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REVIEW ARTICLE

Beyond fluorodeoxyglucose: Molecular imaging of cancer in precision medicine

Malik E. Juweid MD[1,2] | Soud F. Al-Qasem MD[1] | Fadlo R. Khuri MD[3] | Andrea Gallamini MD[4] | Philipp Lohmann PhD[5,6] | Hans-Joachim Ziellenbach Dipl Päd[7] | Felix M. Mottaghy MD[5,8,9]

[1]Department of Radiology and Nuclear Medicine, School of Medicine, University of Jordan, Amman, Jordan

[2]The National Center for Diabetes, Endocrinology, and Genetics, University of Jordan, Amman, Jordan

[3]Division of Oncology, Department of Internal Medicine, American University of Beirut, Beirut, Lebanon

[4]Research and Innovation Department, Antoine Lacassagne Cancer Center, Nice, France

[5]Department of Nuclear Medicine, University Hospital Aachen, RWTH Aachen University, Aachen, Germany

[6]Medical Imaging Physics (INM-4), Institute of Neuroscience and Medicine, Research Center Juelich, Juelich, Germany

[7]Department of Health and Social Affairs, Hamburg Distance Learning University, Hamburg, Germany

[8]Department of Radiology and Nuclear Medicine, Maastricht University Medical Center, Maastricht, the Netherlands

[9]Center of Integrated Oncology Aachen Bonn Cologne Duesseldorf (CIO ABCD), Cologne, Germany

Correspondence
Malik E. Juweid, Department of Radiology and Nuclear Medicine, University of Jordan Hospital, Queen Rania Street, Al Jubeiha, Amman 11942, Jordan.
Email: mjuweid@yahoo.com

Abstract

Cancer molecular imaging is the noninvasive visualization of a process unique to or altered in neoplasia, such as proliferation, glucose metabolism, and receptor expression, which is relevant to patient management. Several molecular imaging modalities are now available, including magnetic resonance, optical, and nuclear imaging. Nuclear imaging, particularly using fluorine-18–fluorodeoxyglucose positron emission tomography, is widely used in the staging and response assessment of multiple cancer types. However, at this writing, new nuclear medicine probes, especially positron emission tomography tracers, are increasingly used or are being investigated for cancer evaluation. This review focuses on these probes, their biologic targets, and the applications or potential applications for their use in the assessment of various neoplasms, including both probes available for commercial use—such as somatostatin receptor ligands in neuroendocrine tumors, prostate-specific membrane antigen ligands in prostate cancer, norepinephrine analogs in neural crest tumors like neuroblastoma, and estrogen analogs in breast cancer—and others in clinical development, such as fibroblast-activating protein inhibitors, C-X-C chemokine receptor type 4 ligands, and monoclonal antibodies targeting receptor tyrosine kinases, CD4-positive or CD8-positive tumor-infiltrating lymphocytes, tumor-associated macrophages, and cancer stem cell biomarkers. These developments represent a major step toward the integration of molecular imaging as a powerful tool in precision medicine, with an expectedly significant impact on patient management and outcome.

KEYWORDS
cancer, estrogen receptor, molecular imaging, positron-emission tomography (PET), precision medicine, prostate-specific membrane antigen (PSMA), somatostatin analogs

INTRODUCTION

Molecular imaging is the in vivo visualization, characterization, and quantification of biologic processes at the cellular and molecular levels, with specific probes assessing physiologic and pathologic pathways. Cancer molecular imaging is the noninvasive visualization of processes unique to or altered in neoplasia, such as proliferation, glucose metabolism, and receptor expression, as well as the interaction of tumor cells with their microenvironment.

Available molecular imaging modalities include magnetic resonance imaging (MRI) or magnetic resonance spectroscopy, entailing contrast-mediated or target-mediated alteration of tissue behavior in a magnetic field, hence influencing T2-weighted or T1-weighted signals to reflect specific tissue biology.[1] Optical imaging is another modality that relies on differences in fluorescence, absorption, reflectance, or bioluminescence of tissue or targeting probes as the source of imaging contrast. Optical imaging applications are largely limited to animal studies, cancer research purposes, and, more recently, image-guided surgery.[2]

At the forefront of cancer molecular imaging is positron emission tomography (PET) and its hybrid imaging counterparts when fused with computed tomography (CT) or MRI (PET/CT and PET/MRI). PET uses positron-emitting radionuclides, such as fluorine-18 (^{18}F) and gallium-68 (^{68}Ga). These radionuclides are used to label large numbers of biologic probes or biomolecules to form compounds known as radioligands or radiotracers. Unlike MRI and optical imaging, PET/CT and, to a lesser extent, PET/MRI are more widely used clinically for cancer molecular imaging, encompassing multiple clinical applications, such as ^{18}F-fluorodeoxyglucose (FDG) PET (FDG PET).[3]

This review focuses on diagnostic PET-based molecular imaging approaches beyond FDG PET that are becoming increasingly important in the contemporary evaluation of cancer, such as prostate-specific membrane antigen (PSMA) imaging in prostate cancer. This development is a reflection of the overall shift in paradigm from a *one-size-fits-all* approach to patient-tailored precision medicine. Upcoming molecular probes with a promising role in cancer molecular imaging are also discussed, including those targeting the tumor microenvironment (TME). This review does not cover the myriad applications of FDG PET, which have been discussed in depth elsewhere,[4] or the role of theranostics in clinical cancer care.

