indicate higher specificity for FDG.[65]

Uptake intensity may overlap between benign and malignant bone lesions. Mean SUVmax was 3.95 in benign lesions against 8.00 in metastases, and although a threshold of 4.1 discriminated between them with an area under the curve of 0.817, the ranges were not separable.[51] Anatomical correlation on CT is therefore essential to interpretation.

The reported sensitivity and specificity depend on how lesions were classified as malignant or benign. Histological confirmation was limited, with tissue diagnosis available in only 2 of 48 patients in one series,[51] and 7 of 68 in the prospective series.[54] The reported accuracy of both tracers therefore rests largely on follow-up imaging rather than histology. While FAPI detects more skeletal metastases than FDG, its effect on overall diagnostic accuracy remains uncertain.

FAP-directed theranostics and radioligand therapy

FAP is a molecular target rather than a metabolic surrogate, and the same inhibitor backbone used for imaging can therefore be labeled with a therapeutic radionuclide, offering a route from diagnosis to treatment.[66] Importantly, preclinical studies show that the antitumor effect of FAP-targeted RLT is mediated by the delivered radiation rather than FAP inhibition.[67,68]

Radioligand therapy in sarcoma

This theranostic option is particularly relevant in sarcoma, where systemic treatment options in advanced disease are limited and prognosis is poor.[19,20] Because FAP-directed radioligand therapy depends on demonstrating that the target is present, FAPI PET serves both to detect disease and to select patients for therapy. The threshold applied in reported series is high FAP avidity, generally an SUVmax of at least 10 on [^{68}Ga]Ga-FAPI-46 PET, in the majority of lesions.[24,69] This requirement restricts eligibility to a defined subgroup, and in a prospective cohort of patients with metastatic soft-tissue sarcoma approximately 45 percent met this threshold.[24]

Clinical experience with FAP-directed radioligand therapy in sarcoma remains limited to small, mostly single-center series and case reports, without randomized or controlled data.[70] The largest experience has been obtained with [^{90}Y]Y-FAPI-46, first reported in a mixed cohort of patients with advanced sarcoma and other solid tumors and subsequently extended in an updated single-center analysis.[69,71] More recent work has employed the cyclic peptide [^{177}Lu]Lu-FAP-2286, which was designed for prolonged tumor retention, in patients with advanced metastatic sarcoma.[72,73] [^{177}Lu]Lu-RTX-2358, a small-molecule inhibitor optimized for prolonged tumor retention, was recently reported in a first-in-human series of six heavily pretreated patients (five with soft-tissue sarcoma), achieving tumor effective half-times over 150 hours.[74] Earlier treatment was also delivered with [^{177}Lu]Lu-FAPI-46 and [^{153}Sm]Sm-FAPI-46.[75,76] These compounds differ mainly in tumor retention. The small-molecule inhibitors used for imaging clear rapidly from tumor, which limits the radiation dose delivered when they are used therapeutically, and longer-retained peptides were developed to overcome this constraint.[77] No study has compared these agents directly to date.

Reported responses have been dominated by disease stabilization rather than tumor regression. In the largest experience with [^{90}Y]Y-FAPI-46, disease control was achieved in 12 of 25 evaluable patients.[71] Patients who achieved disease control had a markedly longer overall survival, with a median of 14.6 months compared with 1.9 months. This benefit was concentrated in solitary fibrous tumor, the subtype with the highest FAP expression.[71] Response across other histologies has been inconsistent, with stabilization or progression reported in different subtypes.[75,78] Overall survival in these heavily pretreated cohorts has generally been short, in the range of several months, consistent with the salvage setting in which the therapy has been applied.[69,72,73] Standardized response criteria have not been established for FAP-targeting PET. In one small pilot study, intensity-based, volumetric, and FAP-derived parameters classified the same patients differently, illustrating the uncertainty in how response should be measured.[73]

FAP-directed radioligand therapy has generally been well tolerated, with toxicity that is predominantly hematologic. Grade 3 or higher thrombocytopenia and anemia have been the principal adverse events with [^{90}Y]Y-FAPI-46, occurring in a minority of patients, and were often difficult to separate from the effects of prior or concurrent systemic therapy.[69,71] Treatment with [^{177}Lu]Lu-FAP-2286 has been associated mainly with low-grade toxicity.[72,73] Taken together, these early results establish the feasibility and safety of FAP-directed therapy and make it the most advanced theranostic approach currently available in sarcoma, with encouraging signals of disease control in selected patients.[70] This evidence remains preliminary, however, based on small cohorts with heterogeneous constructs and dosing, and the selection threshold has not been validated.

Radioligand therapy in metastatic bone disease

FAP-directed radioligand therapy may also have a role in metastatic bone disease, although the evidence is limited. No study has specifically evaluated bone metastases, and the available data come from cohorts defined by primary tumor histology. Nevertheless, the existing evidence consistently demonstrates that FAP-targeted radioligands accumulate in bone metastases and exhibit prolonged retention within these lesions.[77,79,80] For the cyclic peptide [^{177}Lu]Lu-FAP-2286, dosimetry of osseous lesions in patients with advanced adenocarcinomas demonstrated an effective half-life of 44 hours.[77] The albumin-binding construct [^{177}Lu]Lu-LNC1004 showed longer retention in patients with metastatic thyroid and other solid tumors, with an effective half-life approaching 100 hours in bone.[79,80] Reporting on a per-lesion basis is scarce, as responses have generally been assessed at the patient level, but the available data suggest that FAP-directed therapy can produce regression of bone metastases.[77,79] Reductions in bone pain and opioid use have been reported in individual patients.[77] However, transient post-treatment bone-pain flare has also been observed.[79] Hematological toxicity is an inherent concern in this setting. In line with this, grade 3 leukocytopenia and pancytopenia have been reported in patients with diffuse bone-marrow involvement.[77] Overall, current data demonstrate uptake and prolonged retention in bone metastases, with preliminary signs of clinical benefit that require confirmation in prospective studies.

