Molecular imaging in oncology: Common PET/CT radiopharmaceuticals and applications

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ABSTRACT

PET/CT is a commonly used modality in cancer imaging, as it can help in diagnosis, staging and assessment of treatment response in many cancer types. A better understanding of the tumor microenvironment and identification of multiple selective targets are promoting further investigation into different radiotracers for diagnosis and therapy. In the past few decades many radiopharmaceuticals have emerged for specific oncologic indications providing superior detection rate than some morphologic modalities. The purpose of this review is to provide an update on the most current radiopharmaceuticals used in cancer imaging including the mechanism of action, indications and pitfalls.

1. Introduction

Molecular imaging is a powerful tool that allows assessment of cancer and other non-cancer conditions non-invasively. By labeling different radiotracers, different biological functions or targets in the tumor are able to be visualized. Positron emission tomography (PET) is a functional imaging modality that is now well established in oncological imaging. Together with computed tomography (CT), PET/CT provides functional and anotomical information needed in diagnosis, staging and follow-up of many different tumors.

There are many PET tracers available for clinical use and many more under current investigation. The main workhorse continues to be 18F-2-fluoro-2-deoxyglucose (FDG), however various other tracers have emerged in the past few decades for specific indications (Table 1). Rapid changes in our understanding of the tumor microenvironment and identification of multiple selective targets are promoting further investigation into different radiotracers for diagnosis and therapy. This review provides mechanism and clinical indication, as well as limitations and pitfalls of various PET tracers commonly used in cancer imaging.

Standardized uptake value (SUV) is a semiquantitative measure of normalized radioactivity concentration in PET images and is used in many tracers. Other quantitative measurement parameters include mean SUV, peak of SUV, metabolic tumor volume, and total lesion glycolysis.

2. 18F-2-fluoro-2-deoxyglucose (FDG)

2.1. Mechanism of action

Glucose analog 18F-FDG is the most commonly used radiopharmaceutical in oncologic PET imaging. 18F-FDG is incorporated into cells via glucose transporters, and then phosphorylated to FDG-6-phosphate by hexokinases as a part of glycolysis pathway [1]. Phosphorylated 18F-FDG cannot be rapidly metabolized further in the cells, and therefore 18F-FDG is essentially trapped within the cells, which proves as an ideal property for an imaging agent. Most tumor cells show increased 18F-FDG uptake because they preferably use glucose as an energy source and upregulate glucose transporters (GLUT 1) compared to normal cells [1]. 18F-FDG reaches a plateau of accumulation in tumor cells at approximately 45 min post injection, and the best tumor-to-background ratio is reached at 2–3 h post injection. In 18F-FDG, maximum standardized uptake value (SUVmax) is the most commonly used to quantitatively measure radioactivity (FDG accumulation) in the cells.

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2.2. Normal tracer biodistribution

Highest physiologic 18F-FDG activity is noted in the brain and urinary system and, to a lesser extent, other soft tissue organs including liver and spleen. Myocardium can demonstrate high physiologic activity, which can be related to prolonged fasting [2]. The laryngeal, pharyngeal and/or masticator muscles can show increased 18F-FDG uptake if the patient talks or chews gum during the exam. Typically, 4–6 h fasting prior to 18F-FDG injection is recommended [2]. The biodistribution of 18F-FDG is affected by blood glucose levels. High serum glucose can increase secretion of insulin, which will increase muscle metabolism by overexpression of GLUT-1. Therefore, serum glucose level < 150–200 mg/dL is recommended for optimal 18F-FDG PET/CT imaging. Short or regular acting insulin should not be used 2–4 h before the examination [2].

2.3. Applications

18F-FDG PET/CT is commonly used in many malignancies, including lung, skin, head and neck, GI, hepatobiliary, hematologic malignancies, and sarcomas. In this review, we included lung cancer and lymphoma as examples, as they are the most common indications for 18F-FDG avidial mediastinal nodes are false positive [5]. Therefore, pathologic confirmation is usually recommended for suspicious metastatic lymph nodes seen on imaging. For extrathoracic metastases, PET/CT plays an important role for the evaluation of occult metastases, and can upstage or downstage disease, impacting the ultimate management plan. Previous study showed that among 537 patients with NSCLC, 91 (17%) patients were upstaged and 68 patients (13%) were downstaged after PET/CT result [6]. In addition, there were a total of 118 patients (22%) whose therapeutic management was modified because of stage migration realized by the use of PET/CT [6] (Fig. 1). 18F-FDG PET/CT is more sensitive to detect early bone metastases before sclerotic or lytic changes are seen on CT. Previous studies demonstrate that up to 25 % of skeletal metastasis showed 18F-FDG uptake without morphologic changes on CT [7].

