FAPi PET in Pancreatic Ductal Adenocarcinoma:

A Prospective, Exploratory Study

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Introduction:

The estimated worldwide incidence and cancer associated mortality of pancreatic cancer is about 496,000 and 466,000, respectively, according to the 2020 Global Cancer Statistics. (1) The most common (90%) histological subtype of pancreatic cancer is pancreatic ductal adenocarcinoma (PDAC); which we shall henceforth refer to as 'pancreatic cancer'; other subtypes include neuroendocrine tumor, acinar cell carcinoma,and pancreatoblastoma.(2) Pancreatic cancer is typically characterized by intense desmoplastic reactions surrounding the cancer cells.(3-5) The characteristic stromal desmoplastic response plays a key role in tumor invasion, metastasis, and drug resistance.The stromal component comprises up to 80% of the pancreatic tumor mass.(6)

What is Desmoplasia and its relevance in Pancreatic cancer?

Desmoplasia, which is also referred to as the desmoplastic reaction, is a fundamental characteristic of PDAC. It clinically manifests itself in two ways: (7) significant overproduction of extracellular matrix (ECM) proteins, and (8) extensive proliferation of myofibroblast-like cells.(9) The resulting dense and fibrous connective tissue therefore is composed of both cellular and non-cellular components. Desmoplasia, which is a result of the proliferation of alpha-smooth muscle actin-positive fibroblasts (also known as the myofibroblast, or activated pancreatic stellate cell (PSC)) and increased deposition of extracellular matrix (ECM) components, leads to reduced elasticity of tumor tissue with a concomitant increase in tumor interstitial fluid pressure (IFP). Increased IFP results in a decreased rate of perfusion of therapeutic agents and consequently decreased efficacy. This physiological chemoresistance has been shown to be a major contributor to the reduced efficacy of chemotherapeutics in multiple tumor types.(10) In

addition, desmoplasia can result in multiple signaling cascades that increase biological chemoresistance to therapeutic agents.

Fibroblast-Activation Protein and its expression in various cancers:

Fibroblast activation protein (FAP) is strongly expressed on cancer-associated fibroblasts and is a key player in tumor progression (11). High FAP expression is restricted almost exclusively to cancer-associated fibroblasts and serves as an independent negative prognostic factor for multiple types of cancer (12). In vivo depletion of FAP-positive stromal cells inhibits tumor growth by decreasing cancer support, increasing antitumor immunity, and limiting stromal barrier effects (13,14). Recently, FAP inhibitor (FAPi)–targeting ligands labeled with radioisotopes for PET imaging (e.g., 68Ga and 18F for PET) and therapy (e.g., 177Lu and 90Y) have been introduced (15,16). The high tumor uptake that was observed with FAPi PET imaging in various cancers suggests that radiolabeled FAPi compounds have promising potential for diagnostic and therapeutic applications.(17)

In a prospective exploratory study by Mona et al (18), , FAPi PET human biodistribution in cancer was validated against tumor FAP expression as assessed by immunohistochemistry, on a pancancer human tissue microarray (141 patients, 14 different types of cancer). It was concluded that FAP biodistribution on imaging strongly correlated with FAP tissue expression. Hirmas et al, (19) as a part of interim analysis of prospective trial showed a strong correlation between Ga-FAPI SUV max and FAPI IHC scores, especially for sarcoma and pancreatic cancer

Fibroblast-activation protein in Pancreatic Cancer:

Fibroblast-activation protein (FAP) is a serine protease that contains both dipeptidyl peptidase and gelatinase/collagenase activities in vitro [20]. Because of its specific induction in tumor-associated fibroblasts in over 90% of epithelial tumors, including pancreas and breast among others, FAP was used as a platform for studying stromal specific effects on tumor behaviors [21]. It is known that FAP exhibits very restricted expression in normal adult tissue and that

pancreatic stellate cells are the ‘normal’ fibroblastic cells found in the exocrine pancreas. Activated pancreatic stellate cells are believed to be responsible for the fibrosis in chronic pancreatitis and the desmoplastic reactions in pancreatic adenocarcinomas [22].

The experimental approach used to study the role of FAP in tumor invasion utilized an in vivo-like 3D matrix system that has been shown to effectively recapitulate stromal ECMs from various murine and human tissues.[23] In this study, it has been observed that FAP+ fibroblast-derived matrices presented higher organization levels of fibers when compared to FAP- matrices. Importantly, it was shown that FAP+ matrices contain parallel fiber organization features that are reminiscent of tumor-associated ECMs of pancreatic desmoplastic tissues associated with pancreatic adenocarcinoma looking at human normal and tumor ECMs both in vivo and in vitro.

