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Research Article

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PICTORIAL ESSAY OF GALLIUM-68-FIBROBLAST ACTIVATION PROTEIN INHIBITOR (FAPI) IN ONCOLOGICAL MALIGNANCIES: CLINICAL EXPERIENCE AT OCEAN ROAD CANCER INSTITUTE

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Abstract

The type II transmembrane protease known as Fibroblast Activation Protein (FAP) is not present in quiescent fibroblasts but is extensively expressed in Cancer-Associated Fibroblasts (CAFs). Fibroblast Activation Protein Inhibitor (FAPI) expression has been linked to a bad prognosis and increased treatment resistance. FAPI has demonstrated variable expressions in different tumors; high expression has been observed in desmoplastic tumors, these tumors (such as breast, colon and pancreatic carcinoma) have high concentrations of CAF's and mesenchymal tumors (such as sarcoma) which express FAP in both CAF's and tumor cells. FAP demonstrates poor expression in tumors with no significant desmoplastic reaction, such as lymphoma, myeloma, melanoma, Renal Cell Carcinoma (RCC), seminoma, and multiple myeloma. Our pictorial review aims to demonstrate FAPI expression of the ^{68}Ga-FAPI PET performed at our institute.

Keywords: Gallium-68-Fibroblast Activation Protein Inhibitor (^{68}Ga-FAPI); Positron Emission Tomography-Computed Tomography (PET-CT), Oncology; Cancer Associated Fibroblasts (CAF's); Tumors

Introduction

Cancer remains one of the world's major causes of death, with 20 million new cases and 9 million cancer-related deaths in 2022 [1]. Anatomical and molecular imaging in malignancies is essential to every stage of their treatment. Stroma refers to the supportive, non-parenchymal tissue or fluid within a biological structure, like an organ, tissue, or cell. Its key characteristic includes providing a matrix for other cells and tissues within an organ or structure (supportive framework), it is non-parenchymal as opposed to parenchyma, which performs the specialized functions of the organ or tissue, and has variable composition depending on the specific organ or tissue, including connective tissues, blood vessels, and nerves [2]. Over 90% of the mass in tumors is made up of stroma, which interacts with tumor cells to influence their behavior and plays a critical role in tumor growth and progression [2,3]. A transmembrane glycoprotein, The Fibroblast Activation Protein (FAP) is scarce in healthy tissue but highly expressed in stromal Cancer-Associated Fibroblasts (CAFs) [4]. CAFs alter the extracellular matrix and release cytokines and chemokines, which promote tumor development, migration, metastasis, resistance to treatment, and immunosuppression [5]. The studies have also reported that increased FAP expression in tumors is associated with poor prognosis and contributes to resistance to treatment. Current research has been directed towards targeting Tumor Microenvironment (TME) in tumor stroma that aims at the diagnosis and therapy of different cancers [6]. Quinoline- and non-quinoline-based radioligands are among the FAP-targeting radioligands. The quinoline FAPI 4 has undergone various modifications to produce a class of quinoline-based PET tracers, such as FAPI-02, FAPI-42, FAPI-46, and FAPI-74, which have significant washout after 24 hours and rapid in vivo tumoral uptake (beginning 10 minutes after injection) [7]. The non-quinoline FAPI-2286 has a limited washout (10%) at 48 hours after injection and is based on a seven-amino-acid cyclic peptide with an affinity for FAP in the nanomolar range. It also has a DOTA-chelator for labelling with both therapeutic and diagnostic radioisotopes [8]. Due in large part to the hepatobiliary excretion of 18F-labelled FAPI, FAPI labelling with 68Ga has shown an excellent tracer profile in the clinical environment (high tumor uptake, low background uptake) as compared to 18F [9]. Patient preparation for FAPI PET imaging does not require caloric fasting, adaptation of anti-diabetic drugs, or avoiding intense exercise during the previous 24 hours before the procedure. Unlike FDG PET imaging, the patient only requires good hydration to aid clearance of the urinary excreted tracer [9]. FAPI has demonstrated variable expressions in different tumors; high expression has been observed in desmoplastic tumors, these tumors (such as breast, colon and pancreatic carcinoma) have high concentrations of CAF's and mesenchymal tumors (such as sarcoma) which express FAP in both CAF's and tumor cells. FAP is poorly expressed in tumors with no significant desmoplastic reaction (lymphoma, myeloma, melanoma, RCC, seminoma, multiple myeloma) [10]. Our study aims to provide a pictorial review of FAP expression in different cancers done at our institution.

Methodology

Up to date, FAPI PET has demonstrated detection of a wide range of malignancies; up to 28 malignancies have been reported so far, including breast, head-and-neck, and GI cancers [11]. When it comes to detecting GI cancers, liver metastases, and other metastatic locations, FAPI PET imaging has an advantage over traditional FDG PET because of its low background [12]. Based on existing evidence, both diagnostic imaging and prospective therapeutic applications are made possible by FAPI labelled radioisotopes; ongoing research will further hone its function in patient management and potential radioligand therapies.

FAPI is a new radiopharmaceutical in clinical settings; for this, an ethics committee approval was obtained. The labelling of FAPI 4 was done exclusively with the ^{68}Ga radioisotope. PET request forms were reviewed and approved by a nuclear medicine physician for scans. All patients in this review were histologically confirmed cancer patients, and consents for performing ^{68}Ga-FAPI PET were obtained. PET-CT images were acquired between 10 min-30 min after the intravenous administration of about 3 mCi to 5 mCi of ^{68}Ga-FAPI, based on the weight of the patient (0.05-0.06 mCi/kg of body weight). A 3D PET/CT scan was performed from vertex to mid-thigh/feet on a SIEMENS BIOGRAPH mCT-64 slice PET/CT scanner. Multiplanar reformations were then performed on a dedicated workstation. Images and patients' data were extracted from institutional medical archives PACS.

Discussion

Our case series was composed of studies with significant FAPI uptake which indicates malignant disease. These cases have demonstrated the use of FAPI PET in different malignancies in centres with no access to FDG.

In molecular imaging for various cancers, FAPI PET has been described as a potential diagnostic method that performs as well as or better than FDG PET in terms of diagnosis and staging. FAPI PET is backed up with its characteristic low background activity and ability to be expressed not only in the tumor microenvironment but also in cancer cells of certain histopathology, such as mucinous adenocarcinoma and others [10,11]. Most of the existing evidence is delivered from small sample sizes with limited histopathological confirmation; this necessitates additional investigation provided by carefully planned, multi center, prospective studies with histological validation. Recently, there is an increased wave of clinical application of FAPI PET in tumors that have limitations with FDG PET and demographical areas where FDG production is limited and gallium-based radiopharmaceuticals are being deployed as PET tracers. Clinical data and anatomical imaging correlation are very essential for accurate interpretation of FAPI PET scans; additionally, in order to further guarantee appropriate interpretation in clinical practice, quantitative markers like SUV still require validation [9]. Our pictorial overview aims to demonstrate FAPI expressions in the different malignancies as described in recent literature. These scans were performed at our institution as an alternative to FDG PET due to the absence of FDG production at the time when PET-CT scans were requested.