Regarding lymphoma, PET/CT is recommended for staging according to the Lugano classification [8]. Lugano classification is the most commonly used system for lymphoma staging and response assessment [9]. This system emphasized the role of PET/CT in staging of FDG-avid lymphoma and introduced metabolic response criteria (Deauville 5-point scale) which is based on the visual interpretation of tumor metabolism by comparing with FDG uptake in the mediastinal blood pool and liver [8]. Compared to the CT only, 18F-FDG-PET/CT is more sensitive and specific for detecting both nodal and extranodal disease (Fig. 2). According to the study by Barrington et al., among Hodgkin lymphoma patients, 14 % of the patients were upstaged due to 18F-FDG uptake in the marrow non-enlarged lymph nodes, and 6 % were downstaged because of splenomegaly without abnormal 18F-FDG uptake or enlarged lymph nodes without 18F-FDG-uptake on PET/CT [10]. Bone marrow involvement is reliably evaluated on baseline exams and can obviate the need for bone marrow biopsies in most known 18F-FDG-avid lymphomas. Evaluation on follow up 18F-FDG-PET/CT can be challenging in the setting of reactive marrow changes after G-CSF stimulating agent or hyperplastic marrow secondary to cytopenia, and bone marrow biopsy can be performed if it is equivocal. Management of lymphoma depends on the histologic subtype and grade. 18F-FDG uptake varies between histologic subtypes which is important for management plan [8]. Low grade lymphomas, such as follicular lymphoma or marginal zone lymphoma, generally show lower 18F-FDG uptake compared to the aggressive subtypes such as diffuse large B cell lymphoma, with SUVmax usually less than 10 [11,12]. If an area of intense 18F-FDG uptake (SUVmax greater than 10) is identified in a patient with low grade lymphoma, it may suggest histologic transformation [13] (Fig. 3). Retrospective analysis of transformed lymphoma by Noy et al. showed that SUVmax can predict the aggressive lymphoma with > 80 % certainty using SUVmax cut-off of 10, and with > 90 % certainty using Sums of SUVmax cut-off of 15 [12]. Therefore, 18F-FDG PET/CT can aid in selecting biopsy site when there are findings suspicious high-grade transformation. After treatment, 18F-FDG avidity of lesions can be significantly decreased when there may be lesser degree of change in the anatomical extent of disease. Therefore, Lugano criteria (Deauville score) using 18F-FDG uptake is commonly used for treatment response evaluation in lymphoma. 18F-FDG PET/CT after treatment has a predictive value for clinical outcome [8].
coexistent inflammation and malignancy are possible. Several malignancies are known to demonstrate low \(^{18}\)F-FDG avidity, including indolent lung adenocarcinomas, lobular subtype breast cancer, well differentiated hepatocellular carcinoma, prostate cancer, or signet-ring cell type gastrointestinal malignancy, thus the sensitivity for disease detection is decreased.

3. \(^{68}\)Ga-DOTA-conjugated peptides

3.1. Mechanism of action

Somatostatin receptor (SSTR) is highly expressed in the well-differentiated neuroendocrine tumor (NET) as well as normal organs including brain, peripheral neurons, endocrine pancreas, and gastrointestinal tracts. \(^{68}\)Ga-DOTA-conjugated peptides including \(^{68}\)Ga-DOTA\(^5\)-Tyr\(^3\)octreotide (\(^{68}\)Ga-DOTA-TOC), \(^{68}\)Ga-DOTA\(^3\)-1Na\(^+\)octreotide (\(^{68}\)GaDOTA-NOC), and \(^{68}\)Ga-DOTA\(^2\)-Tyr\(^3\)octreotate (\(^{68}\)GaDOTATE), as well as \(^{64}\)Cu analogs are radiolabeled somatostatin analogs that specifically bind to SSTR and can be used for PET imaging. All three agents bind to SSTR type 2, which is the most commonly found SSTR in NET, with a slightly different affinity profile for other SSTR subtypes. For example, \(^{68}\)Ga-DOTA-NOC has a high affinity for SSTR type 3 and 5 and \(^{68}\)Ga-DOTA-TOC for SSTR type 5 \([14,15]\). \(^{68}\)GaDOTATATE is widely used for PET/CT imaging of SSTRs in United States and has shown a selective and highest affinity for SSTR type 2 \([16]\). Compared to \(^{111}\)In-pentetreotide (a gamma emitter SSTR tracer imaged on SPECT), \(^{68}\)GaDOTATATE shows 100 times greater affinity to SSTR type 2, and therefore shows significantly improved diagnostic performance with lower radiation dose, superior imaging quality and shorter imaging acquisition time \([17]\). Currently, \(^{68}\)GaDOTATATE is a key component in the imaging workup for neuroendocrine tumor work up according to the national comprehensive cancer network (NCCN) guideline.