CANCER PET-BASED MOLECULAR IMAGING APPROACHES BEYOND FDG BY THEIR BIOLOGIC TARGET: THE ESTABLISHED PROBES

Over the years, numerous non-FDG nuclear molecular imaging approaches for cancer imaging have been investigated, each of them characterized by their unique biologic targets and clinical settings. Table 1 summarizes the most relevant targets, their radiotracers, and current or potential applications.[5–16]

Receptor or antigen expression-based imaging

Somatostatin receptor-based imaging

Somatostatin receptors (SSTRs) regulate the proliferation and secretory function of primarily neuroendocrine cells and typically show increased expression in well differentiated neuroendocrine tumors (NETs; grade 1, 2, and 3 with a Ki-67 proliferation index of <3%, 3%–20%, and >20%, respectively) arising from the neural crest. These include carcinoid, pituitary tumors, paraganglioma, pheochromocytoma, medullary thyroid carcinoma, neuroblastoma, and small cell lung cancer. SSTRs are also expressed in other neoplasms, such as meningioma and lymphoma. There are five different SSTR subtypes expressed to varying degrees in the various neoplasms.[17]

PET tracers in the form of ^{68}Ga and copper-64 (^{64}Cu) dodecane tetraacetic acid (DOTA)-labeled somatostatin analogs have become the mainstay for molecular imaging of SSTR-positive tumors.[5] Widely available SSTR PET ligands are SSTR agonists, which include ^{68}Ga-DOTA-octerotide (^{68}Ga-DOTATOC), ^{68}Ga-DOTA-octreotate (^{68}Ga-DOTATATE), and ^{64}Cu-DOTATATE. SSTR tracer antagonists are under development, including ^{68}Ga-labeled and ^{18}F-labeled JR11, LM3, and LM4 (Figure 1), which have been shown to outperform ^{68}Ga-agonists.[18,19] Head-to-head comparison studies of different SSTR agonistic and antagonistic tracers have demonstrated significantly better diagnostic performance of antagonists for NETs, primarily because of lower background tracer uptake and a higher target-to-background ratio.[18,19] For instance, Viswanathan et al. demonstrated that, in 50 patients with gastroenteropancreatic NETs, PET/CT with the SSTR antagonist ^{68}Ga-labeled DATA5m-LM4 identified significantly more metastatic lesions (94.28%) versus PET/CT with the SSTR agonist ^{68}Ga-DOTA–1-Nal(3)–octerotide (^{68}Ga-DOTANOC; 83.46%; $p < .0001$), and the authors reported pooled sensitivities for the staging and restaging settings.[19] ^{68}Ga-DATA5m-LM4 was particularly more sensitive than ^{68}Ga-DOTANOC in the liver (100% vs. 89.4%, respectively; $p < 0.0001$) and bones (100% vs. 82.9%, respectively; $p = .005$).[19]

In the context of well differentiated NETs, SSTR PET (using either combined PET/CT or PET/MRI systems) significantly enhances diagnostic accuracy when combined with conventional imaging over conventional imaging alone.[20] It also helps locate the origin of metastatic NETs when the primary tumor is undetectable through standard imaging.[5,21] For example, a meta-analysis by Graham et al. indicated that, when using ^{68}Ga-DOTATOC for NETs, the overall sensitivity and specificity pooled by the authors for the various indications of staging, restaging, and identifying primary lesion were 92% and 82%, respectively.[21] Those authors also reported an overall management change in about 51% of cases, highlighting the clinical importance of this imaging method in managing these conditions. Consequently, the National Comprehensive Cancer Network (NCCN) clinical practice guidelines recommend the use of SSTR PET for staging, post-therapy evaluation of NETs, and detecting unknown primary NETs.[5] Furthermore, SSTR PET is essential for determining patient eligibility before SSTR-

TABLE 1 Summary of biologic targets and associated radiotracers in molecular cancer imaging.