Normal biodistribution

The normal biodistribution of ^{68}Ga-FAPI PET shows a high concentration of activity in the kidneys, urinary bladder (due to excretion) and uterus. Lower uptake will be noticed in the salivary glands, pancreas, Waldeyer's ring, breasts, striated muscles, thyroid, prostate, ovaries, testes, adrenal glands, heart, and blood pool. FAP can express a high concentration in the gallbladder, cystic duct, and bile duct with ^{18}F-radiopharmaceutical (Figure 1).

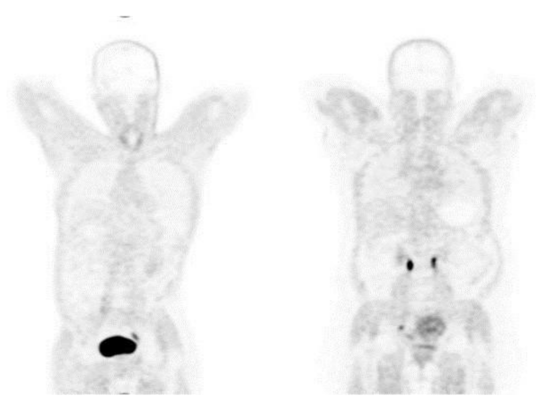

Figure 1: ^{68}Ga-FAPI PET images, male patient on the left and female patient on the right. Both images demonstrate normal physiological concentration of FAPI activity, with noticeable uptake in the uterus on the right image.

Breast cancer

Breast cancer accounts for 11.6% of all cancer cases worldwide, making it the second most prevalent form of cancer in women, and 6.9% of all cancer deaths globally, making it the fourth most common cause of cancer mortality [1]. Both anatomical and molecular imaging modalities have been deployed in the imaging of breast cancer patients. As regards molecular imaging, FDG PET has been shown to be useful in staging locally advanced disease, inflammatory breast cancer, detecting recurrence, and restaging [13]. FDG PET provides information on extra axillary nodes and distant metastases (chest, abdomen and bone) which refines the prognostic stratification and influences management. Breast cancer is among desmoplastic tumors, which usually express high Cancer-Associated Fibroblasts (CAF's) present in the stroma [11]. FAPI PET has shown promising performance in breast cancer for detection of primary tumors and metastatic lesions showing FAPI avidity that is comparably higher than or equal to that observed in traditional F-FDG PET [14]. The study by Ji Bin et al, on the comparison of ^{18}F-FDG PET and 18F-FAPI PET in the systemic staging of 38 patients who were newly diagnosed with breast cancer (stage IIb - IIIc), found that there was an overall detection rate in upstaging of 47.4% *vs* 34.2%, unexpected extra nodal disease of 97.6% *vs* 52.4% ($P<0.001$) and distant metastases of 98.1% *vs* 67.3% ($P<0.001$), for FAPI PET and FDG PET, respectively [15]. Our breast cancer cases for restaging and for recurrence demonstrated ^{68}Ga-FAPI PET in breast tumors and distant metastases (Figures 2 and 3).

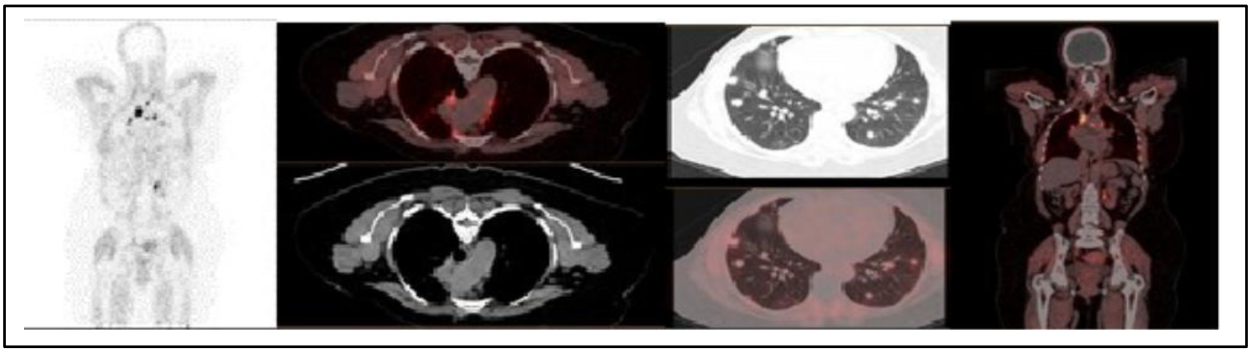

Figure 2: Adult patient known to have right breast cancer had MRM, chemotherapy, and radiotherapy.