3.2. Normal tracer biodistribution

The normal biodistribution pattern for DOTATATE includes pituitary gland, liver, spleen, kidneys, and adrenal glands \([18]\). SSTRs are highly expressed throughout the nephron and collecting tubule, resulting in
Neuroendocrine tumors (NETs) comprise a heterogeneous group of neoplasms that arise from neuroendocrine cells of the upper airways, collecting systems and bladder.

According to mitotic count and proliferative index (Ki-67), morphologic appearance (well to poorly differentiated), as well as characteristic neuroendocrine immunophenotype, NETs are classified based on the malignant potential of the cells. NETs are further classified into well-differentiated and poorly differentiated NETs based on the degree of differentiation and the presence or absence of metastases.

Well-differentiated NETs are typically associated with better outcomes and include tumors such as gastrinomas, insulinomas, glucagonomas, and somatostatinomas. These tumors are often resectable and may respond well to medical therapy. On the other hand, poorly differentiated NETs are associated with more aggressive behavior and a higher risk of metastasis. Examples of poorly differentiated NETs include carcinoid tumors, pancreatic islet cell tumors, and neuroendocrine carcinomas.

3.3. Applications

Neuroendocrine tumors (NETs) comprise a heterogeneous group of neoplasms that arise from neuroendocrine cells of the upper airways, small intestine, duodenum, and pancreas. NETs are classified based on morphologic appearance (well to poorly differentiated), as well as according to mitotic count and proliferative index (Ki-67). Ga-DOTA-TATE PET/CT is the imaging modality of choice for the initial staging of well-differentiated NET when there is a clinical suspicion of metastases (e.g., elevated chromogranin and synaptophysin) or surgical treatment is being considered. CT and MRI are commonly used in conjunction for the evaluation of the primary mass due to excellent imaging resolution and anatomic details, and the addition of Ga-DOTA-TATE PET/CT is useful in detecting unexpected metastases. Previous studies show that Ga-DOTA-TATE PET/CT is superior to identify both hepatic and extraparenchymal metastases compared to CT or MRI alone, therefore it is a preferred imaging modality for the initial staging of tumor extent [19,20]. In addition, Ga-DOTA-TATE PET/CT provides an estimation of SSTR density and functionality, detection of tumor heterogeneity, and information to select the patient cohort who would benefit from SSA or peptide receptor radionuclide therapy (PRRT). Well-differentiated less aggressive NET (Ki-67 < 3 %) typically shows high uptake on Ga-DOTA-TATE PET/CT, and higher-grade NET shows less uptake due to loss of SSTR expression [21].

Fibroblast Activation Protein Inhibitors (FAPI-tracers)

4.1. Mechanism of action

Fibroblast activation protein (FAP) is a novel target for molecular imaging. Tumors are comprised of two types of cells: cancer cells (malignant) and stroma (non-malignant). Stroma constitutes the predominant component of tumors, in some cases up to 90 % of the tumor mass (colon cancer, breast, and pancreas) [29-33]. Stromal cells include immune cells, endothelial cells, fibroblasts, and others. All of these cells have the potential to transform into cancer-associated fibroblasts (CAFs). CAFs account for the majority of the tumor stroma and contribute to tumor proliferation, invasiveness, angiogenesis, and metastasis via expression of the surface antigen FAP [29,34-36]. A variety of tumors that have shown FAP overexpression [30], which is associated with more aggressiveness and poor prognosis [37,38]. Many FAP-ligands variants have been progressively developed to accomplish higher tumor specificity and retention, and some have potential theranostic role, including FAPI-04, FAPI-46 and FAPI-74 [39]. While the majority of FAPI-derivates are labeled with 18F or 68Ga (FAPI-74) [39].

4.2. Normal tracer biodistribution

While FAP expression in healthy tissues is lower than in malignancy, it is expressed in some normal tissues including uterine stroma (particularly in proliferative phase), pancreas alpha cells, human placenta, and some dermal fibroblasts [39,40]. Each variant of FAP-ligand (FAPI-01, FAPI-02, FAPI-04 among others) shows a slightly different biodistribution profile with varying degrees up uptake in certain organs, however, they commonly demonstrate low uptake in the brain parenchyma, liver, and oral mucosa [40]. Compared to 18F-FDG, there is less uptake in the brain, myocardium, blood pool, renal cortex, bowel, and pancreas [41]. An advantage of radiobound FAP compared to other tracers is high accumulation in tumors and low uptake in the majority of healthy tissues, providing a high tumor to background ratio. The tracer is rapidly cleared from the blood stream and is excreted renally, with expected activity in the renal pelvis and bladder at the time of imaging [32].