Biologic target	Examples of radiotracers	Neoplasm	Applications and potential applications
Somatostatin receptor (SSTR)	^{68}Ga-DOTATATE,[a] ^{68}Ga-DOTATOC,[a,b] ^{64}Cu-DOTATATE,[a] ^{68}Ga-NODAGA-JR11	Neuroendocrine tumors (Shah 2021[5])	Diagnosis, initial staging, post-therapy follow-up, evaluation before SSTR radioligand therapy
		Meningioma (Albert 2024[6])	Diagnosis, initial staging, post-therapy response assessment, restaging, selection for SSTR radioligand therapy
Prostate-specific membrane antigen (PSMA)	^{68}Ga-PSMA-11,[a,b] ^{18}F-rhPSMA-7.3[a],^{18}F-DCFPyL[a,b]	Prostate cancer (Schaffer 2024[7])	Initial staging, evaluation of biochemical recurrence/persistence, evaluation before PSMA radioligand therapy
Norepinephrine transporter	^{123}I-MIBG,[a,b] ^{124}I-MIBG, ^{18}F-MFBG, ^{18}F-fluorodopamine, ^{11}C-HED	Neuroendocrine tumors, primarily neuroblastoma and pheochromocytoma (Shah 2021,[5] Taïeb 2019,[8] Brisse 2011[9])	Diagnosis, initial staging, post-therapy follow-up, evaluation before ^{131}I-MIBG radioligand therapy
Estrogen receptor (ER)	^{18}F-FES[a]	Breast cancer (Ulander 2023[10])	Evaluation of ER expression status, endocrine therapy selection
Cell proliferation	^{18}F-FLT, ^{11}C-thymidine, ^{18}F-FMAU	Lymphoma, breast cancer, lung cancer, brain tumors (Minamimoto 2020,[11] Christensen 2021,[12] Kostakoglu 2015,[13] Bashir 2020[14])	Post-therapy response assessment, including response to CDK4/CDK6 inhibition therapy
Cell membrane synthesis	^{11}C-choline,[a] ^{18}F-fluorocholine	Prostate cancer (Schaffer 2024[7])	Evaluation of biochemical recurrence
Amino acid metabolism	^{18}F-FDOPA,[a,b] ^{18}F-FACBC,[a,b] ^{18}F-FET, ^{11}C-methionine	Glioma, paraganglioma, pheochromocytoma, medullary thyroid carcinoma, and prostate cancer (Schaffer 2024,[7] Taïeb 2019,[8] Law 2019,[15] Filetti 2019[16])	Diagnosis, initial staging, biopsy planning, post-therapy response assessment, evaluation of biochemical recurrence (^{18}F-FACBC in prostate cancer)

Abbreviations: ^{11}C, carbon-11; ^{18}F, fluorine-18; ^{64}Cu, copper-64; ^{68}Ga, gallium-68; ^{123}I, iodine-123; ^{124}I, iodine-124; ^{131}I, iodine-131; CDK, cyclin-dependent kinase; FACBC, fluorocyclobutane carboxylic acid; FDOPA, fluorodihydroxy phenylalanine; FES, fluoroestradiol; FET, fluroethyltyrosine; FLT, fluorothymidine; FMAU, fluoromethylarabinofuranosyluracil; HED, hydroxyephedrine; MFBG, metaflurobenzylguanidine; MIBG, meta-iodobenzylguanidine; rhPSMA, radiohybrid prostate-specific membrane antigen.

[a]Approved by the US Food and Drug Administration.

[b]Approved by the European Medicines Agency.

targeted radioligand therapy (RLT), also known as peptide receptor radionuclide therapy (PRRT), a widely adopted approach for treating metastatic or inoperable differentiated NETs. This recommendation originates from the phase 3 clinical NETTER trial (ClinicalTrials.gov identifier NCT01578239), which demonstrated improved progression-free survival (PFS) and overall survival (OS) among patients with midgut NETs that were positive on SSTR PET who received SSTR RLT (lutetium-177 [^{177}Lu]-DOTATATE) together with long-acting hormonal therapy versus hormonal therapy alone.[22]

In other oncologic settings, SSTR PET also plays multiple important and distinct roles. For de novo and recurrent meningioma, SSTR PET/CT is able to discriminate tumor from tumor-free brain tissue with overall sensitivity and specificity of 90% and 73%, respectively, as demonstrated by Rachinger et al.[23] Moreover, SSTR PET has been identified as complementary to contrast-enhanced MRI, the current imaging gold standard in meningioma diagnosis and treatment planning. In a small cohort of eight patients, SSTR PET used for radiation therapy planning allowed for a reduction in treatment volumes compared with MRI-guided planning. This approach minimized radiation exposure to normal brain tissue without increasing the risk of local recurrence within 6 months.[24] Joint practice guidelines/procedure standards for the diagnostics and therapy of meningioma using SSTR PET have been developed by the European Association of Nuclear Medicine, the European Association of Neurooncology, the PET Task Force of the Response Assessment in Neurooncology Working Group, and the Society of Nuclear Medicine and Molecular Imaging and recommend the use of SSTR PET in initial meningioma staging to confirm the meningioma histology in lesions that appear ambiguous on MRI, in post-therapy response assessment, and in determining RLT eligibility.[6]

In head and neck paragangliomas and pheochromocytomas/paragangliomas with cluster 1A mutations, ^{68}Ga-labeled SSTR PET is considered the most sensitive imaging modality, demonstrating a lesion-based detection rate reaching 99% (Figure 2) in the post-therapy setting (the authors did not distinguish between restaging or suspected recurrence), as demonstrated by a prospective study comparing the diagnostic performance of ^{68}Ga-DOTATATE with ^{18}F-FDG among other molecular imaging modalities for the evaluation of cluster 1A pheochromocytoma and paraganglioma.[25] With regard to