Future perspectives

FAPI is increasingly emerging as a complementary tracer to FDG rather than a replacement. FAPI detects low-grade and

stromal-rich disease that may be missed on FDG, while FDG retains important advantages for tumor grading, prognostication, and specificity in selected sites. This complementary biology may ultimately favor subtype-specific imaging strategies or dual-tracer protocols instead of a single universal tracer. Early studies indicate that same-session, dual-tracer FDG and [^{68}Ga]Ga-FAPI-46 PET is feasible and can combine the strengths of both tracers.[81,82] Whether this approach improves patient management sufficiently to justify additional cost and radiation exposure remains an important question for prospective evaluation. Available evidence provides limited insight into the clinical impact of additional lesions detected by FAPI PET, and whether these findings influence staging, treatment selection, or outcomes remains an important area for future investigation.

For FAP-targeted radionuclide therapy, proof of feasibility has largely been established. The central challenge is now demonstrating therapeutic efficacy. Prospective controlled studies are needed to determine whether treatment provides clinically meaningful benefit compared with the natural history of advanced disease. At the same time, optimization of patient selection and response assessment will be essential. The working SUVmax threshold of $\geq$10 is met by fewer than half of metastatic soft tissue sarcomas in reported cohorts. Validated imaging criteria for treatment eligibility and standardized response criteria would improve comparability across studies and facilitate future clinical implementation.

Continued development of next-generation therapeutic ligands is likely to further improve the therapeutic potential of FAP-directed radionuclide therapy. Small-molecule FAP inhibitors achieve high tumor uptake but relatively short tumor retention, consequently limiting absorbed dose. Novel approaches including cyclic peptides, albumin-binding conjugates, and multimeric constructs aim to prolong intratumoral retention and increase tumor absorbed dose while maintaining favorable normal tissue kinetics. In parallel, the therapeutic landscape is expanding beyond β-emitting radionuclides. The first sarcoma-specific clinical evaluation of an α-emitting FAP ligand has begun with the ATLAS trial investigating [^{225}Ac]RTX-2358.[83] Combination strategies also warrant investigation. Given the stromal targeting mechanism of FAP-directed therapy, integration with immunotherapy or other systemic treatments represents a biologically attractive direction that is currently supported primarily by preclinical evidence. FAP-directed radioligand therapy could potentially be combined with external-beam radiotherapy (EBRT) to exploit their complementary treatment characteristics. Whereas radioligand therapy delivers radiation systemically, EBRT provides highly localized dose deposition and could therefore be used to consolidate dominant or oligometastatic lesions. A major unresolved challenge, however, is how to quantify and interpret the combined radiation dose. Because EBRT and radioligand therapy differ in dose rate, spatial and temporal dose delivery, and radiobiological effects, their absorbed doses cannot simply be added.[84] A robust framework is therefore required to relate the dose contributions of both modalities to their combined biological effects in tumors and organs at risk. Nevertheless, this treatment concept is not entirely unprecedented, as combinations of EBRT with other radioligand therapies, most notably [^{177}Lu]-PSMA-617, have already been explored in preclinical and clinical studies, supporting the feasibility of combining systemic radioligand therapy with focal EBRT.[85]

Finally, future research should broaden the spectrum of diseases under investigation. Most available evidence has been generated in soft tissue sarcoma, while bone sarcomas, chordoma, and several rare musculoskeletal malignancies remain largely unexplored. Expanding clinical experience in these entities will be important to define where FAPI imaging and therapy can provide the greatest clinical value.

Conclusion

FAPI PET has emerged as a promising imaging modality in musculoskeletal oncology, particularly for soft tissue sarcoma and metastatic bone disease, where it frequently provides higher lesion detection than FDG. Because FAPI and FDG reflect different tumor biology with distinct strengths, the two are best regarded as complementary rather than competing tracers. The ability of FAPI PET to identify patients for FAP-directed radioligand therapy further supports a theranostic approach. However, current evidence remains limited, and prospective studies are needed to determine its effect on clinical management and patient outcomes.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Constantin Lapa reports a relationship with Blue Earth Diagnostics Ltd that includes: consulting or advisory. Constantin Lapa reports a relationship with PentixaPharm that includes: consulting or advisory. Constantin Lapa reports a relationship with Pfizer that includes: consulting or advisory. Constantin Lapa reports a relationship with Novartis that includes: consulting or advisory. Robert Seifert reports a relationship with Novartis that includes: speaking and lecture fees and travel reimbursement. Robert Seifert reports a relationship with Boston Scientific Corporation that includes: speaking and lecture fees and travel reimbursement. Robert Seifert reports a relationship with Horton Health Foundation that includes: funding grants. Robert Seifert reports a relationship with Else Kröner Fresenius Foundation that includes: funding grants. Robert Seifert reports a relationship with Boehringer Ingelheim Funds that includes: travel reimbursement. Axel Rominger reports a relationship with Siemens AG that includes: funding grants and speaking and lecture fees. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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CRediT authorship contribution statement

Anja Dietze: Conceptualization, Visualization, Writing — original draft, Writing — review & editing. **Daniel M. Aebersold:** Writing — review & editing. **Axel Rominger:** Writing — review & editing. **Constantin Lapa:** Resources, Writing — review & editing. **Robert Seifert:** Conceptualization, Supervision, Writing — original draft, Writing — review & editing.

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