4.3. Applications

According to the previous study by Kratochwil et al., highest tumor uptake (SUVmax > 12) was found in lung, breast and esophageal cancers, cholangiocarcinoma, and sarcoma [42]. Colon and pancreatic cancers showed intermediate uptake (SUVmax 6–12), even though these have the highest desmoplastic reaction on histology. Relatively low uptake was seen in renal cell carcinoma, pheochromocytoma, and 94.1 %, respectively, compared to 131I-MIBG imaging with sensitivity and accuracy of 46.7 % and 52.9 %, respectively or 18F-FDG PET/CT with sensitivity and accuracy of 90.9 % and 91.7 % [23] (Fig. 4).

3.4. Limitations and pitfalls

The pancreatic head and uncinate process may demonstrate relatively increased physiologic uptake due to higher physiologic SSTR expression, which must be considered for image interpretation. Ga-DOTA-conjugated peptides are limited for evaluation of poorly differentiated NET due to low SSTR expression in the cell membrane. Combination of 18F-FDG and 68Ga-DOTA-peptides not only helps overcoming the limitation, with increased detection of high-grade component [24], but also provides prognostic information of NET [25]. Radiotracer uptake can potentially be seen in other non-NETs, including meningioma, pituitary adenoma, intrasosseous hemangioma, or prostatitis [26-28] (Fig. 5).

![Fig. 5. Metabolic pattern of 18F-FDG suggesting transformation to high-grade lymphoma. 49-year-old woman with recently diagnosed stage I-II follicular lymphoma on an excisional biopsy of a left axillary lymph node. Patient presented with new acute onset abdominal pain and underwent evaluation with 18F-FDG PET/CT. (A and B) MIP and coronal fused PET/CT shows extensive 18F-FDG avid disease including lymphadenopathy above and below the diaphragm and involvement of the liver, stomach, left kidney, bladder, uterus, multiple muscles and left clavicle involvement. High intensity of 18F-FDG uptake (SUVmax 22) is discordant with finding on pathology. 18F-FDG pattern of uptake is consistent with transformed follicular lymphoma to a high-grade lymphoma. Intense physiologic uptake, combined with renally excreted tracer in the collecting systems and bladder.](image)
neuroendocrine tumors (including medullary thyroid cancer and insulinomas) [42].

FAPI-PET/CT has a very promising role in the imaging of multiple tumors, particularly in those that have low $^{18}$F-FDG consumption, or even on those patients with challenging glucose control. Chen et al. compared $^{18}$F-FDG and $^{68}$Ga-FAPI-04 in a total of 75 patients, 56 biopsy-confirmed primary lesions in 14 types of cancer [43]. $^{68}$Ga-FAPI-04 showed higher sensitivity (98.2%) compared to $^{18}$F-FDG (82.1%) in detecting primary lesions. Ten malignant lesions not seen on $^{18}$F-FDG were visualized on $^{68}$Ga-FAPI-04 (gastric cancer, lung adenocarcinoma, cholangiocarcinoma, pancreatic cancer, hepatocellular cancer, cervical cancer, and diffuse astrocytoma). The only cancer not visualized on $^{68}$Ga-FAPI-04 PET/CT was a pancreatic cancer in the uncinate process, obscured by diffuse background pancreatic uptake due to tumor-induced pancreatitis, which interestingly showed focally increased FDG uptake [43]. $^{68}$Ga-FAPI-04 showed higher sensitivity in the detection of biopsy-proven nodal disease but there were no statistically significant differences in the specificity between the tracers. Meanwhile, $^{68}$Ga-DOTA-FAPI-04 PET/CT showed superior sensitivity in the detection of metastatic lesions than $^{18}$F-FDG PET/CT in patients with neuroendocrine tumors expressing somatostatin receptors. 71-year-old woman with SDHD mutation and multiple paragangliomas. (A) MIP image demonstrates increased $^{68}$Ga-DOTATATE uptake at multiple soft tissue lesions. Axial PET, CT and fused PET/CT in the (B) skull base (right glomus vagale), (C) pericardial recess and (D) tail of the pancreas in the left upper quadrant consistent with paragangliomas expressing somatostatin receptors.

Fig. 4. Systemic evaluation of neuroendocrine tumors expressing somatostatin receptors. 71-year-old woman with SDHD mutation and multiple paragangliomas. (A) MIP image demonstrates increased $^{68}$Ga-DOTATATE uptake at multiple soft tissue lesions. Axial PET, CT and fused PET/CT in the (B) skull base (right glomus vagale), (C) pericardial recess and (D) tail of the pancreas in the left upper quadrant consistent with paragangliomas expressing somatostatin receptors.

Fig. 5. Neuroendocrine tumor imaging and pitfalls. $^{68}$Ga-DOTATATE PET/CT in a patient with metastatic neuroendocrine tumor. (A) MIP shows multiple foci of increased radiotracer uptake in lymph nodes of the mediastinum, left supraclavicular region, upper and lower abdomen as well as many hepatic metastases. Faint $^{68}$Ga-DOTATATE uptake projecting in the left lower skull (solid arrow) corresponds to a partially calcified extra-axial lesion in the left posterior skull seen on fused PET/CT and CT (B and C). Subsequent MRI shows signal characteristics compatible with meningioma on T2 fat-sat and post-contrast T1 (D and E).