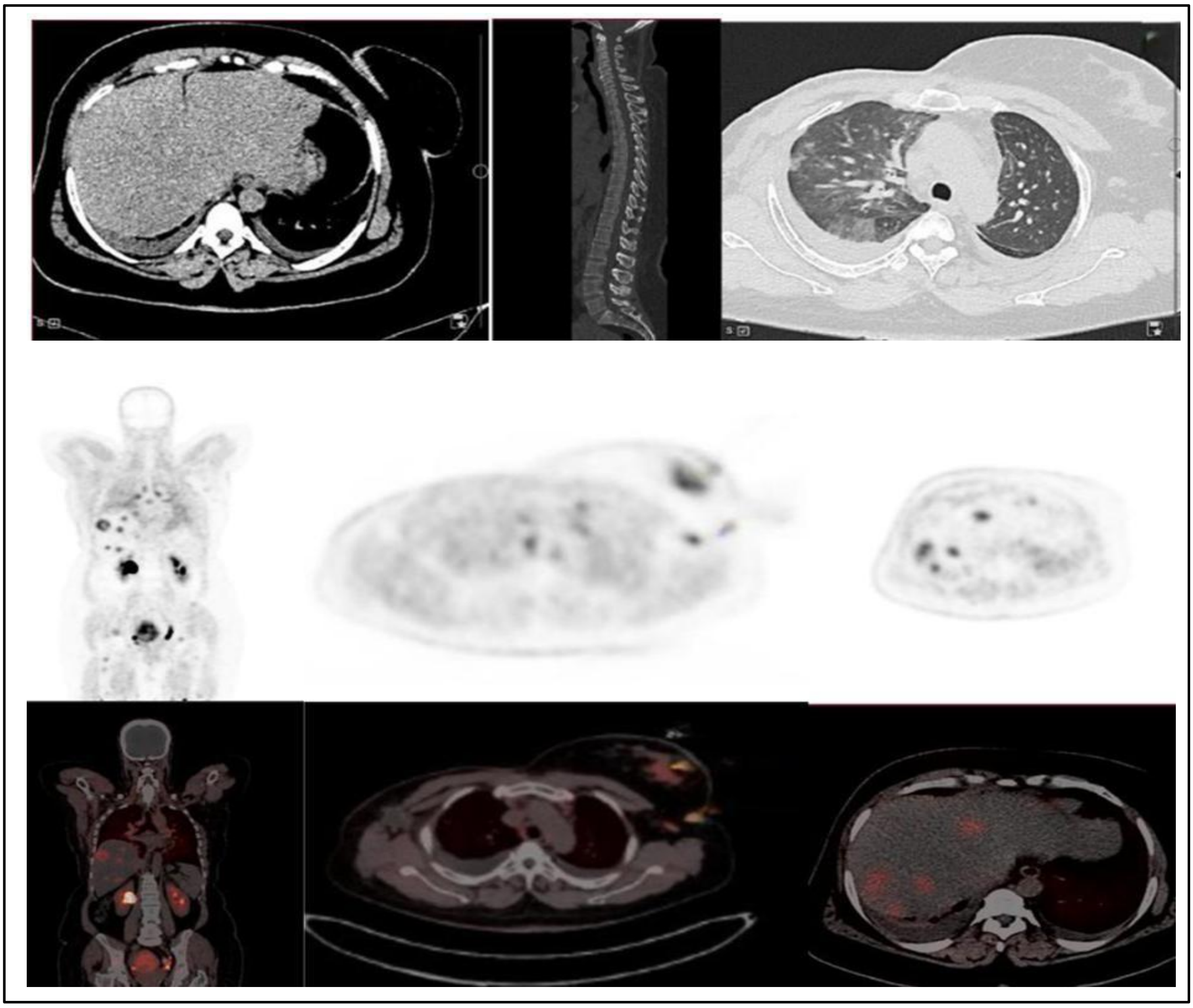

Figure 3: Adult patient known to have right breast cancer (IDC, triple negative, cT4N1Mo, pT4N1Mo).

Six months post-treatment follow-up, she was clinically well with no complaints; a CT scan showed no new lesion. The patient was then referred for a PET-CT scan to assess active disease and distant metastasis. ^{68}Ga-FAPI PET-CT showed no tracer uptake in the right breast region, the site of the known primary tumor; however, there was evidence of locoregional mediastinal nodes and pulmonary metastases, which showed variable FAPI avidity inconsistent with known treatment.

She had MRM, CRT, and chemotherapy; post-treatment FDG-PET showed no significant FDG-avid lesions to suggest malignancy. After 3 months, the patient presented with significant clinical symptoms. On imaging workup, diagnostic CT scans were performed (first row images). A chest CT showed subpleural infiltrates (right upper lobe), bilateral ground glass opacities, and bilateral pleural effusion. Total Spine CT Survey: Degenerative changes and Abdominal CT: No abnormal findings. A 68Ga-FAPI PET-CT scan (second and third row images) was then performed and demonstrated disease progression with tracer uptake in the left breast (contralateral breast), nodal (left supraclavicular, left axillary, mediastinal, bilateral hilar), multiple hepatic lesions in both lobes, and multiple mixed skeletal lesions. The PET-CT scan revealed no FAPI avidity for lung changes, which would indicate metastatic disease. Biopsies of the left breast lesion, left axillary node, and hepatic lesions were performed by the IR team; histopathology revealed malignant disease.

Soft tissue sarcoma

Sarcomas are a class of tumors with over 150 subtypes that develop from soft tissue and bone connective tissue. These tumors are rare and express heterogeneity, and subtypes include low-grade, intermediate, or unpredicted tumors. The median overall survival period for patients with metastatic soft tissue sarcoma is 12-18 months, which is a bad prognosis [16]. Numerous clinical studies have lately shown that FAPI uptake is high in a variety of solid tumors, including sarcomas [17]. Histogenesis-specific FAPI expression in sub-entities of several sarcomas has been reported; however, FAPI uptake has shown high intensity in intratumoral assessment [18,19]. FAPI PET imaging has shown good performance for accurate diagnosis and its potential as an imaging modality in advanced-stage disease; this plays a significant role in the selection of patients for ongoing FAPI radioligand therapy trials [20]. Our illustrated case shows intense FAPI uptake in the primary tumor and metastatic nodal disease; this case demonstrates high avidity of FAPI in sarcoma and potential FAPI radioligand therapy in advanced cases (Figure 4).

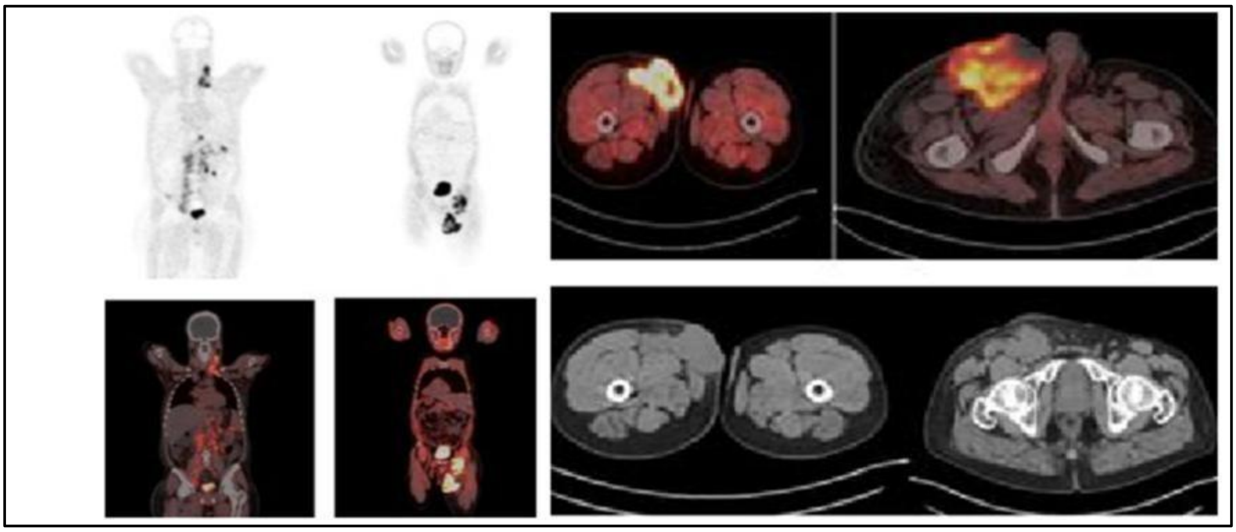

Figure 4: Adult patient with a history of right lower limb swelling, with rapid progression associated with pain.