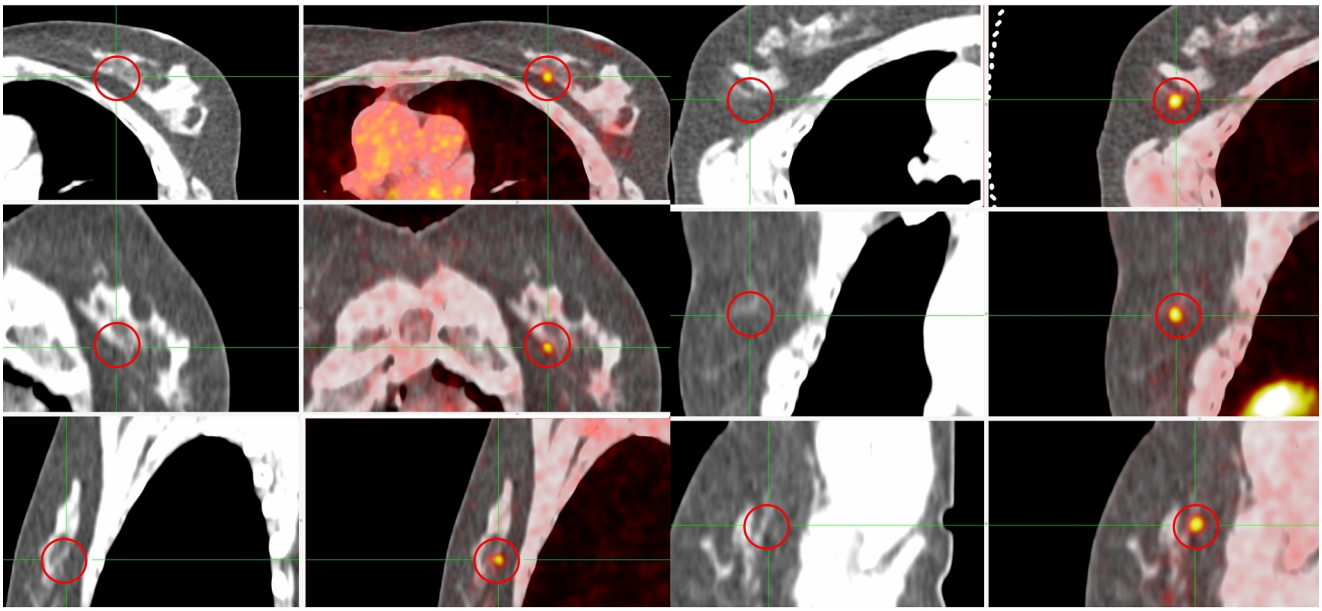

FIGURE 1 ^{68}Ga-DATA5m-LM4 SSTR antagonist PET/CT detects very small histopathologically proven metastases in both breasts (red circles) in a patient with a well-differentiated neuroendocrine tumor of the ileum that are not seen on conventional CT or MRI. ^{68}Ga-DATA5m, gallium-68–labeled (6-pentanoic acid)-6-(amino)methyl-1,4-diazepinetriacetate; CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; SSTR, somatostatin receptor.

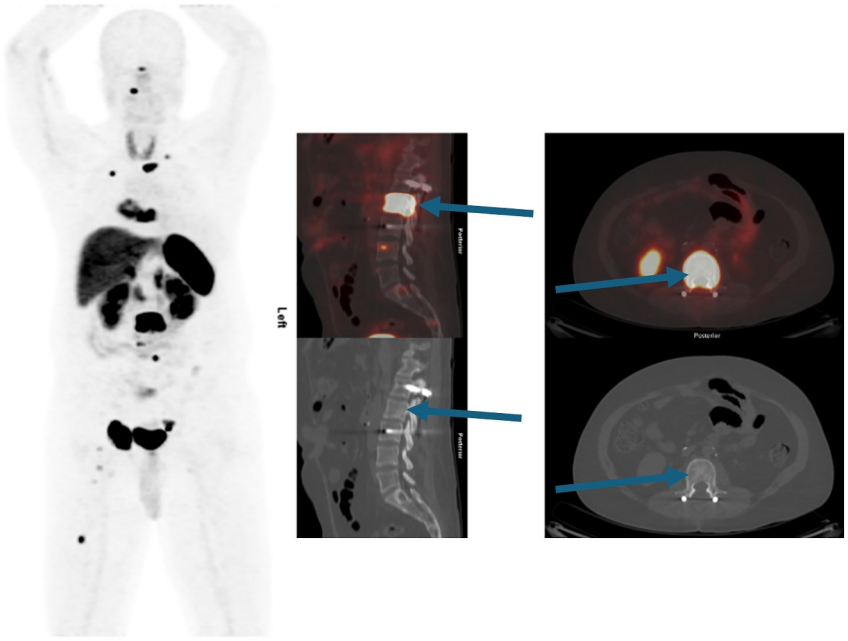

FIGURE 2 Case example of an excised retroperitoneal paraganglioma with metastasis involving several skeletal regions visible on SSTR ligand ^{68}Ga-DOTANOC imaging. This includes an intensely avid L2 vertebral bone marrow lesion (arrow) showing only mild, nonspecific sclerosis on CT but confirmed by MRI to be a metastasis. CT indicates computed tomography; ^{68}Ga-DOTANOC, gallium-68–labeled dodecane tetraacetic acid–1-Nal(3)–octerotide; MRI, magnetic resonance imaging; SSTR, somatostatin receptor.

pretherapy evaluation, another prospective study by Janssen et al. reported that the lesion-based detection rate for sporadic metastatic pheochromocytoma and paraganglioma was 98%.[26] Hence it is recommended for adult and pediatric staging and follow-up of sporadic head and neck paraganglioma, metastatic/multifocal disease, presurgical staging when the primary tumor is ≥5 cm and, notably, in disease detection screening in asymptomatic succinate dehydrogenase (*SDH*) mutation carriers.[5,8] In the setting of medullary thyroid

cancer, the NCCN recommends the use of ^{68}Ga-DOTATATE: (1) for staging in patients with a high tumor burden, (2) in cases characterized by a calcitonin plasma level >400 pg/mL, (3) in the presence of a high carcinoembryonic antigen level, and (4) when there is evidence of biochemical recurrence.[27]

