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The Clinical Impact of FAPI PET Imaging: HCC, CCC, CUP & Peritoneal Carcinoma

Emil Novruzov Eduards Mamlins, Yuriko Mori, Jens Cardinale, and Frederik L. Giesel

In recent years, FAP-targeted imaging has emerged as a highly-promising modality as a pan-cancer agent. Until now, several studies and review articles have focused on efficacy of FAPI imaging in epithelial malignancies with a high global incidence and prevalence such as lung cancer or GI-tumors. This work sought to shed light on diagnostic performance and clinical impact of FAPI imaging in rather low-incidence tumor-entities, which are nevertheless characterized by a poor outcome.

Introduction

The great success with PSMA- and SSTR-directed patient management in recent decades has reinforced the concept of personalized medicine. This concept has gained extra attention with the recent introduction of FAP-directed imaging owing to small molecule radiolabeling of FAP ligands, that is, ^{68}Ga- or ^{18}F-labelled FAPI (fibroblast activation protein inhibitors). In contrast to prior theranostic targets, FAP enables targeted radiopharmaceuticals for a wide variety of epithelial malignancies that appears to qualify FAPI as the novel and the only pan-cancer agent with theranostic utility.[1,2]

So far, the only widely applied pan-cancer agent is [^{18}F]FDG, which has been dominating oncological molecular imaging due to its vast potential for diagnosis of practically all tumor entities with moderate to high Warburg effect. Indeed, [^{18}F]FDG imaging has been shown to outperform the conventional radiological imaging in most of clinical settings for numerous tumor entities, although its diagnostic accuracy and use have suffered from its unspecific nature, pitfalls and drawbacks such as prescan patient preparation, high physiological background or limited use in tumor entities with lower glucose metabolism. In the light of these drawbacks, the added value of [^{18}F]FDG imaging has often been critically questioned by expert panels, whether this would justify the substantially increased economic burden to healthcare systems. Thus, for instance in Germany, [^{18}F]FDG imaging is being reimbursed as standard imaging by conventional authorities for only few oncological diagnoses such as hematological or pulmonary malignancies. Whereas the management plan of remaining oncological entities integrates [^{18}F]FDG imaging mostly as a part of recurrency work-up.[3-6]

In this regard, the novel FAP-targeting pan-cancer agents need to be investigated in all aspects of oncological management from primary staging to therapy response monitoring and also recurrency staging with respect to its cost-effectiveness and diagnostic accuracy. A closer look at the bibliography revealed that radiolabeled FAPI tracers have been deployed mostly for the investigation of pancreatic cancer (18.2%), colorectal cancer (13.9%), gastric cancer (11.4%), liver and bile duct cancer (12.9%), breast cancer (13.2%), and lung cancer (12.2%), where mostly ^{68}Ga- (72.7%) and ^{18}F- (17.5%) labelled FAPI-PET tracers have been deployed. A substantial number of publications on FAPI applications were case reports and series, though. National and international guidelines require high-level published evidence and clinical experience to include the molecular imaging methods.[7-9]

The current evidence level regarding the aforementioned tumor entities has been elucidated by several research groups, recently.[10-14] Therefore, in this comprehensive literature review, we aim to evaluate and summarize the current evidence of low-incidental, however, clinically relevant tumor entities with a high lethal burden. Exclusion criteria were: duplicates, non-English language papers and studies outside the field of interest.

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Tumor Microenvironment and the Role of CAFs

Meanwhile, evidence has proven the pivotal role of tumor microenvironment (TME) for the initiation and development of the so-called cancer hallmarks such as proliferation, immune response evasion, cell death resistance, angiogenesis, invasion and progress. Although the exact signaling pathways and interaction patterns are still largely unknown, the prerequisite for this phenomenon is certainly a complex interaction of malignant cells with the surrounding extracellular matrix, stromal cells and immune cells. The so-called "soil-and-seed theory" might be an elucidating explanation for this phenomenon, as malignant cell foci have been shown to start modulating its surrounding after reaching a size of at least 2 mm, which in turn triggers a positive feedback loop of progression (Fig. 1). This distinct interplay might be cause for intriguing therapy outcome in numerous clinical settings in oncological patient management.[15-17]

TME has been shown primarily to consist of tumor-associated macrophages (TAMs) and cancer-associated fibroblasts (CAFs), which are, however, also found in some benign conditions including inflammatory or fibrotic processes. CAFs appear to occur in various subsets with varying proportion of cellular biomarkers which seem to arise from highly different sources including resident tissue fibroblasts, bone marrow, and epithelial cells.[18,19] CAFs modulate ECM via its various cellular biomarkers, secretion of various chemokines and cytokines and, thus, promote the tumor growth and invasiveness.[20]