Initial excision of the swelling was performed; histopathology revealed alveolar soft tissue sarcoma. 3 weeks post-surgery, there was clinical evidence of disease progression with two new swellings on the same side and a palpable left supraclavicular node. A CT scan of the pelvis revealed a left inguinal mass with regional lymphadenopathy, and a CT scan of the chest and abdomen revealed suspicious nodes, hepatomegaly, and no evidence of pulmonary metastasis. After tumor board discussion, surgeons deemed the tumor to be resectable. PET-CT was requested for staging in light of clinical and CT findings to further assess the burden of disease before further management. ^{68}Ga-FAPI PET-CT images revealed intense tracer uptake in the region of the known primary tumor and lymph node metastasis (locoregional and distant).

Laryngeal cancer

Any region of the larynx, but particularly the glottis, can develop laryngeal carcinoma, a common respiratory malignancy [21]. The most common histotype is squamous cell carcinoma, and the risk of recurrence and/or death is high. Convectional imaging (CT, MRI) as well as molecular imaging with FDG PET have been used

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for accurate staging. FDG PET has been shown to be favorable for local tumor characterization, regional nodal disease, and distant metastasis at initial staging as well as treatment response assessment [22,23]. Current studies have reported a higher detection rate of FAPI PET imaging compared to FDG PET imaging in head and neck malignancies in both primary and nodal disease; this advantage is significantly contributed to by the minimal background activity observed in FAPI PET imaging [24]. Xia R et al, studied patients who had pathologically confirmed laryngeal squamous cell carcinoma with both FAPI PET and FDG PET imaging [25]. In terms of tumor identification, staging, and delineation, FAPI PET imaging was reported to perform better than FDG PET imaging (100% FAPI *vs* 85.7% FDG). ^{68}Ga-FAPI PET-CT shows strong tracer uptake in the primary laryngeal squamous cell carcinoma (Figure 5).

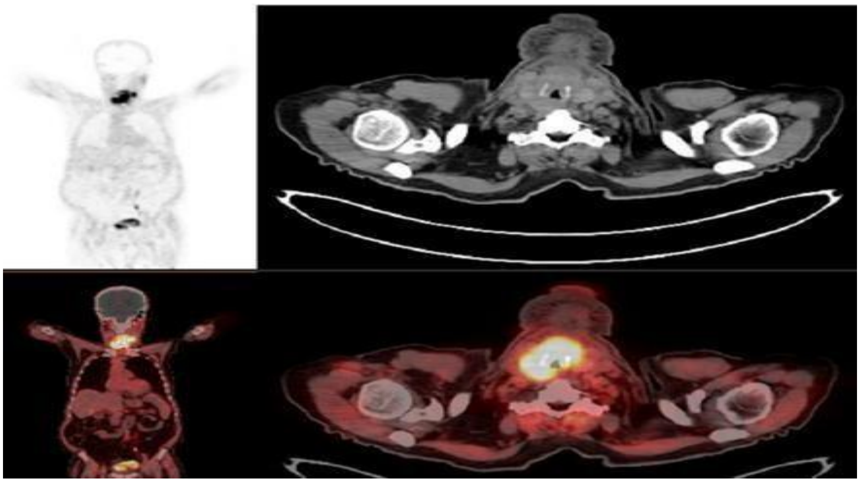

Figure 5: Adult patient known to have locally advanced laryngeal cancer treated with radical radiotherapy had a history of dyspnea after treatment, and a tracheostomy was inserted.

On follow-up, six months post-treatment, Computed Tomography (CT) of the head and neck showed bilateral vocal cord thickening (right>left) suggestive of residual disease. 68Ga-FAPI PET-CT showed intense tracer uptake in the residual primary laryngeal tumor and metastatic right cervical lymph node.

Thymoma

Thymomas, which make up between 0.2% and 1.5% of all malignant neoplasms, are the most common kind of mediastinal epithelial tumors. They make up 20% of all adult mediastinal neoplasms and are frequently the cause of anterior mediastinal masses [26]. Because of their variability and the danger of making predictions about their prognosis based on particular cell types, thymoma categorization has largely been a contentious issue. In 2021, the World Health Organization (WHO) classified thymomas into several subtypes (Type A, AB, B1, B2-formerly thymoma, B3-formerly atypical thymoma and thymic carcinoma), their classification was based on their microscopic appearance, primarily focusing on the types of cells present and their relative proportions [27]. The study by Xiuling et al, looked at the evaluation of thymic epithelial tumors using ^{68}Ga-FAPI PET and ^{18}F-FDG PET [28]. Findings showed that ^{68}Ga-FAPI PET was superior to ^{18}F-FDG PET in differentiating thymomas from thymic carcinomas (AUC: 0.99 *vs* 0.90, P=0.02), higher specificity in detecting nodal metastasis (67% *vs* 93%, P<0.001) and higher sensitivity in detecting distant metastases (49% *vs* 97%, P<0.001). FAPI avidity also correlated with both SUVmax and tumor-mediastinal ratio (both r=0.843, P<0.001). Figure 6 is our case demonstrating FAPI avidity of the superior anterior mass (primary disease) and metastatic disease (skeletal with soft tissue components and abdominal soft tissue mass) (Figure 6).

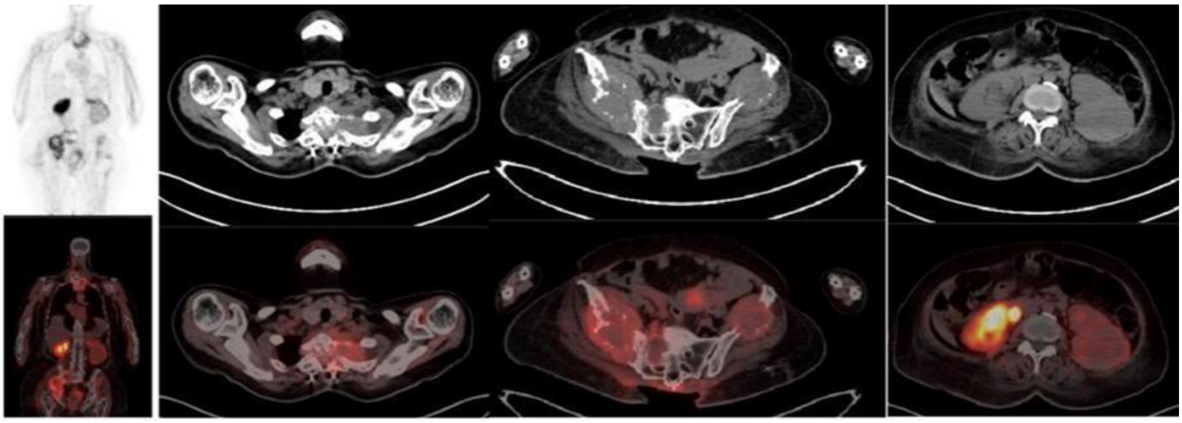

Figure 6: Adult patient diagnosed with metastatic atypical thymoma of superior anterior mediastinal mass.