^{68}Ga-DOTATATE and ^{68}Ga-DOTANOC PET have also shown potential utility in prostate cancer that has neuroendocrine differentiation, with high uptake of these tracers indicating a poor prognosis.[28] The degree of SSTR PET uptake in these tumors can also be used to determine eligibility for SSTR RLT, which has already been attempted a few times in the literature.[29]

^{68}Ga-DOTA SSTR PET has been identified as more sensitive on a per-lesion basis than conventional norepinephrine-based imaging (see below) for the evaluation of neuroblastoma with suspected metastasis.[30,31] Its potential lies particularly in meta-iodo-benzylguanidine (MIBG)-negative, relapsed or refractory disease.[32] Finally, ^{68}Ga-DOTATATE PET may also be useful in pituitary tumors, differentiating postsurgical scar from disease recurrence, and for RLT planning.[33]

PSMA-based imaging

PSMA is a transmembrane protein expressed by prostatic tissue and proven to be an excellent biologic target for molecular imaging of prostate cancer. Current probes specific to PSMA are inhibitor peptides that bind to the extracellular domain of the antigen and are labeled with positron-emitting radionuclides, such as the US Food and Drug Administration (FDA)-approved ^{68}Ga-PSMA-11, ^{18}F-radiohybrid (rh)PSMA-7.3, and ^{18}F-DCFPyL as well as others not yet FDA-approved.[34,35] Both ^{68}Ga-PSMA-11 and ^{18}F-DCFPyL are also approved by the European Medicines Agency.

The clinical value of PSMA-targeting PET in the diagnosis and management of prostate cancer has been thoroughly investigated, leading to the incorporation of this imaging modality into updated clinical guidelines on prostate cancer management, including the European Association of Urology–European Association of Nuclear Medicine–European Society for Radiotherapy and Oncology–European Society of Urogenital Radiology–International Society of Urological Pathology–International Society of Geriatric Oncology guidelines and the NCCN guidelines.[7,36–38] PSMA PET/CT is now used in the routine initial staging of prostate cancer in patients with unfavorable intermediate-risk features (Gleason score 4 + 3, prostate-specific antigen [PSA] 10–20 ng/mL, and/or T2b–T2c clinical stage) or high-risk features (Gleason score ≥4 + 4, PSA >20 ng/mL, and/or T3–T4 clinical stage).[7] In the randomized controlled proPSMA trial (Australian New Zealand Clinical Trials Registry number ANZCTR12617000005358), greater diagnostic accuracy was reported in the staging of high-risk prostate cancer by PSMA PET/CT using ^{68}Ga-PSMA-11 compared with the traditional combination of CT and technetium-99 isomer (^{99m}Tc)-diphosphonate bone scan, such as ^{99m}Tc-methylene diphosphonate or MDP (area under the receiver operating characteristic curve [AUC], 92% [95% confidence interval (CI), 88%–95%] vs. 65% [95% CI, 60%–69%]).[39] The few studies that compared the diagnostic performances of the different PSMA-targeting PET tracers (i.e., ^{68}Ga-PSMA-11, ^{18}F-rhPSMA-7(.3), and ^{18}F-DCFPyL) demonstrated that they are comparable for initial diagnosis and biochemical recurrence of prostate cancer.[40–42]

PSMA PET/CT and multiparametric MRI of the pelvis are likely to be complementary for locoregional (tumor [T] and lymph node [N]) staging. In a meta-analysis by Ma et al., staging PSMA PET/CT pooling different tracers together (i.e., ^{68}Ga-PSMA-11, ^{68}Ga-PSMA-617, ^{18}F-PSMA-1007, and ^{18}F-DCFPyL) was more sensitive for primary lesion and lymph node detection (90% vs. 84% and 67% vs. 36%, respectively), whereas multiparametric MRI was more sensitive for seminal vesicle involvement and extracapsular extension (60% vs. 51% and 66% vs. 59%, respectively).[43] Staging PSMA PET/CT using ^{18}F-PSMA-1007 was also compared with whole-body MRI for the detection of distant metastasis in a clinical trial by Anttinen et al. and was found to outperform MRI in sensitivity for bone (100% vs, 69%, respectively) and soft tissue lesions (82% vs. 73%).[44] In light of the very high overall accuracy in cancer staging with PSMA PET, the few retrospective studies comparing PSMA PET with conventional MRI staging indicated improved survival using the former.[45,46] No data from prospective randomized studies are available to assess the influence of staging PSMA PET on survival, but several clinical trials are ongoing to address this question (e.g., ClinicalTrials.gov identifiers NCT04175431, NCT05000827, and NCT06003556).

Another important role is played by PSMA PET/CT in the follow-up of patients with prostatic cancer after potentially curative prostate cancer treatment. In this regard, PSMA PET is valuable in tumor localization in case of biochemical recurrence (defined as PSA rise >2 ng/mL above nadir after radiotherapy and an increase in PSA to ≥0.2 ng/mL confirmed by a second PSA level >0.2 ng/mL after prostatectomy with PSA measured at 6–13 weeks postsurgery) or in case of biochemical persistence (defined as a persistently elevated PSA ≥0.1 ng/mL more than 6 weeks after prostatectomy).[7] Figure 3 shows an example of a patient who had biochemical recurrence with a metastatic bone lesion best appreciated on PSMA PET/CT.