Imaging of Pancreatic Cancer:

Contrast-enhanced Computed Tomography (ceCT) is recommended as the primary imaging modality for resectability evaluation according to the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) guidelines.[24,25] Pancreatic cancer is usually seen as a mass lesion that exhibits hypoenhancement compared to the adjacent parenchyma in the pancreatic phase. It may cause interruption and upstream dilatation of the pancreatic or bile duct, abutment or encasement of adjacent vascular structures, direct invasion of adjacent organs, and regional lymph node enlargement. In meta-analyses, ceCT has shown sensitivity of 89–91% and specificity of 85–90% for the diagnosis of pancreatic cancer.[26] Also, for assessment of resectability, ceCT has shown a better diagnostic performance than MRI.[27]

PET/CT imaging for Pancreatic Cancer:

Although it is the most widely used PET tracer in nuclear oncology, 18F-fluorodeoxyglucose(18F FDG) has several limitations in the diagnosis and staging of pancreatic

cancer.[28] First, 18F-FDG PET/CT sometimes yields false-negative results in the detection of small, isodense

pancreatic cancers. Second, 18F-FDG PET/CT has a low-to-moderate sensitivity in the evaluation of metastatic lymph nodes (LNs). It underestimates the N (node) stage, limiting its utility in the surgical planning for patients with pancreatic cancer.[29] Furthermore, 18F-FDG PET/CT exhibits poor performance in the detection of liver metastases and peritoneal carcinomatosis, which are common forms of metastasis in pancreatic cancer.[30]

FAPI PET/CT in Pancreatic Cancer:

As FAP is overexpressed on the CAFs of 90% of the types of malignant epithelial cancer and exhibits negative/low expression in healthy tissues, it has attracted much attention as a tracer of choice where FDG has limited utility. Recently, a series of quinoline-based FAP inhibitors (FAPIs) have been developed and these have yielded encouraging results in preclinical and clinical molecular imaging studies.[31,32] In a preclinical study, a patient-derived orthotopic xenograft model of pancreatic adenocarcinoma displayed a significantly higher tumor-to-muscle ratio with 68Ga-FAPI-04 than with 18F-FDG.[33] The favorable image contrast obtained with 68Ga-FAPI PET/CT may allow its clinical use for the detection of early-stage pancreatic cancer. In a subsequent clinical investigation of a larger patient cohort, 68Ga-FAPI (FAPI-04) PET/CT exhibited intense radiotracer uptake and favorable tumor-to-background contrast ratios in various cancers, including pancreatic cancer (maximum standardized uptake value [SUVmax] > 10 in pancreatic cancer, n 5 51).[34] In a study reported by Rohrich and colleagues,[35] 19 patients with PDAC (7 primary, 12 progressive/recurrent) demonstrated intense 68Ga-FAPI (FAPI-04) uptake in the primary tumors (SUVmax: 13.37 5.45), LN metastases (SUVmax: 14.13 8.50), and distant metastases (SUVmax: 7.34 2.48). These first experiences of 68Ga-FAPI PET/CT in pancreatic cancer highlight its potential use in tumor staging, recurrence detection, and individual oncologic management.

Comparison of FDG PET and FAPI PET:

In the first head-to-head comparative study in pancreatic cancer (68Ga-FAPI-04 vs 18F-FDG), 68Ga-FAPI PET/CT exhibited significantly higher radiotracer uptake than 18F-FDG in primary tumors (SUVmax, 21.4 vs 4.8; P < .001), involved LNs (SUVmax, 8.6 vs 2.7; P < .001), liver metastases (SUVmax, 7.4 vs 3.7; P < .001), peritoneal metastases (SUVmax, 8.4 vs 2.8; P < .001), and bone metastases (SUVmax, 10.6 vs 2.3; P 5 .001).[36] In contrast to 18F-FDG, 68Ga-FAPI was not taken up by the brain tissue, and exhibited lower background activity in the liver, heart, and gastrointestinal tract. 68Ga-FAPI PET/CT yielded a favorable image contrast with low background activity throughout the body. [37] Regarding the diagnostic accuracy, 68Ga-FAPI PET/CT exhibited significantly higher sensitivity than 18F-FDG PET/CT in the detection of primary tumors (100% vs 73%), involved LNs (82% vs 59%), and bone and visceral metastases (92% vs 44%).[38]

Conclusion: FAP expression has been documented in pancreatic cancers, in animal models as well as human studies, which has formed the basis of using the FAP inhibitor - FAPi radioligand for imaging. This needs systematic prospective study of Ga-68-labeled FAPi PET/CT imaging in pancreatic lesions suspicious of malignancy as well as biopsy proven pancreatic ductal adenocarcinomas for staging and restaging to assess the imaging parameters.