The most relevant biomarker of CAFs is fibroblast-activation-protein-α (FAP) which is proven to be upregulated in over 90% of epithelial malignancies. FAP has been demonstrated to correlate with tumor growth and poor outcome. This is a membrane protein with both postproline peptidase (exopeptidase) and endopeptidase activity from serine protease family that are responsible for modulation of peptide growth factors in TME and ECM-remodeling. Especially tumor entities with extensive tumor stroma have been shown to exhibit upregulation of FAP expression, for example, breast, colorectal, pancreatic, and lung cancer. Additionally, normal human adult cells and quiescent fibroblasts show no FAP expression that makes FAP an attractive target both for diagnostic and therapeutic purposes. Among a number of approaches attempting to exploit this target, only small-molecule tracers with radiolabeled FAPI could show a clinical breakthrough.[21-23]

FAP-Targeted Imaging and FAPI

Among several approaches targeting FAP for diagnostic or therapeutic purposes, only small molecule radiopharmaceuticals have found a way to effective clinical utilization. Jansen et al. were the first to develop a quinoline-containing core compound, N-4-quinolinoyl-Gly-(2S)-cyanoPro scaffold, as a selective FAP inhibitor (FAPI). The Johns Hopkins group were then the first to develop and preclinically investigate the pharmacophore appropriate for radiolabeling,[24,25] whereas Heidelberger research group achieved the clinically breakthrough by development of FAP inhibitors (FAPI) that inhibit the enzymatic action of FAP with a high affinity leading to internalization of the ligand-receptor complex.[26-28] As the current bibliographic results underscore, FAPI agents have been mostly radiolabeled by either ^{68}Ga or ^{18}F, even though new approaches employing the radiolabeling via ^{99m}Tc or ^{188}Re might have certain advantages over FAPI PET tracers.[8,9,29] Most ^{68}Ga-labelled FAPIs are suitable for theranostic use due to its 1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA)-chelator, whereas [^{18}F]AlF-FAPI-74 displays only diagnostical value due to its NOTA-chelation.[30]

Relatively limited intra-tumoral retention time represents the main drawback of quinoline-based FAPI agents, preventing to unfold its fully potential especially for therapy radionuclides with longer half-lives. This drawback has been attempted to be overcome by chemical modification of quinoline-based small-molecule inhibitors or developing novel FAP-binding radiotracers utilizing cyclic peptides as binding motifs. An alternative approach might be to optimize the treatment protocol with theranostic agents based upon quinoline-based FAPI.[12,31-34] This topic is, however, beyond the scope of our review.

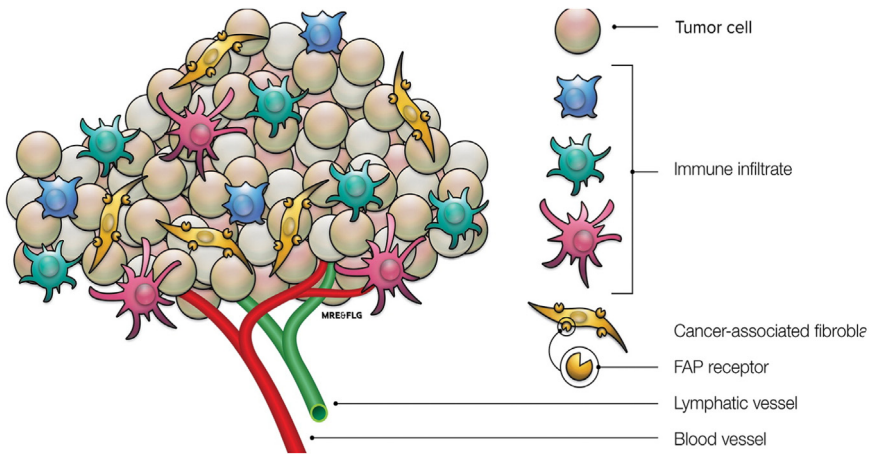

Figure 1 Depiction of tumor microenvironment consisted of various cell lines and matrix elements such as basement membrane, immune cells, vascular network, and cancer-associated fibroblasts (CAF), adapted from.[5]