The pooled sensitivity and specificity of PSMA PET/CT using different PSMA radiotracers for biochemical recurrence has was 84% and 97%, respectively, based on a meta-analysis by Jeet et al.,[47] with PSMA PET/CT detecting locoregional and distant disease in up to 70% of patients with castration-resistant prostate cancer who were negative on conventional imaging.[48] With regard to the sensitivity for distant metastasis in the setting of biochemical recurrence, PSMA PET/CT using ^{68}Ga-PSMA-11 proved superior to whole-body MRI with an AUC of 90% (95% CI, 85%–95%) versus 67% (95% CI, 54%–80%), as reported by Emmett et al.[49]

Madan and colleagues' group raised a crucial question about whether the earlier detection of disease sites using PSMA PET/CT—and the subsequent more aggressive treatment based solely on positive findings from this imaging tool—actually leads to improved patient outcomes compared with treatment decisions based on conventional imaging alone.[50] This is being prospectively evaluated in ongoing clinical trials (e.g., ClinicalTrials.gov identifier NCT05919329).

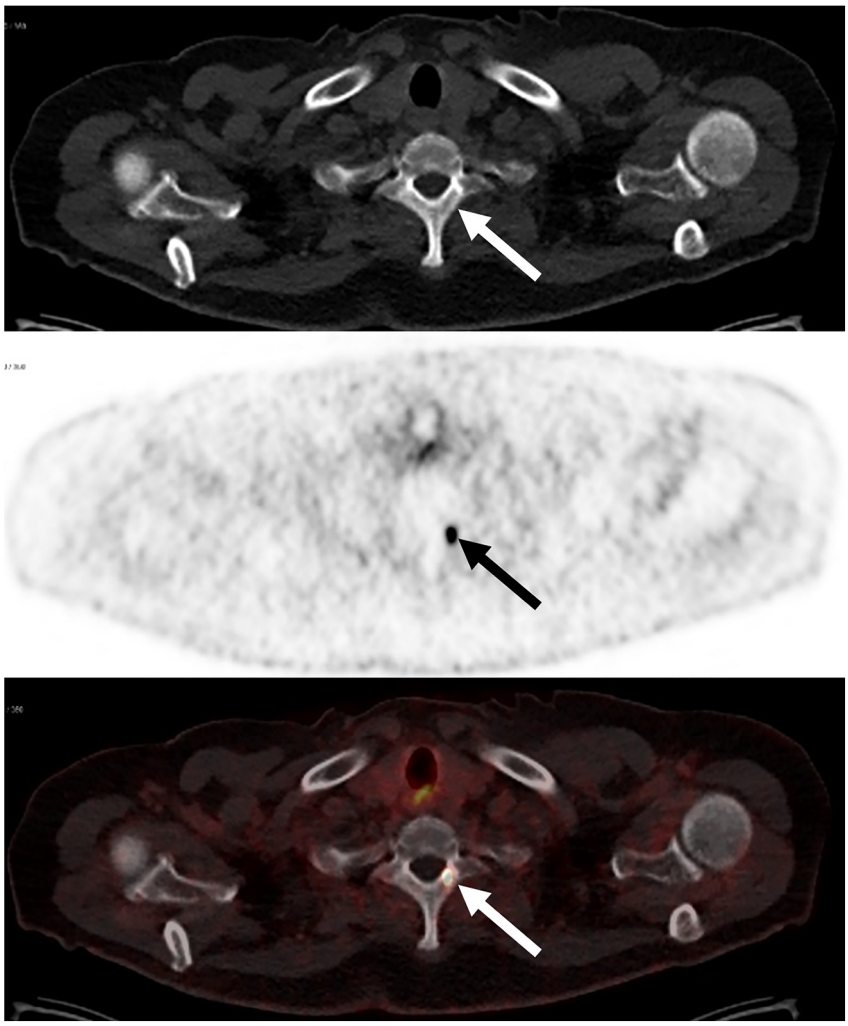

FIGURE 3 Example of a patient with biochemical prostate cancer recurrence (PSA, 0.25 ng/mL) with a solitary, metastatic, T1 vertebral bone lesion (arrows) best appreciated on PSMA PET. PET indicates positron emission tomography; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen.

Another important application of PSMA PET/CT is assessing eligibility before RLT with ^{177}Lu-PSMA-617 for metastatic castration-resistant prostate cancer, a new treatment recently approved by the FDA after the phase 3 VISION trial (ClinicalTrials.gov identifier NCT03511664) demonstrated that ^{177}Lu-PSMA-617 prolonged PFS and OS when added to standard-of-care management of these patients.[7,51]

Additional applications of PSMA PET that are not yet part of the routine management of prostate cancer include its use for radiotherapy planning.[52] In a clinical trial by Armstrong et al., PSMA PET using ^{68}Ga-PSMA-11 changed management in 45% of patients before salvage radiotherapy for biochemical recurrence compared with a 22% change in those who did not undergo PSMA PET ($p = .002$).[53] Zamboglou et al. retrospectively demonstrated the ability of PSMA PET-guided salvage radiotherapy to improve biochemical recurrence-free survival versus radiotherapy not informed by PSMA PET ($p = .01$).[54] Prospective studies assessing the survival impact of using PSMA PET in this setting are needed. PSMA PET may also be used for response assessment after systemic treatment for metastatic prostate cancer.[55]