Wide local excision of the mediastinal mass was performed, spinal cord decompression surgery was performed, and she has received six cycles of palliative chemotherapy. There was clinical disease progressing with a wound of the soft tissue mass on the buttocks for which wide local debridement was done, PET was requested to assess disease status and ^{68}Ga-FAPI PET-CT revealed tracer uptake in the primary residual mediastinal mass and indicated metastatic disease in the skeleton accompanied by soft tissue components. Additionally, a round abdominal soft tissue lesion was observed adjacent to the inferior border of the left kidney, which exhibited circumferential minimal tracer uptake.

Carcinoma of Unknown Primary (CUP)

A tumor that causes metastatic disease and is found using a standardized diagnostic workup in the hunt for the concealed primary is characterized as a carcinoma of unknown primary [29]. Although CUP makes up 5% of all cancers, its poor prognosis with a median survival of 6 months to 9 months makes it a greater cause of cancer-related deaths. There are 15% squamous cell carcinomas, 5% undifferentiated neoplasms, and 50% well-differentiated to moderately-differentiated adenocarcinomas and 30% poorly-differentiated or undifferentiated adenocarcinomas in the histology [30]. CUP diagnostics involves a vigorous search for the hidden primary cancer, with CT, MRI, and FDG PET currently being the preferred imaging modalities. FAPI PET imaging has recently shown excellent performance in the detection of disease in oncology; a systematic review by Justine et al, looked at the role of FAPI in CUP, both in head and neck malignancy as well as general CUP [31]. The study found that both SUVmax and the Tumor-To-Background Ratio (TBR) on FAPI PET for primary disease were high for general CUP, at 9.6 and 6.7, respectively.

When comparing FAPI PET to FDG PET, SUVmax and TBR for metastatic lymph nodes were 9.2 vs 7.9 ($p=0.03$) and 9.1 *vs* 4.9 ($p<0.01$), respectively. These results indicated increased sensitivity in identifying primary tumors and metastatic lesions, which could lead to better diagnostic precision, especially when current imaging modalities are inadequate. Our case of CUP showed FAPI-avid disease involving the liver, head and uncinate process of the pancreas, and third part of the duodenum (Figure 7).

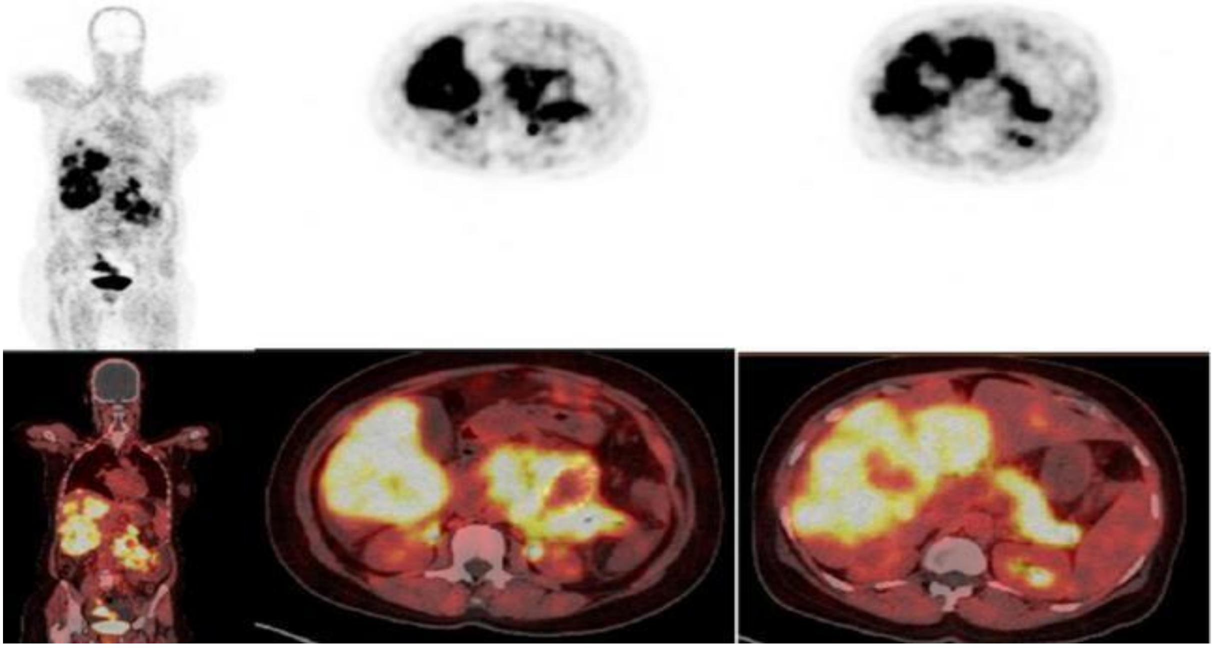

Figure 7: Adult patient presented with a history of loss of weight (10kgs in 8 months) and severe abdominal pain.

MRI (abdomen) showed hepatic lesions, pancreatic mass, duodenal mass, and abdominal ascites. Blood tests: Elevated CA-125. The origin is unknown; a PET scan was recommended to search for the primary tumor and assess its behaviour. ^{68}Ga-FAPI PET-CT showed intense tracer uptake in the liver, head & uncinate process of the pancreas, and third part of the duodenum. The rest of the scan showed no abnormal areas of tracer uptake.