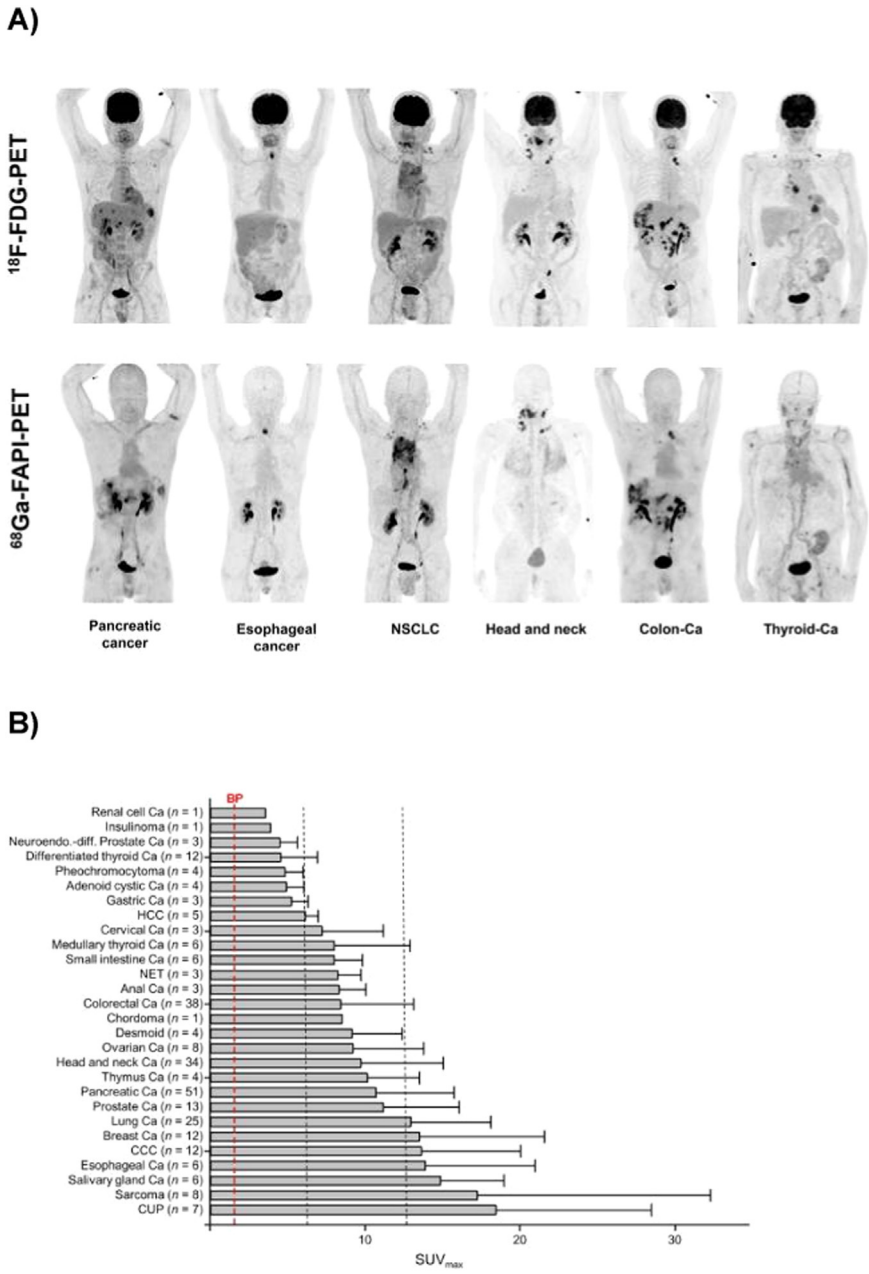

Figure 2 (A) Intraindividual comparison of FDG and FAPI tracers in 6 different tumor entities within a time interval of 9 days. (B) ^{68}Ga-FAPI biodistribution in various cancers. Notably, in contrast to [^{18}F]FDG, all entities displayed a moderate favorable to excellent tumor-to-background ratio due low background signal. Adapted from.[35,36]

The clinical translation of quinolone-based FAPI agents revealed highly promising results for a wide variety of epithelial malignancies with excellent lesion contrast. To the first time, [^{68}Ga]FAPI-04 was evaluated in a cohort of 50 patients with various tumor entities in a head-to-head comparative manner with [^{18}F]FDG imaging by Giesel et al. This evaluation highlighted the favorable pharmacokinetics and feasibility of this novel tracer family and besides, lacking prescan patient preparation and an excellent safety profile underlined its potential for the clinical use (Fig. 2A).[35] In the following study in a cohort of 80 patients with 28 tumor entities, the authors reported an overall favorable tumor-to-background ratio (TBR) especially for the epidemiologically relevant tumor entities such as breast, lung, pancreatic, head–neck, and colorectal cancer (Fig. 2B).[36] Further data in the literature supported the efficacy of FAPI agent for pancreatic, breast, ovarian, gastro-intestinal and pulmonary cancer.[12] However, exact clinical impact of FAPI agents regarding those entities is still missing, as quantification of diagnostic performance in terms of positive predictive (PPV) and negative predictive value (NPV) was beyond the scope of those studies. Currently, ongoing studies in the pipeline aimed to gain approval from according authorities.[37]

Various works could shed light on efficacy of FAPI agents primarily for the high-incidental, globally relevant tumor entities and those entities that dominate the current research

landscape. However, the added value of FAPI agents need to be evaluated with respect to the so-called low-incidental, however, highly lethal tumor entities as well. Thus, this review aimed to elucidate the current status of FAPI research landscape in this regard.