In the United States, Australia, and most of Europe, PSMA PET and other forms of molecular prostate cancer imaging, such as ^{18}F-fluciclovine PET (see below), are accessible for routine clinical use. However, PET in general is not readily accessible in many developing countries, unlike traditional gamma cameras that can be used to image ^{99m}Tc-based tracers. To meet the demand for molecular prostate cancer imaging in regions with limited access to PET devices or tracers, the single-photon emission CT (SPECT) tracer ^{99m}Tc-PSMA has been developed, and a few retrospective studies have compared the performance of ^{99m}Tc-PSMA SPECT/CT and ^{68}Ga-PSMA PET/CT for prostate cancer diagnosis, recurrence, or restaging. Available data suggest that they are comparable in the detection of lesions ≥1 cm and at PSA levels ≥2 ng/mL, thus providing a potentially cheaper and more accessible form of valuable PSMA-based imaging for countries and peoples that need it.[56–59]

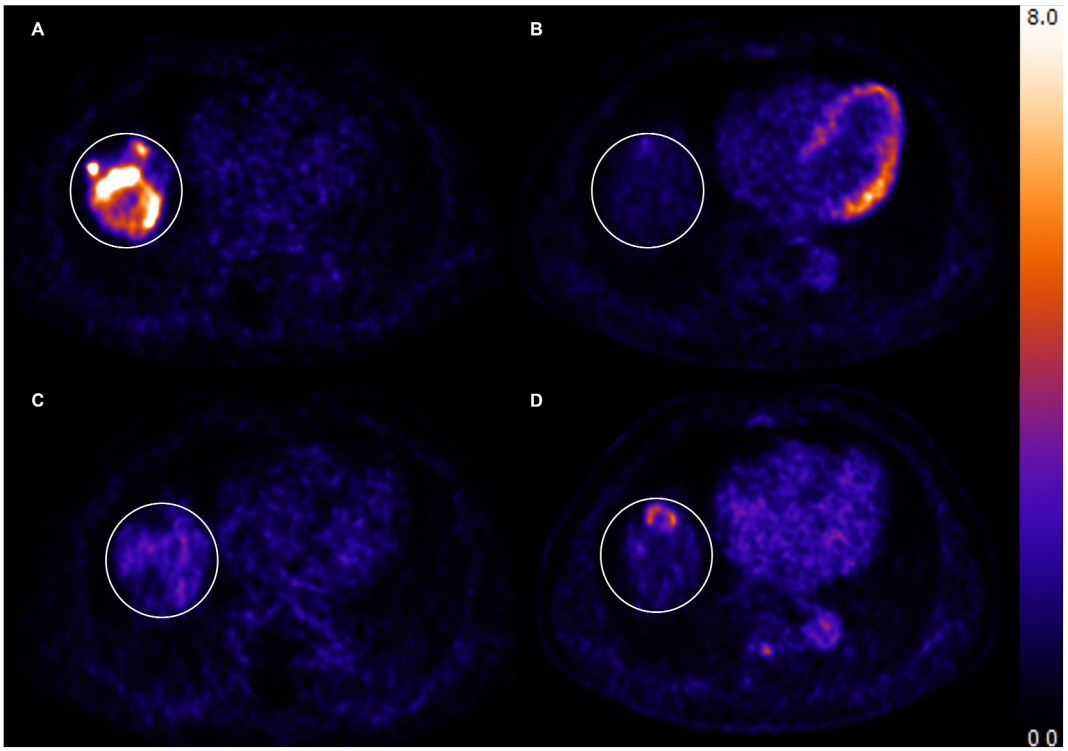

FIGURE 4 (A) Baseline, axial PSMA PET slice through the lower chest and upper abdomen in a patient with CRPC revealing hepatic metastases with uptake greater than normal liver (white circle). (B) Baseline axial FDG PET slice showing negligible FDG uptake in the same liver metastases (white circle) with intense PSMA uptake. (C) After three RLT cycles, the PSA level dropped from approximately 76 ng/mL to approximately 30 ng/mL, and a fourth RLT cycle was given followed by a PSMA scan that revealed a good imaging response in the liver metastases (white circle), with other liver, bone, and lymph node metastases following a similar pattern, resulting in the administration of a fifth RLT cycle. (D) Because of a rising PSA level before the fifth RLT cycle, which was discordant with the good imaging response on PSMA PET, FDG PET was performed to assess for disease dedifferentiation. The FDG PET scan shows increased FDG uptake in the same region of liver metastases (white circle) as well as other metastases (not shown) that were negative on follow-up PSMA, indicating disease dedifferentiation. CRPC indicates castration-resistant prostate cancer; CT, computed tomography; FDG, fluorodeoxyglucose; MRI, magnetic resonance imaging; PET, positron emission tomography; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; RLT, radioligand therapy.