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either newly diagnosed or previously treated cancers, particularly those in the brain, liver, and peritoneum (Figs. 6 and 7) [44]).

For lung cancer, a prospective study by Wang et al. comparing 18F-FDG and 68Ga-FAPI PET/CT showed that solid lung lesions were better delineated with FAPI, even though the metabolic tumor volume was not statistically significant [45]. An advantage of FAPI over 18F-FDG is that there should not be avidity within postobstructive atelectasis or pneumonia, whereas delineation of the tumor would likely be limited on 18F-FDG PET/CT. 68Ga-FAPI PET/CT performed better or equally in depicting positive lymph nodes compared to 18F-FDG PET/CT in 84%. 68Ga-FAPI PET/CT performed better than 18F-FDG PET/CT in the visualization of positive lymph nodes in 73%. Overall 68Ga-FAPI performed better on depicting distant lesions, with significant differences found in bones and pleural metastases. While 68Ga-FAPI outperformed 18F-FDG in the detection of brain metastasis, detection of brain metastasis is still poorer than that of MRI.

Breast cancer is also accompanied by high desmoplastic reaction, for which FAPI could be a suitable diagnostic agent. A prospective study by Komek et al. compared 68Ga-FAPI-04 and 18F-FDG in 20 female patients with breast cancer, predominantly intraductal carcinoma. FAPI-04 was superior to 18F-FDG in detecting the primary tumor as well as metastatic disease. The sensitivity and specificity of FAPI and 18F-FDG for detecting primary lesion were 100% and 95.6% using FAPI PET/CT and 78.2% and 100% using 18F-FDG [46]. FAPI also detected brain metastasis, that were not seen on 18F-FDG and were subsequently confirmed on contrast-enhanced MRI [47].

The study by Koerber et al. evaluated the role of FAPI in colon, sigmoid, rectal, and anal cancers and concluded that primary and metastatic lesions could be accurately detected by FAPI, changing TNM status and disease management [48]. Evaluation of glioblastoma with FAPI led to increased gross tumor volumes (GTVs) compared to MRI, thus changing radiation treatment fields [49]. FAPI can also aid in the delineation of target volume in esophageal cancer [42], as well as in the evaluation of nodal staging [43,50].

Many hepatobiliary tumors are characterized by a substantial fibrotic reaction. An example is pancreatic ductal adenocarcinoma (PDAC), in which fibrotic reaction leads to scarring and ductal dilation, which can be one of the early signs of disease. PDAC expresses high levels of FAP (> 90%), leading to high uptake, and favorable target-to-background ratio. There is limited literature regarding the potential role of FAPI in pancreatic cancer, however it has shown higher sensitivity compared to 18F-FDG for the detection of local and metastatic disease. While in some cases tumor staging may be upgraded with FAPI, it is unclear how this tracer can change the overall management of patients [51].

FAP is expressed in 97% of all ovarian cancers and degree of expression correlates with poor clinical prognosis, chemotherapy resistance and shorter time until recurrence. 18F-FDG has limitations in detecting serosal implants due to physiological activity in the bowel, whereas FAPI has shown to be able to depict peritoneal disease not seen on 18F-FDG.

### 4.4. Limitations and pitfalls

FAP targets overexpression by CAFs, not tumor cells, and therefore can be found in healthy tissues and multiple benign processes. Elevated uptake in the uterus of pre-menopausal and post-partum patients has been reported, and therefore the use of FAPI in endometrial and cervical malignancies may be limited. Also, normal uptake in sites of fibrosis, including post treatment fibrosis could lead to a false positive [47]. FAP are also expressed in non-oncologic processes, such as wound healing, chronic inflammation, arthritis, atherosclerotic plaques, and fibrosis including cirrhosis [33], which must be considered when interpreting studies. In addition, there is limited role for hematological malignancies.

### 5. 18F-Fluoroestradiol 16α-[18F]fluoro-17β-estradiol (18F-FES)

#### 5.1. Mechanism of action

18F-fluoroestradiol binds to estrogen receptors, serving as a good correlate for ER expression as measured by immunohistochemistry assay.
(IHC) and FES [52]. In conjunction with 18F-FDG or other techniques, 18F-FES has the potential to assess heterogeneity in ER expression and identify sites that have lost ER expression.

5.2. Normal tracer biodistribution

18F-FES is highly extracted and metabolized by the liver, resulting in rapid early blood clearance and stable blood activity over time after injection. Activity within the gastrointestinal tract is also high. 18F-FES metabolites are renally excreted and uptake in the bladder is high at the time of imaging. There is no uptake in the brain, resulting in good detection of brain metastases.