1. Primary Liver Malignancies

a) Hepatocellular carcinoma

Background

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy, arising from the malignant transformation of hepatocytes, with a high lethal burden. HCC arises typically from a chronic fibrotic/cirrhotic process in the liver parenchyma caused by infectious diseases such as Hepatitis B & C. In developed countries, this process is mostly induced by alcoholic- (ASH) and non-alcoholic steatohepatitis (NASH), and to a lesser extent, inherited metabolic disorders such as hemochromatosis, porphyria, and type-1 glycogen storage diseases, though. To date, the surgical therapy has been the only curative therapy; namely, surgical resection of a local tumor with a clear resection margin or conduct of orthotopic liver transplantation (OLT), if prerequisites for Milan criteria are fulfilled. Milan criteria are defined as the presence of a single tumor focus up to 5 cm in diameter or two to three tumor foci 3 cm in diameter with no evidence of macroscopic vascular invasion.[38-40]

Nevertheless, a relatively high intrahepatic recurrence rate is observed following local resections, whereas conduct of OLT is associated with a better 5-year-survival rate.[41,42] Therefore, a timely and accurate staging work-up seems to be essential for an optimal therapy management. In addition, the liver is the first target organ for metastases of gastro-intestinal tract, which is, however, beyond the scope of this review.

The Specific Role of FAP in HCC and Limitations of Conventional Imaging

HCC is characterized by highly enhanced angiogenesis on a cirrhotic or fibrotic liver parenchyma, leading to vascular hyperpermeability, remodeling of the extracellular matrix, and endothelial cell activation which is further promoted by dual blood-supply of liver. These alterations and unique conditions regarding blood supply in TME complicate an adequate therapy approach due to aggressive progression and infiltration with therapy resistance even at initial stages.[41] Recent research underlines desmoplastic response in liver parenchyma, where CAFs have been shown to play a pivotal role in the tumorigenesis on cirrhotic changed liver parenchyma. Those seem to originate from quiescent hepatic stellate cells because of a sustained wound-healing response to chronic liver injury.[42,43]

Increased arterial uptake of tumor focus followed by washout is specific for the presence of HCC accompanied by high tumor marker levels, which was, however, reported to display a substantial false-negative rate of 20%-30% in small lesions of 1 and 2 cm in size with atypical features. Moreover, MRI has been shown to outperform contrast-enhanced CT with a diagnostic accuracy rate of 80% and 68%, respectively. The diagnostic accuracy of conventional imaging modalities sinks even further in detecting sub-centimetric lesions with 31% for contrast-enhanced CT and 48% MRI, respectively. Furthermore, early detection of lymph node or osseous metastases in initial stages is also challenging.[41,44,45] Notably, [^{18}F]FDG imaging displays no better diagnostic performance than conventional imaging for primary staging. The main advantage of [^{18}F]FDG imaging relies in detection of extrahepatic metastases pooled sensitivity and specificity of 46% and 95%, respectively, and recurrence work-up pooled sensitivity and specificity of 65% and 95%, respectively. High background uptake of liver accompanying cirrhotic processes and a lack of specificity seem to be the limiting factors for [^{18}F]FDG diagnostic[46] (Table 1).

Current State of the Research in FAP Imaging

Various meta-analyses underline the excellent sensitivity and high specificity of FAPI imaging in the detection of primary liver cancer, as Jiao et al. reported a sensitivity of 96% (95% CI: 0.73-0.99) and specifity of 76% (95% CI:0.01-1.00), respectively. The meta-analysis by Singh et al. revealed even a slightly better pooled sensitivity of 98.5% (95% CI: 91.7%-100%) for FAPI imaging, while pooled sensitivity for [^{18}F]FDG imaging was reported to be 60.9% (95% CI: 47.9%-72.9%). FAPI imaging appears to display substantially improved diagnostic performance than conventional imaging even for intrahepatic lesions smaller than 2 cm in diameter. Regardless of FAP expression intensity, FAPI imaging has been shown to outperform [^{18}F]FDG imaging. Certain studies, e.g. of Shi et al. and Zhang et al., underlined the potential of FAPI imaging with respect to accurate discrimination of [^{18}F]FDG negative intrahepatic lesions with respect to malignancy. For instance, Zhang et al. reported a sensitivity and an overall diagnostic accuracy of 96.0% and 83.8%,

Table 1 Overview of Cellular Biomarkers on Normal Fibroblasts and CAFs in Tumorigenesis of HCC (Adapted From[43])