Cancer of cervix

Cervical cancer is the fourth most common cancer among women worldwide and the most common malignancy detected in women. Many cases occur in the low- to middle-income nations (131.1 per 100,000 women in 2020) and mortality (90% of global deaths in 2020); this phenomenon is caused by low coverage of extensive screening services and lack of adequate and timely treatment with curative intent [32,33]. When it comes to cervical cancer diagnosis and treatment planning, both radiological and molecular imaging have been crucial, ultrasound and MRI for primary staging, and CT and/or FDG PET for assessing extra pelvic spread in advanced local and metastatic disease [34]. Current literature has reported the application of FAPI in gynecological carcinomas, including a systematic literature review and meta-analysis by Anita et al, that compares FAPI PET and FDG PET in these cancers, as well as interest in cervical tumors [35]. For primary disease detection, both tracers demonstrated a detection rate of 96% to 100%; however, the nodal detection rate was higher with FAPI PET compared to FDG PET, while there was no statistically significant difference for non- peritoneal metastases. Our case demonstrates metastatic lesions (pulmonary and nodal) in a cervical cancer patient (Figure 8).

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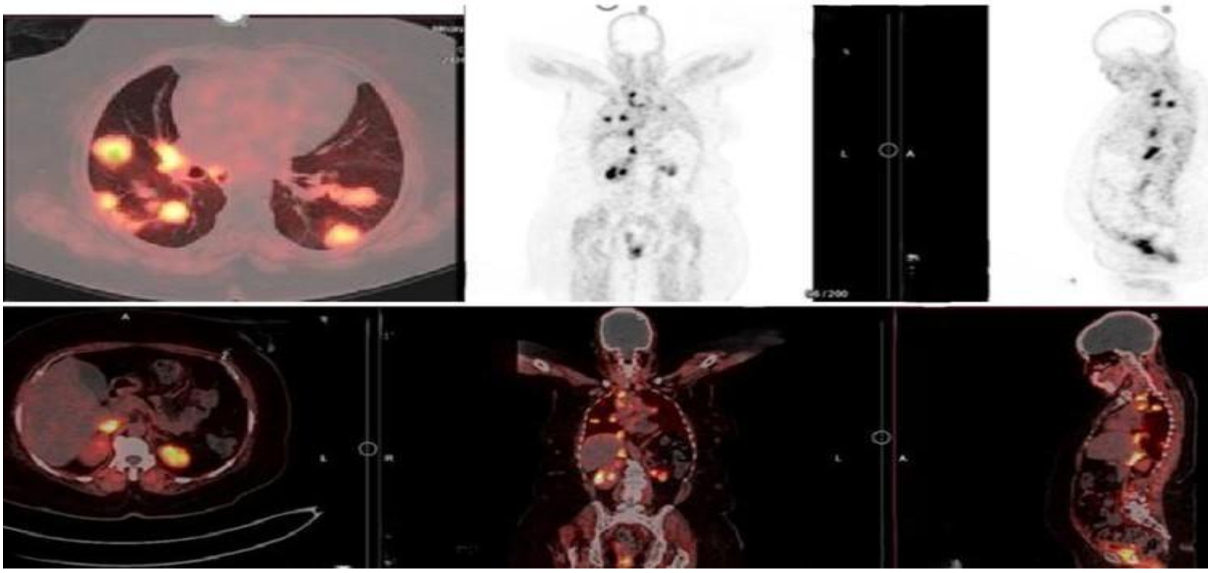

Figure 8: Adult patient known to have metastatic cervical cancer (lungs and spine).

Adult patient known to have metastatic cervical cancer (lungs and spine), was referred for post-treatment PET, 68Ga-FAPI. PET-CT showed intense tracer uptake in the primary cervical tumor and distant metastasis (nodal, pulmonary), there were lytic skeletal changes on CT; however, they were non-active, most likely due to known treatment.

Colorectal cancer

The second most common cause of cancer-related deaths and the third most prevalent cancer is Colorectal Cancer (CRC) [1]. The overall 5-year survival percentage for early-stage disease, which is frequently treated with the goal of curing it, ranges from 80% to 90%, whereas the 5-year survival rate for advanced disease, when systemic therapy is the primary treatment, is only 13% [36]. CRC staging is essential for choosing a successful treatment strategy that will enhance patient outcomes. FDG PET is currently the preferred molecular imaging technique for tumor staging; nevertheless, due to physiological FDG uptake in the colon and in tumor histology types such as mucinous, its diagnostic accuracy in colorectal cancer is frequently limited. There have been numerous studies that compare FAPI PET and FDG PET side by side; a study by Komek et al, reported the specificity and overall accuracy of FAPI PET/CT were superior to those of FDG PET [37]. The study by Erol et al, showed FDG PET exhibited high uptake in tubular and tubulovillous adenomas, whereas FAPI PET showed no abnormal uptake, suggesting that FAPI PET may aid in distinguishing between benign and malignant tumors [38]. Regarding tracer uptake in primary CRC, this remains inconsistent across the existing literature, possibly contributed to by histopathological subtypes. This is demonstrated in the study by Lin et al, which compared FAPI PET to FDG PET [39]. The findings showed higher FAPI SUVmax in signet-ring and mucinous carcinomas but lower FAPI uptake in poorly differentiated carcinomas. The pooled sensitivity and specificity of ^{68}Ga-FAPI PET/CT were 0.98 (95% CI, 0.94-1.00) and 0.81 (95% CI, 0.23-1.00), respectively, according to a systematic review and meta-analysis by Jiqi Ouyang [40]. In contrast, the results for ^{18}F-FDG PET/CT were 0.73 (95% CI, 0.60-0.84) and 0.77 (95% CI, 0.52-0.95). While both imaging modalities exhibited nearly equal diagnostic efficacy in colorectal cancer, ^{68}Ga-FAPI PET/CT performed better for certain tumors, especially in gastric, liver, biliary tract, and pancreatic malignancies [40]. Our cases demonstrate FAPI uptake in both primary and metastatic disease in rectal and colon cancer.

CT (Abdomen-pelvic) showed circumferential rectal wall thickening, subcentimeter inguinal lymph nodes, and a solitary lung nodule. Staging 68Ga-PET CT showed intense tracer uptake in the primary rectal tumor and metastatic osteosclerotic lesions (bilateral ilia, 9th right rib and 3rd left rib). The lung nodules and inguinal nodes reported on CT were non-avid (not shown in this figure 9).

Staging ^{68}Ga-FAPI PET-CT demonstrated intense tracer uptake in the primary sigmoid colon tumor corresponding to circumferential irregular wall thickening on CT (top row images) and nodal metastases (bottom row images) involving the right mesorectal, bilateral internal iliac, left common iliac, and para-aortic (highest lymph node at the level of L3). The remainder of the scan was unremarkable (Figures 9 and 10).