5.3. Applications

Female breast cancer has surpassed lung cancer as the most commonly diagnosed cancer worldwide, and the second leading cause of death worldwide [53]. One of the histologic and treatment driving features of breast cancer is hormonal expression profile. Approximately 75 % of newly diagnosed breast cancers are estrogen-receptor positive (ER+). ER+ breast tumors are associated with a more favorable prognosis and potential response to hormonal therapy [53]. The most common histology is invasive ductal carcinoma (IDC) which accounts for 80 % of cases, followed by invasive lobular carcinoma (ILC) representing 10–15 % of cases. Nearly 95 % of ILC are ER+ [54]. 18F-FES PET/CT is used for the detection of ER+ lesions, as an adjunct to biopsy, in patients with advanced, or metastatic breast cancer [54]. Currently, ER expression measured with IHC assay, requires biopsies and are subject to sampling errors [53]. 18F-FES can provide an in vivo assessment of the ER expression across all tumor sites and limit the sampling error from biopsies. In addition, overall evaluation of the patient’s ER status can help predict endocrine responsiveness as higher levels of tumor ER expression are associated with greater clinical benefit from endocrine therapy [54]. There is limited evidence of utility for detection or staging in early breast cancer, but there is ongoing investigation on the role of FES PET/CT for detection or staging in early breast cancer. However, 18F-FES is most useful detecting metastases in vivo. Several studies have demonstrated that contrary to the primary tumor, metastatic lesions may no longer express ER or be non-functional, which is extremely important for patients with recurrent or metastatic disease.

The lobular subtype of breast cancer is difficult to evaluate with 18F-FDG PET/CT due to low 18F-FDG avidity. However, it is nearly always estrogen-receptor positive (95 %), and 18F-FES PET/CT can better detect metastases including osseous lesions and serosal implants compared to 18F-FDG PET/CT. A meta-analysis of 9 studies (8 prospective) reported pooled sensitivity of 82 % and specificity of 95 % to detect ER+ tumors by quantitative assessment of lesions [55] (Fig. 8).

5.4. Limitations and pitfalls

One of the main limitations is that the sensitivity of FES decreases if there is concomitant treatment with ER down-regulator or modulator such as Fulvestrant or Tamoxifen and patients ideally would need to be off therapy for several weeks prior to the scan. Due to high hepatic uptake related to physiologic hepatobiliary excretion, detection of hepatic metastases may be poor. Therefore, other imaging modalities such as contrast-enhanced CT or MRI must be performed for the evaluation of hepatic metastasis. 18F-FES PET/CT ideally should be performed in conjunction with 18F-FDG PET/CT, which in practice can create challenges for insurance reimbursement.

6. Commonly used radiotracers in prostate cancer

Prostate cancer is the most diagnosed cancer among men worldwide and the second most common cause of oncologic death in men in the US (11 %), following lung cancer. However, the 5-year relative survival for all stages combined is the highest (98 %)[56]. Biochemical recurrence occurs in approximately 20–30 % of patients with prostate cancer after curative prostatectomy, and recurrence is normally identified by elevation of PSA levels. Localizing the site of active metastatic disease can sometime be challenging. Conventional imaging techniques have traditionally failed to detect nodal disease in lymph nodes smaller than 8 mm. In addition, bone scan, commonly used for staging of bone metastatic disease, may not be specific enough. While there have been many approaches to overcome these limitations, the most promising strategy is to develop strategies for diagnosis and monitoring of tumor growth in response to treatment. An ideal imaging agent would allow detection of disease progression and would be able to identify sites that have lost ER expression. A major advantage of 18F-FES PET/CT is that it can provide an in vivo assessment of the ER expression across all tumor sites and limit the sampling error from biopsies.
different tracers used in the past decades including $^{11}$C-choline and $^{18}$F-fluciclovine, PSMA-based tracers have become the preferred tracer for diagnosis of prostate cancer in specific scenarios for biochemical recurrence.

6.1. Prostate specific membrane antigen (PSMA) agents

6.1.1. Mechanism of action

PSMA, also known as glutamate carboxypeptidase II, is a type II transmembrane glycoprotein overexpressed by up to 1000-fold in prostate cancer epithelial cells [52]. Higher levels of PSMA expression are associated with poorer prognostic outcomes. PSMA expression levels increase with higher stage and tumor grade, and in castration resistant prostate cancers. However, aggressive tumors can undergo neuroendocrine differentiation and lose PSMA expression. This glycoprotein is located on the apical surface of cells. The intricacies of the molecular structure are beyond the scope of this review, but the newer radionuclide-based PSMA agents are internalized by the PSMA-expressing cells, which is the base of therapeutic applications. The imaging and therapeutic molecule is an anti-PSMA antibody targeting PSMA expressed in cells.