	Quiescent Hepatic Stellate Cells (Fibroblast)	Quiescent hepatic Stellate cells (Myofibroblast)	Cancer Associated Fibroblasts (CAFs)
Morphology	Spindle shape with intracellular fat-droplets	Spindle shape	Spindle shape
Origin	Mesoderm	Quiescent hepatic stellate cells	Activated hepatic stellate cells
Location	Space of Disse, sinusoidal spaces	Periportal lesion	Tumor stroma
Biological Markers	Desmin	αSMA, p75NTR	αSMA, COL11A1, FAP
Function	Store the vitamin A and fat	Wound healing fibrosis	Tumor progression

respectively.[47-51] Moreover, based upon FAPI uptake pattern, an accurate discrimination of primary and secondary liver malignancies does not seem to be feasible, as dynamic FAPI PET acquisition combined with kinetic modelling might overcome this drawback.[52]

In addition, FAPI imaging has been shown to highlight also in accurate detection of extrahepatic metastases, as Liu et al. pointed out a high sensitivity for detection of metastatic disease with 91% (95% CI: 0.90-0.93) compared to [^{18}F]FDG PET/CT with a sensitivity of 71.4% (95% CI: 0.68-0.74). The per-lesion analysis by Singh et al. found out a pooled sensitivity of 94.3% (95% CI: 90.6-96.8) for FAPI PET/CT that underscores the overall highly accurate detection rates of FAPI imaging in HCC.[52,53]

Conclusively, FAPI imaging emerges as a highly promising imaging modality for the primary as well as re-staging of HCC. However, larger, prospective designed studies are warranted to identify the prognostic potential and clinical impact of FAPI imaging.

b) Biliary Tract Cancer (BTC)

Biliary tract cancer represents all types of cholangiocellular carcinoma (CCC) arising from the epithelial lining of biliary tree including intrahepatic and extrahepatic parts. This is a rare cancer type with insidious-onset and poor outcome. Even aggressive surgical resection accompanied by adjuvant therapy protocols usually cannot spare patients from an unfavorable outcome due to frequently recurrent course of disease or advanced stage at initial diagnosis. Conventional imaging modalities including [^{18}F]FDG imaging have a limited diagnostic accuracy. Currently, the only clinical scenario with a potential curative-intent therapy goal is represented by the surgical resection of the primary in an early-stage CCC, which is encountered up to 20%. [^{18}F]FDG imaging demonstrates its supremacy mainly in detecting extrahepatic CCC with a sensitivity of 77%-100% compared to 51.3% for radiological imaging and in nodal staging a sensitivity and specificity rate of 88.4% and 69.1%, respectively. High background uptake of liver, however, hinders an adequate diagnostic power for intrahepatic lesions or lesions adjacent to liver. Moreover, frequent local infections and medical devices such as stenting in the biliary tree hinder an adequate diagnostic performance of [^{18}F]FDG imaging. Thus, [^{18}F]FDG imaging has been shown to display an overall sensitivity of only 50% in CCC.[52,54-57]

There is an unmet clinical need especially for intrahepatic lesions of CCC. CCC is one of the tumor entities with a distinct desmoplastic response which is highly promising for the use of FAPI imaging.[58,59] The intralesional pattern of desmoplastic response appears to be varying depending upon the local composition of tumor and fibrous tissue. Notably, fibrotic areas are characterized by steadily decreased arterial blood supply with large interstitial spaces. In accordance with this phenomenon, gadoxetate-enhanced MRI has its limitations for those areas, as this yields its best diagnostic performance in hypervascular regions with increased perfusion. Thus, the conclusion can be drawn that the utility of FAPI PET/CT scan might display a positive correlation with increased aggressiveness, i.e. increased FAP expression of CCC. The immunohistochemical examination results of patient cohort in the study by Pabst et al. underscored this assumption. Zhang et al. indicated increased efficacy of FAPI PET/MRI than both FAPI PET/CT and [^{18}F]FDG PET/CT in terms of accurate lesion delineation and increased detection rates for intrahepatic lesions.[55,60-62] To combine the advantages of both modalities, widespread use of FAPI PET/MRI could be an alternative, which, however, would face serious logistic and reimbursement issues.