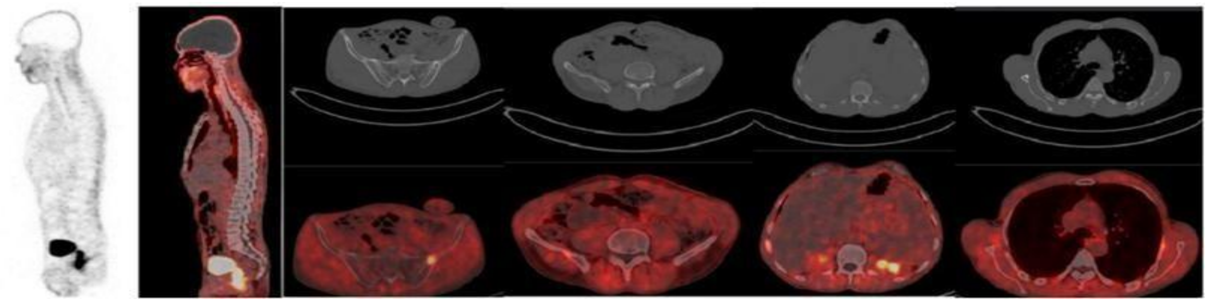

Figure 9: Adult patient who was newly diagnosed with rectal cancer (moderately differentiated adenocarcinoma).

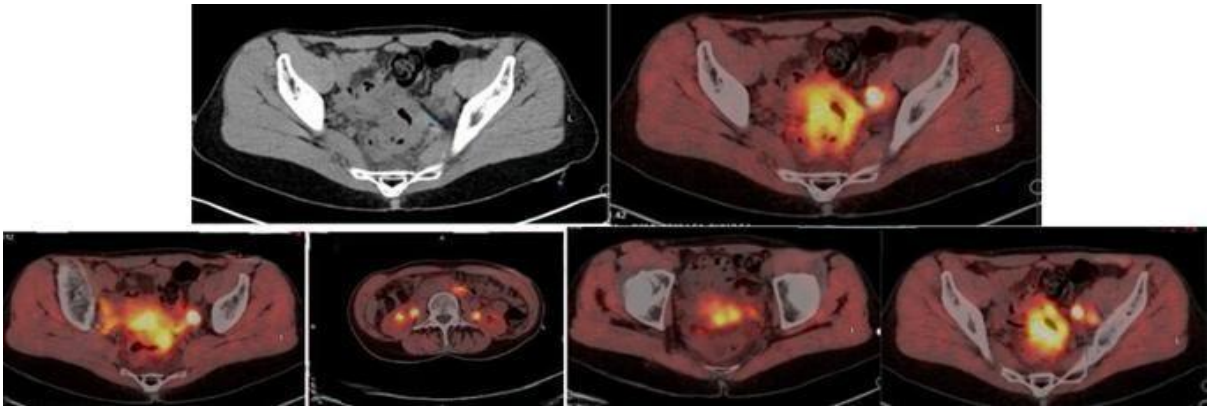

Figure 10: Adult patient who was newly diagnosed with sigmoid adenocarcinoma following colonoscopy.

Bladder cancer

Bladder Cancer (BCa) is among the most aggressive and potentially life-threatening diseases. According to Globocan, bladder cancer has moved from the 10th to the 9th as one of the most commonly diagnosed cancers worldwide, with increasing incidence and mortality [1]. It is reported to be the 6th most common cancer among men. Urothelial carcinoma makes up 90% of bladder cancer, with the remaining 10% consisting of less prevalent histologies such lymphomas, adenocarcinomas, and squamous cell carcinoma [41]. Bladder cancer can be classified as carcinoma in situ, invasive BCa, Muscle-Invasive BCa (MIBC), or Non-Muscle-Invasive BCa (NMIBC) based on its variable morphology that changes with tumor growth and progression [42]. Radiological workup strategies have included ultrasound, Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) for initial diagnosis (conjunction with cystoscopy and biopsy), tumor invasion, and assessment of distant disease [43,44]. In addition, molecular imaging with FDG PET has shown a limited role in primary tumor assessment due to urogenital excretion of the tracer causing masking of tumors in the urinary tract, a meta-analysis study by Wang et al, found that FDG PET was not superior to CT and MRI in detecting local BC [45]; FDG PET showed pooled sensitivity and specificity of 80.0% (95% CI: 71.0-87.0%) and 84.0% (95% CI: 69.0-93.0%), respectively. Current literature indicates that small cohort studies have compared FAPI PET to traditional FDG PET in BCa; FAPI PET, however, shows promise as a diagnostic radioligand for identifying distant disease and primary tumors in individuals with bladder cancer [46]. Figure 11 demonstrates tracer uptake suggestive of distant metastases (skeletal and pulmonary) in a BCa on ^{68}Ga-FAPI PET-CT.

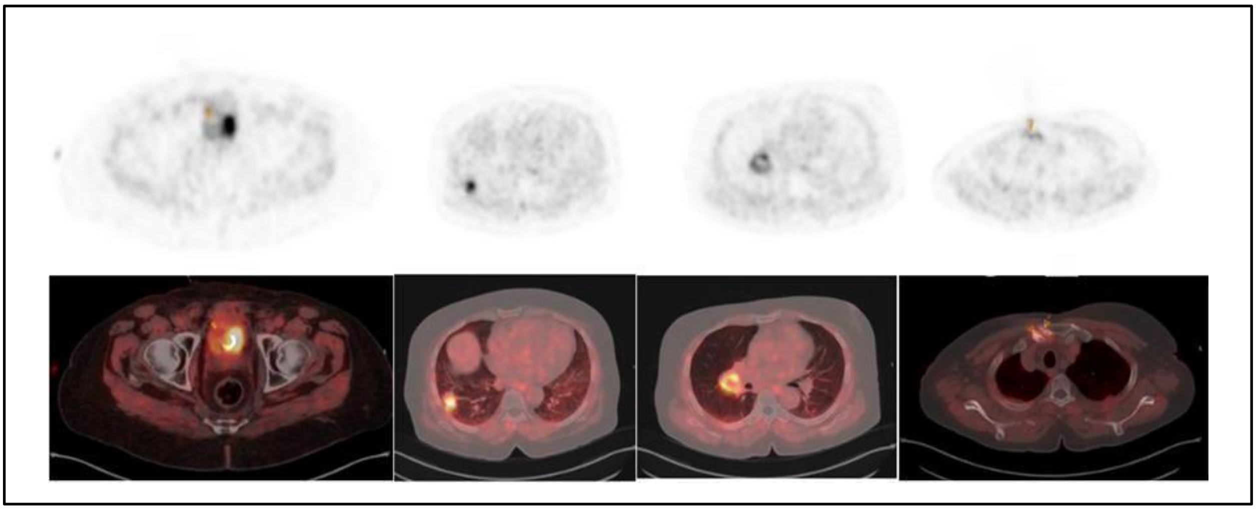

Figure 11: Adult patient with a history of urinary bladder transitional cell carcinoma (TCC) underwent radiotherapy and chemotherapy.