Up to date, many prostate-specific membrane antigen (PSMA) based agents have been developed for management of prostate cancer. The most used in clinical practice are either $^{68}$Ga, such as $^{68}$Ga-PSMA-11 and $^{68}$Ga-PSMA-617, or $^{18}$F labeled compounds, with $^{18}$F-DCFPyL and $^{18}$F-PSMA-1007 already established in clinical practice (Fig. 9). There is limited data on direct comparison of both agents, however there are probably no substantial differences in diagnostic accuracy.

6.1.2. Normal tracer biodistribution

PSMA expression has been found in the normal salivary and lacrimal glands, breast, proximal renal tubules, brain parenchyma, duodenal epithelium (brush border), Kupffer cells, cervical and stellate ganglion as well as nerve roots, commonly sacral nerve roots. There is no significant uptake in the bone marrow, which allows for good evaluation of osseous on marrow disease. Kidney, spleen, and salivary uptake are higher on $^{68}$Ga-PSMA-11 compared to $^{18}$F-DCFPyL, while the liver shows slightly lower uptake. Blood pool uptake is similar with both tracers. Both $^{68}$Ga-PSMA-11 and $^{18}$F-DCFPyL are renally excreted, so activity is seen in the ureters and the bladder. $^{18}$F-PSMA-1007 has hepatobiliary clearance and might improve local detection of prostate cancer. In all PSMA tracers, the highest uptake organ is the kidney.

6.1.3. Applications

The most recently published Appropriate Use Criteria for PSMA PET reported by Society of Nuclear Medicine and Molecular Imaging (SNMMI), in conjunction with other organizations, deems it appropriate to perform PSMA PET/CT in new prostate cancer diagnosis of unfavorable intermediate, high-risk/very high-risk patients for staging, particularly if conventional techniques (CT, MRI, or bone scan) have none to 5 distant metastasis or are equivocal, to help evaluate metastatic disease and help guide therapy options. On the contrary, if there is widespread metastatic disease on conventional techniques, PSMA PET/CT would not be indicated, as management would not change. PSMA PET/CT is usually not indicated for low-risk patients, or patients with Gleason score < 7. In rising PSA levels after radical prostatectomy or definitive radiotherapy, PSMA PET would also be appropriate (Fig. 10). PSMA can upgrade TNM staging in patients with early castrate-resistant prostate cancer (CRPC) or high-risk from M0 (on CT or bone scan) to M1 in up to 55 % of cases in retrospective studies [57]. PSMA PET/CT could also help confirm oligometastatic status for a more targeted therapy. Currently, PSMA PET/CT can also be performed to evaluate eligibility for PSMA-targeted radioligand therapy. Multiple studies have shown that PSMA has moderate sensitivity but very high specificity for nodal metastasis in intermediate and high-risk patients with reported sensitivity of 0.40 and specificity was 0.95 [58].

6.1.4. Limitations and pitfalls

As previously mentioned, a limitation of both $^{68}$Ga-PSMA-11 and $^{18}$F-DCFPyL, is renal excretion. For local prostate disease, PSMA PET has less spatial resolution than MRI, and therefore cannot be substitutive. Anecdotally, other prostatic entities have been described to show increased PSMA uptake, including granulomatous prostateitis [59]. PSMA uptake can be seen in other malignancies, including breast cancer, glioblastoma multiforme, pancreatic ductal adenocarcinoma, NSCLC, colorectal cancer, transitional cells carcinoma, gastric adenocarcinoma, and renal cell carcinoma (Fig. 11) In addition, some benign osseous lesions have demonstrated PSMA uptake, but the degree of uptake is generally much less than that seen in prostate cancer. Single rib lesions with low level of tracer uptake are likely benign [60].

6.2. $^{18}$F-fluciclovine

6.2.1. Mechanism of action

$^{18}$F-fluciclovine (anti-1-amino-3-$^{18}$F-fluorocyclobutane-1-carboxylic acid) is a radiolabeled synthetic amino acid analog of leucine that enters the cell via amino acid transporters, upregulated in prostate cancer.

![Fig. 9. 69-year-old male with history of metastatic castration resistant prostate cancer with rising PSA on Cabazitaxel. Rising PSA levels, 4.98 ng/mL in September 2021 and 14.8 ng/mL in April 2022. (A) MIP $^{18}$F-DCFPyL PET/CT in October 2021 with multifocal PSMA-avid disease including uptake at the prostate bed (dashed arrows), pelvis nodes and bones of the axial and appendicular skeleton. (B) MIP PET/CT of $^{68}$Ga-PSMA-11 (May 2022) shows similar extent of disease. (C) $^{68}$Ga-PSMA-11 axial PET and fused PET/CT with focal uptake in the prostate gland at the right apex (dashed arrows). (D) $^{68}$Ga-PSMA-11 axial PET and CT showing right pelvic PSMA-avid lymph node.](image-url)
However, it is not a prostate cancer specific agent and can be taken up by multiple other malignancies, including lung cancer, lymphoma, renal cell carcinoma and multiple myeloma [61].