Regarding the use of FAPI PET in CCC, there is only few data in the literature. Pabst et al. investigated the tumor uptake pattern of [^{68}Ga]FAPI-46 in a small cohort of 10 patients, that is, two patients in primary staging and eight patients in re-staging, in a comparative manner with conventional imaging modalities including [^{18}F]FDG imaging, of which six patients had intrahepatic CCC and four patients had extrahepatic lesions, respectively. [^{68}Ga]FAPI-46 exhibited a significantly higher tumor uptake in terms of SUV_{max} value compared to [^{18}F]FDG imaging for primary tumor, lymph nodes, and distant metastases, for example, for primary lesions 14.5 vs 5.2 or for distant metastases 9.5 vs 5.3. [^{68}Ga]FAPI-46 was highlighted especially due to excellent lesion contrast of intrahepatic lesions compared to that of [^{18}F]FDG imaging with a TBR of 12.1 and 1.9, respectively, although the SUV_{max} value itself did not vary significantly between intrahepatic and extrahepatic lesions. Moreover, [^{68}Ga]FAPI-46 appeared to outperform [^{18}F]FDG imaging in per-lesion based analysis regarding lymph node (10 vs 11) and distant metastasis (4 vs 6) detection. Because of advanced stage during PET scans, a therapy changes following [^{68}Ga]FAPI-46 imaging was not observed. Jinghua et al. assessed the efficacy of FAPI imaging in a prospective study with 47 patients which revealed a superior diagnostic performance compared to [^{18}F]FDG imaging regarding the detection of primary lesions (97.62% vs 85.71%), lymph node (90.05% vs 87.06%) and distant metastases (100% vs 83.67%). In contrast to results of Pabst et al., this study showed a significantly increased SUVmax value with FAPI PET regarding all intrahepatic and extrahepatic lesions. Particularly favorable lesion contrast for intrahepatic lesions was also observed in this study as reported by Pabst et al. Despite an overall more favorable sensitivity, clinical impact of FAPI PET did not vary from that of [^{18}F]FDG imaging in terms of therapy change, whereas this remained higher than that of conventional modalities such as CT or MRI.[62,63]

In conclusion, despite the scarcity of literature data, initial studies indicate FAPI PET as a highly promising agent in management of CCC. Hence, further studies with larger patient cohorts are warranted to assess the diagnostic performance and clinical impact of FAPI PET imaging in CCC.

2. Carcinoma of Unknown Primary (CUP)

Cancer of unknown primary (CUP) represents a heterogeneous group of cancers with a unifocal or widespread metastatic spread without a detectable primary origin through conventional clinical and imaging methods. This group of

entities accounts for 8% of total lethal burden of malignancies despite a globally low-incidence of only 2%-5%, which seems to rely on its insidious-onset with aggressive clinical course and, sometimes, intriguing metastatic pattern compared to cases with known primary. Mean age at disease-onset is 65-90 years with a slight male predominance. The common histology of CUP consists of adenocarcinomas of well or moderate differentiation (60%), undifferentiated or poorly differentiated adenocarcinomas (30%), squamous-cell carcinomas (5%), and undifferentiated neoplasms (5%). The autopsy series in previous decades reported a primary lesion detection rate of 73% which eventually revealed a heterogenous pattern, that is, 27% pulmonary, 24% pancreatic, 8% hepatobiliary tract tumors, 8% renal or adrenal tumors, 13% gastrointestinal tumors, lung (27%) and 7% genital system. Otherwise, liver and lymph nodes are the most frequent sites of metastases with 45%-50% and 35%, respectively, followed by lung, bone and brain with 31%, 28% and 15%, respectively.[64-66] A notable subset of CUP is also cervical lymph node metastasis of squamous-cell carcinoma constituting for 5% of all head and neck cancers.[67]

European Society of Medical Oncology (ESMO) recommends an extensive diagnostic work-up including clinical methods and conventional radiological imaging such as MRI, Mammography and CT for the identification of primary lesions, so that [^{18}F]FDG imaging remains only as a second-line imaging technique for detection of disease extent in patients with uni- or oligometastatic spread and also cervical lymph node metastasis of squamous cell carcinoma.[65] The current evidence indicates a high clinical impact and detection rate of [^{18}F]FDG imaging, as a therapy change rate of up to 69% has been reported following [^{18}F]FDG PET/CT in patients with CUP owing to detection of primary lesions or metastatic spread. The recent meta-analyses and systematic reviews underline an overall sensitivity of 41%-74 % with [^{18}F]FDG PET/CT. Notably, the meta-analysis by Willemse et al. reported varying sensitivity of [^{18}F]FDG imaging based upon the metastatic site, as the most favorable diagnostic performance was achieved in patients with brain (74%) or hepatic metastases (54%) compared to patients with peritoneal or lymph node metastases (37%-38%). Moreover, Saidha et al. reported a superior sensitivity of [^{18}F]FDG imaging for cervical than extracervical CUP with 61% and 40%, respectively.[68-70]