During the one-year follow-up after treatment, a CT scan of the abdomen and pelvis revealed post-treatment changes in the bladder wall and bilateral inguinal lymphadenopathy, while a separate CT scan of the chest showed a soft tissue mass and a lung nodule in the Right Lower Lobe (RLL). ^{68}Ga-FAPI PET-CT demonstrated intense tracer uptake of the lung findings reported on previous CT; additionally, there was also intense tracer uptake in the manubrium and sternum associated with lytic CT changes. Mild tracer uptake was observed in the bladder wall.

Neuroendocrine tumor

A rare and diverse class of cancers, neuroendocrine tumors (NETs) typically develop in the lungs and Gastroenteropancreatic (GEP) tract [47]. Somatostatin Receptors (SSTRs), more often type 2, are overexpressed on the cell membrane of these malignancies [47]. Recently, there has been increased early detection of NETs, which has given room for better and improved management, leading to longer survival in these patients. Molecular imaging has been a key imaging modality in the management of NETs, where FDG PET is used for poorly differentiated NETs and SSTRI PET is used for well-differentiated tumors, while a dual imaging method is used to study tumor behaviour and for assessment prior to radioligand therapy [48]. There is an association between dual imaging with prognosis and overall survival in patients with NETs, typically divided into three groups: patients with only FDG PET positive lesions, patients with positive lesions on both FDG and SSTRI PET, and those with SSTRI negative/FDG positive (significant discordant is observed in multiple lesions), the last category of patients tends to have poor prognosis and overall survival [49]. Studies have assessed the role of FAPI PET as a prognostic marker compared to traditional FDG PET, and a study by Kerstin et al, assessed the outcome prediction in patients with high- grade NETs [50]. The study found that there was no significant difference in the quantitative analysis of both tracers; tumor heterogeneity with discordant FDG-positive/FAPI negative lesions in substantial fraction of patients (45%), also median PFS of patients with FDG positive /FAPI negative lesions was significantly shorter (4 months) than that of patients without FDG-positive/FAPI-negative metastases (9 months). These findings could help guide treatment decisions or identify lesions for additional stereotactic approaches. Our case was a patient with NET who had a previous negative SSTRI PET; ^{68}Ga-FAPI PET-CT was done to assess tumor heterogeneity for restaging (Figure 12).

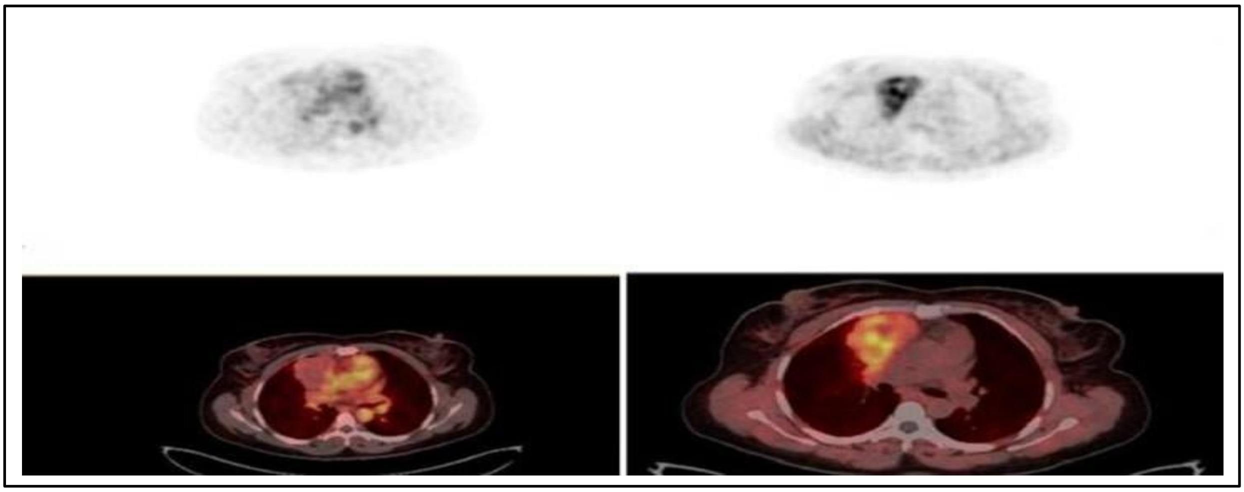

Figure 12: Adult patient known to have a mediastinal neuroendocrine tumor was treated with chemotherapy and reported significant chest symptoms.

Post-treatment imaging workup for assessment of mediastinal mass was performed. CeCT (chest) showed anterior mediastinal mass. 68Ga- DOTNOC PET on the right-sided column showed no SSTR expression; however, ^{68}Ga-FAPI on the right side demonstrated intense tracer uptake suggestive of high-grade neuroendocrine tumoral behavior.

Conclusion

This study aims to provide our clinical experience of this new tracer and its applicability in different cancers.

Gallium-68 Fibroblast Activation Protein Inhibitor (^{68}Ga-FAPI) PET/CT imaging represents a significant advancement in oncological diagnostics, offering high tumor-to-background contrast and improved lesion detectability across a broad spectrum of malignancies. Our clinical experience at Ocean Road Cancer Institute demonstrates that ^{68}Ga-FAPI is particularly valuable in assessing tumors characterized by desmoplastic stroma, including breast, gastrointestinal, gynaecological, and head-and- neck cancers. The tracer's rapid uptake and clearance profile allow for efficient imaging workflows, while its sensitivity enhances the detection of both primary and metastatic disease, even in settings where conventional FDG PET/CT may have limitations.

Through this pictorial essay, we highlight the diverse imaging patterns, clinical utility, and potential impact of FAPI imaging in routine oncological practice. The cases presented illustrate its role in initial staging, restaging, treatment response assessment, and identification of otherwise occult lesions. As FAPI imaging continues to evolve, its integration into clinical protocols may offer more accurate disease characterization and improved patient management.

Limitations

This study is limited by lack of histopathological confirmation of FAPI avid lesions.

Authors' Contributions

Bright Awadh Sangiwa was responsible for study design, data collection, analysis, interpretation, and manuscript writing. Alita Mrema, Faraji Sabaya, Baraka Fundo, Swahibu Ramadhani and Brown Mwangosi were responsible for data collecton, analysis and manuscript editing. All the authors have read and agreed to the final manuscript.

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Declarations

The authors certify that they have obtained ethical approval. A waiver of informed consent was granted as a retrospective pictorial study that imposes no risk to the subjects.

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Competing Interests

The authors declare no competing interest

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