6.2.2. Normal tracer biodistribution

Intense physiologic uptake is seen in the pancreas, followed by the liver. Moderate uptake is seen in the salivary glands and pituitary gland and variable mild to moderate uptake in the gastrointestinal tract. The red bone marrow uptake peaks at 10–15 min and muscle uptake is mild initially and increased over time. There is minimal uptake in the brain and minimal excretion through the kidneys, however the usual protocols scan from the pelvis to the skull to optimize visualization of pelvic structures at an earlier time. Organs with little to no uptake include the brain parenchyma and lungs. Increased fluciclovine uptake has been seen in infectious or inflammatory processes and adrenal adenomas [62]. Other malignancies may exhibit increased fluciclovine uptake, such as lung, breast, brain (including meningioma), gynecological malignancies and even osteoid osteoma.

6.2.3. Applications

Fluciclovine has been extensively studied in recurrent prostate cancer. The diagnostic performance of $^{18}$F-fluciclovine has been proven superior to CT in the setting of recurrent prostate cancer for detection of disease at the local prostatectomy bed or prostate, metastatic nodal or distant disease. fluciclovine in patients that have received prostate-sparing therapies may demonstrate non-specific pattern of uptake and can be confounded with prostate hypertrophy and chronic inflammation. More recent studies have shown that PSMA-agents have better detection rates compared to fluciclovine in patients after prostatectomy following radical prostatectomy, particularly in detection of distant disease [61,63]. Calais et al. performed a single-centered prospective trial in 50 patients who underwent both fluciclovine and $^{68}$Ga-PSMA-11 PET/CT with biochemical recurrence after radical prostatectomy and reported a detection rate of 26 % for fluciclovine and 56 % for PSMA, 8 % compared to 30 % with $p = 0.0034$ for pelvic nodal disease and 0 % compared to 16 % with $p = 0.0078$ for extrapelvic disease. There were no statistically significant differences at the prostate bed, although this may have been due to small sample. After stratifying according to serum PSA levels there were no statistically significant differences, which may have been also due to small sample size [64].

6.2.4. Limitations and pitfalls

While primary prostatic cancerous lesions have higher uptake than background prostate, there is some overlap with non-malignant prostate uptake. As mentioned earlier, already treated prostate, benign prostatic hypertrophy or chronic inflammation can also show diffusely increased prostate uptake, which is one of the reasons why it’s role on primary staging is limited. Inguinal lymph nodes may show mild symmetric uptake and should not be interpreted as positive. There is significant bone marrow uptake with may mask underlying lesions. Uptake in lytic osseous lesions is typically intense, moderate in mixed lesions and absent on sclerotic lesions, which then additional imaging should be considered [64]. Ongoing therapy with androgen deprivation therapy may impact detection of disease. Early appearance of bladder or ureteral activity could be confused by local recurrence or abnormal pelvic lymph nodes.

7. Conclusion

This review explored some of the current tracers in use for cancer imaging with PET/CT. While $^{18}$F-FDG has been the major agent for many years, this is an exciting time in molecular medicine and imaging with the many recent developments in cancer- and receptor-specific tracers.

Fig. 10. Detection of subcentimeter active prostate disease with PSMA-based radiotracers. 79-year-old man with history of prostate cancer treated with prostatectomy, radiotherapy, and adjuvant androgen deprivation therapy (ADT) with biochemical recurrence and raising PSA levels, 2.02 ng/ml around the time of the scan. (A) MIP $^{18}$F-DCFPyL PET/CT and (B and C) axial PET, fused PET/CT and CT through the retroperitoneum show intense focal uptake in the right common iliac nodal station of the pelvis (dashed arrow). (B) 4 mm left para-aortic (blue arrow) and (C) 3 mm retro-aortic lymph nodes (white arrow) that would have not otherwise been detected on conventional imaging due to small size.

Fig. 11. Non-prostatic lesions with increased PSMA uptake. 71-year-old man with history of metastatic renal cell carcinoma and prostate cancer. (A) Axial CT and fused PET/CT in the upper chest shows increased focal PSMA uptake associated with lytic bone lesions in a right anterior rib (white arrow) and (B) faint lytic lesion in the right scapula (blue arrow), consistent with metastases from renal cell carcinoma.
for diagnostic use in cancer imaging. These novel tracers have shown superior detection of disease when compared to traditional imaging modalities and are changing the landscape of staging and disease management for patients all over the world. These new diagnostic tracers serve as an important platform in the development of parallel theranostic agents, giving patients new treatment options for improved survival and quality of life.

Declaration of Competing Interest

The authors 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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