Despite an overall appreciable diagnostic performance of [^{18}F]FDG imaging in CUP, there is room for improvement in diagnostic accuracy. Given the heterogeneity of CUP, as a novel pan-cancer agent, FAPI PET might act as a complementary tool in CUP work-up especially for the [^{18}F]FDG negative cases. The efficacy of FAPI PET in CUP has not been extensively investigated, yet. The few existing studies, however, yielded promising results. In this regard, Chen et al. investigated the efficacy of [^{68}Ga]Ga-DOTA-FAPI-04 in a heterogenous cohort of 68 patients with unclear [^{18}F]FDG findings in the context of primary staging and re-staging by dividing into several subgroups. Detection rate of [^{68}Ga]Ga-DOTA-FAPI-04 for primary lesion was 66.7%, while tumor stage upgrading was recorded as 33.3%. Moreover, in the subgroup with suspected recurrency, this was validated in 87% of patients. The authors reported an overall per-lesion based diagnostic performance in terms of the sensitivity, specificity, PPV, and NPV 94.5%, 58.2%, 84.0%, and 82.1%, respectively.[71] Gu et al. investigated the FAPI uptake pattern of [^{18}F]FDG negative lesions prospectively in a cohort of 18 patients with head and neck cancer of unknown primary (HNCUP). FAPI PET could detect primary lesion in 38% of cases and displayed an overall moderate to high FAPI uptake (SUV_{max}, 8.79; 2.6-16.5) with an excellent lesion contrast.[72] Shu et al. also investigated FAPI PET prospectively in a cohort of 44 patients with an equivocal or negative [^{18}F]FDG lesions that displayed an overall detection rate of 68% detection rate. Notably, FAPI PET could detect malignancy in all patients with equivocal [^{18}F]FDG findings, whereas an accurate discrimination was possible for [^{18}F]FDG negative findings only in 55% of cases.[73]

Regarding the complementarity of [^{18}F]FDG and FAPI tracers, the Cologne researcher group suggested a remarkable acquisition protocol, that is, a single-session/dual-tracer PET/CT protocol, which holds the promise exploiting the synergistic effect of these two tracers by combined application at once (Fig. 3). The preliminary results underlined an enhanced

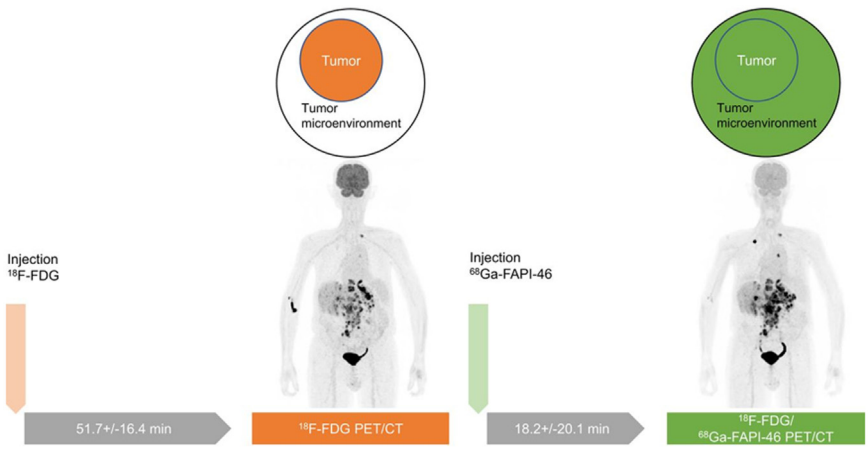

Figure 3 The schematical overview of single-session/dual-tracer PET/CT protocol with combination of [^{18}F]FDG and FAPI tracers, *adapted from*.[74]

lesion contrast and increased detection rate of malignant lesions.[74,75] From this point of view, this protocol might be a viable option for the use in patients with CUP and even for further entities, that are known to have only a moderate diagnostic success with [^{18}F]FDG or FAPI PET imaging separately. This novel concept warrants, however, further investigation in larger, multi-centrical studies.

3. Peritoneal Carcinoma

The peritoneal involvement in many cancer types represents advanced stage disease with a poor outcome and, thus, is a highly relevant, prognosis-crucial factor in patient management. This is most encountered in gastro-intestinal tumors and gynecological malignancies, as the majority of peritoneal metastases has the epithelial origin. Once detected, this compels a therapeutic shift to palliative approach, while alternative therapies such as cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (HIPEC) might substantially prolong survival in well selected cases. Owing to spatial structure, peritoneum displays a distinct pattern of metastatic distribution including intraperitoneal seeding, direct invasion and hematological or lymphatic spread, which poses challenges for imaging experts in regular clinical care.[76]

The mainstay of detection and assessment of peritoneal metastasis burden is still CT, as this offers a reliable, fast and cost-effective option. However, CT examination has been shown to underdiagnose the subtle small lesions and underestimate peritoneal cancer index (PCI) especially in patients with absence of concordant ascites and limited intraabdominal fat, which is important for patient selection for cytoreductive surgery. [^{18}F]FDG imaging, on the other hand, has also its own limitations regarding accurate detection of peritoneal involvement. High background uptake in normal organs, very small nodular lesions of peritoneum with < 5 mm and relatively low-metabolic activity in certain tumor entities do not allow a substantial added benefit of [^{18}F]FDG imaging.[76-78]