Current status of FAPi PET:

FAPi PET is an established imaging modality in Europe and United States with majority of the literature involves studies realted to gastro-intestinal cancers. In the Indian scenario, FAPi peptide was made available in India in 2021 and is routinely used in clinical practice, with the earliest multi-center study in 2021 involved All India Institute of Medical Sciences [39],wherein they showed increased tumor accumulation and retention time, with no abnormal biosdistribution at other sites. Since then, FAPi has been extensively used in almost 15-20 centres, both in public and private hospitals. In Department of Nuclear Medicine at Tata

Memorial Hospital, we have been using FAPi in select cases since 2021, and our retrospective audit is already in process which is an TMC IEC approved project (No - 4167).

Rationale of our study:

- Tata Memorial Hospital is an apex referral center for pancreatic cancer, with approximately 200-250 new patients visiting the out-patient department every year.
- In current western literature, FAPi labeled PET imaging has shown strong potential for diagnosis, staging and restaging of pancreatic cancers.
- There is availability of this radioligand in our facility which has provided us with the opportunity to design this study.

Aims and Objectives:

Aim: To evaluate utility of FAPI PET/CT in

- Histopathologically proven pancreatic cancer for staging/restaging
- Post neoadjuvant therapy response assessment

Objective: To calculate sensitivity, specificity, positive predictive value and negative predictive value of quantitative and semi-quantitative parameters on FAPi PET

Methodology:

Type of Study: Prospective, exploratory

Centers -

Dept of Nuclear Medicine, Tata Memorial Hospital, Mumbai and ACTREC, Navi Mumbai

Sample Size - Since this is an exploratory study, a sample size of 60 (approximately 30 each for diagnosis/staging and restaging)

Study Duration:

Recruitment: From the date of approval to 12 months

Follow-up period: 12 months from the recruitment of last patient

Inclusion Criteria:

- Any gender with age more than 18 years
- Patients with pancreatic cancer referred to TMH and ACTREC
- Patient willing to participate in study

Exclusion criteria:

- Patient with concurrent malignancy

Imaging Time-points:

Baseline and post NACT response assessment - within 2 weeks of ceCT

Imaging Protocol:

Patients referred from GI-OPD shall be explained the procedure and consent will be taken

After detailed history taking, an intravenous access will be secured. In-house synthesis and labeling of Ga-68-FAPi shall be performed. As is recommended, 3-4 mCi of radiotracer shall be injected IV and the patient shall be asked to wait in the radiation waiting facility for 45-60 mins. Patients then will be positioned supine in PET/CT scanner for scan acquisition.

Acquisition protocol:

After obtaining a scout image whole body CT will be performed first in craniocaudal direction (120kV, slice thickness 5mm,pitch-0.83, voltage 120kV, FOV 600mm, rotation time - 0.5sec, automated mA, image matrix-512x512). Non-contrast CT was used for diagnostic purposes and for attenuation correction of the PET data. PET scanning was performed immediately after the CT acquisition, without changing the patient position. Approximately twelve bed positions shall be used for imaging, with an acquisition time of 60-90 seconds for each position. PET shall be acquired in 3D mode. Fusion PET/CT images will be generated and can be viewed on workstation.

Image Interpretation:

Lesion detection:

	ceCT (size)	Interpretation	FAPI PET (SUV max)	Interpretation

Primary				
Nodes				
Metastases Liver Other				

Semi-quantitative parameters:

Maximum standardised uptake value (SUV max) and FAPi metabolic volume:

System-generated automated region of interest will be drawn on the lesion

Tumor-to-normal liver ratio: SUV max of lesion in liver and normal liver will be calculated with automated ROI

Gold Standard: Follow-up imaging or histopathology

Statistical analysis:

Data analysis will be performed using SPSS software Version 25 (IBM)

Following variables will be analyzed for the calculation of sensitivity, specificity, PPV & NPV of FAPI PET/CT;

1. SUVmax of the primary and metastatic sites.
2. Ratio of SUVmax of the lesion to the SUVmax in the mediastinal blood pool.

Optimal cutoffs will be derived using ROC curve and Youden's index

Above mentioned continuous variables will be stratified based on the optimal cutoffs obtained from the ROC curve.

FAPI PET/CT findings will be confirmed either with follow up imaging or histopathological correlation wherever available.

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