Given the epithelial origin of majority of peritoneal metastases, FAPI PET imaging may emerge as a promising tool to address this clinical gap. Literature evidence in this regard is still limited; however, the existing data underscores the potential of FAPI PET imaging. A meta-analysis involving the head-to-head comparison of [^{18}F]FDG and FAPI PET imaging by Gege et al. revealed a lesion-based pooled sensitivity of 27.3% (95% CI, 11.2%-43.4%) and 99.9% (95% CI, 99.5%-100.0%), respectively. Also, patient-based sensitivity was more favorable for FAPI imaging than [^{18}F]FDG imaging with a pooled sensitivity of 98.2% (95% CI, 96.1%-100.0%) and 55.9% (95% CI, 33.9%-77.9%), respectively.[79,80] Additionally, Fu et al. reported a significantly increased accuracy of FAPI imaging in detection of advanced peritoneal lesions (PCI $\geq$ 20) in their retrospective, single-center study involving gastric cancer patients, as a high peritoneal metastasis burden of PCI $>$ 20 indicates a poorer outcome, compelling more aggressive therapy regime.[81,82] A similar result was also reported by Dong et al., as FAPI imaging displayed a higher PCI than [^{18}F]FDG with a median value 11 an 4 ($P < 0.001$), respectively.[83] Another meta-analysis by Wang et al. conducted a comprehensive investigation of all types of hybrid images involving [^{18}F]FDG PET/CT or -MRI and FAPI PET/CT or -MRI imaging in patients with gastric cancer, in which FAPI imaging outperformed [^{18}F]FDG with a sensitivity of 100% vs 44.7%, respectively.[84] The meta-analysis by Sun et al. assessed the efficacy of FAPI imaging in peritoneal involvement of gynecological malignancies, as this evaluation revealed also a superior sensitivity of FAPI than [^{18}F]FDG imaging with 98% (95% CI = 0.93-1) and 71% (95% CI = 0.55-0.86), respectively.[85]

Table 2 FAP-RADS Version 1.0 for Reporting Findings in FAP Imaging, Adapted From[86]

Score	Description
FAP-RADS 1 (Benign)	Typical benign FAP ligand uptake in normal organs (such as joints or background activity)
FAP-RADS 2 (Likely benign)	Equivocal lesions with slight to intense FAP ligand uptake with no suspected anatomical correlate (degenerative/inflammatory changes, post-traumatic or postinterventional changes)
FAP-RADS 3 (Suggestive of malignancy)	
FAP-RADS 3A	Equivocal uptake in sites typical for the "suspected malignancy" without anatomic correlate Follow-Up Imaging recommended
FAP-RADS 3B	Equivocal FAP ligand uptake in sites typical for the suspected malignancy with (un-)specific anatomic correlate or highly suspected lesions (morphologic correlate) with no significant FAPI uptake; follow-up imaging or biopsy recommended
FAP-RADS 4 (Malignancy highly likely)	Intense FAP ligand uptake* in sites typical for suspected malignancy with unspecific or no anatomic correlate; biopsy recommended
FAP-RADS 5 (Consistent with malignancy)	Intense FAP ligand uptake* in sites typical for the suspected malignancy with corresponding findings on conventional imaging; biopsy or initiation of therapy (surgery, radiotherapy, or chemotherapy) recommended
Overall RADS score (ORS)	Defined by the highest FAP-RADS score of any of the individual target lesions

*Intense FAP ligand uptake defined as 3-fold of SUV_{max} in blood pool in descending aorta.

A distinct phenomenon of peritoneal involvement might represent the peritoneal CUP. This entity is rare with very poor outcome. The accurate diagnosis and identification of disease extent is particularly challenging in cases with small-nodular lesion distribution, as HIPEC in well-selected patients may still be a good option. Such cases might also be appropriate for the conduct of single-session/dual-tracer PET/CT protocol (Fig. 3).[74]

Conclusion

The initial data highlighted FAPI PET imaging as a highly-promising diagnostic tool in rare cancer entities. While this might replace [^{18}F]FDG imaging in certain clinical scenarios, special acquisition protocols, i.e. single-session/dual-tracer PET/CT protocol, could exploit the complementary strengths of those two pan-cancer tracers in entities such as CUP. The ongoing research should focus on diagnostic performance and clinical impact of FAPI imaging including rare tumor entities as well, which may be facilitated by implementation of the recently introduced standardized reporting framework (FAP-RADS Version 1) in regular clinical care and clinical trials (Table 2).[86]

Declaration of competing interest

FLG has a patent application for quinolone-based FAP-targeting agents for imaging and therapy in nuclear medicine and shares a consultancy group for iTheranostics. FLG is also an advisor at ABX, Telix, Alpha Fusion and SOFIE Biosciences. The other authors declare no conflict of interest regarding this manuscript.

CRediT authorship contribution statement

Emil Novruzov: Writing – original draft. **Eduards Mamlins:** Resources, Investigation. **Yuriko Mori:** Writing – review & editing. **Jens Cardinale:** Writing – review & editing, Supervision, Formal analysis. **Frederik L. Giesel:** Writing – review & editing, Supervision, Project administration, Methodology.

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