Our patient coauthor (H.J.Z.) provides an interesting perspective regarding the use of PSMA PET in prostate cancer. He has castration-resistant prostate cancer metastatic to the liver, bone, and lymph nodes and underwent a baseline ^{68}Ga-PSMA PET scan to assess PSMA uptake before administering ^{177}Lu-PSMA RLT. All lesions had higher tracer uptake than the normal liver, deeming him eligible for treatment, and he subsequently underwent three cycles of RLT with a good response (PSA decreased from approximately 76 ng/mL at baseline to approximately 30 ng/mL after the three cycles). A fourth RLT cycle was then given followed by a PSMA PET scan about 3 weeks thereafter showing a good imaging response, and a fifth cycle was then administered. However, it was observed that the PSA level actually increased to approximately 65 ng/mL before the fifth cycle. This discordance between the *good* imaging response and the rising PSA level was later investigated by performing an FDG PET scan to determine whether there might have been a prostate cancer cell dedifferentiation resulting in a more aggressive disease course with negative PSMA but positive FDG.[60] Indeed, the FDG PET scan performed 2 weeks after the fifth cycle showed increased FDG uptake in the PSMA-negative metastatic lesions, including the liver lesions, with further rise in PSA to approximately 102 ng/mL, indicating increased cancer aggressiveness/dedifferentiation and the need to adjust treatment (Figure 4). He states the following: "I, the patient H.J.Z., am appreciative of the fact that molecular imaging using two different radiotracers in my case contributed to the individualization of my management. I found the PSMA and FDG PET scans easy to undergo without any side effects or significant inconvenience. I also had no concerns regarding the radiation dose delivered from these tests, which is trivial compared to the radiation dose I received from radioligand therapy and is justified considering the benefit-to-risk ratio."

Despite the name, PSMA is not a specific biomarker for malignant or benign prostate tissue, and its expression has been demonstrated in several tumor types in which PSMA PET has exhibited potential clinical value. PSMA PET using ^{68}Ga-PSMA-11 has shown potential in the diagnosis and prognosis of glioma and glioblastoma, particularly in distinguishing low-grade from high-grade glioma, with higher PSMA avidity in the latter.[35] For example, a study that compared pretherapy PSMA PET with FDG PET in distinguishing low-grade from high-grade glioma, Liu et al. found that PSMA PET with ^{68}Ga-PSMA-617 was superior, with an AUC of 0.96 versus 0.79

for FDG.[61] PSMA PET has also been shown to be useful in the diagnostic evaluation of salivary gland tumors, renal cell carcinoma, and thyroid carcinoma.[62–64]

A relatively recent advancement in radiotherapy is the development of biology-guided radiotherapy enabled by the RefleXion X1 radiotherapy system, which has opened a new avenue for the use of PET tracers for the real-time, tracer signal-guided administration of ionizing radiation. Rather than guidance by anatomic imaging alone, biology-guided radiotherapy allows radiotherapy dose delivery directly to PET-avid tumor tissue because the PET tracer signals are detected with dose adjustments made in real time, accounting for target movement and sparing normal tissue.[65] It has been demonstrated that this novel technology is effective, and it has been approved by the FDA for use in primary or metastatic lung and bone tumors using ^{18}F-FDG PET/CT.[66] Preliminary studies have also demonstrated feasibility in its use with PSMA PET/CT in the treatment of prostate cancer[67] and renal cell carcinoma.[68]

Norepinephrine transporter-based imaging

The noradrenaline (norepinephrine) transporter (NAT) is a transmembrane protein responsible for synaptic terminal transportation of endogenous norepinephrine in neurons and adrenal chromaffin cells. Like the SSTRs, NATs are expressed by cells of neuroendocrine origin and are optimal targets for molecular imaging using radiolabeled norepinephrine analogs.

The most common radioligand/analog for NAT imaging is radioiodine-labeled MIBG in the form of the SPECT tracers iodine-123 [^{123}I]-MIBG and ^{131}I-MIBG. However, MIBG imaging can also be done using the PET tracer ^{124}I-MIBG. This tracer has shown a greater lesion detection rate compared with SPECT tracers when performed in children who have relapsed neuroblastoma, with ^{124}I-MIBG detecting lesions throughout the body that were undetected by ^{123}I-MIBG SPECT/CT, but its routine clinical use in place of the more accessible SPECT tracers needs further justification.[69]

For neuroblastoma, ^{123}I-MIBG SPECT remains the first-line imaging agent for staging and follow-up imaging, despite the good performance of SSTR PET in this setting.[9] In contrast, the diagnostic performance of MIBG SPECT for nonsporadic pheochromocytoma and paraganglioma is less satisfactory as opposed to sporadic pheochromocytoma, in which it has an estimated sensitivity of 83%–100% and specificity of 95%–100%.[8]

Outside the realm of radioiodine-labeled tracers, ^{18}F-metaflurobenzylguanidine, carbon-11 (^{11}C)-hydroxyephedrine, and ^{18}F-fluorodopamine are PET tracers that target the norepinephrine transporter and show potential to outperform MIBG SPECT in the pretherapy and post-therapy evaluation of neuroblastoma and/or pheochromocytoma and paraganglioma.[70,71] Their clinical use, however, has been limited by the short half-life of ^{11}C and ^{18}F, hampering delayed imaging, complex labeling procedures, and radionuclide distribution challenges. Furthermore, it is not clear whether the superiority of these tracers over MIBG SPECT is caused by the use of PET technology or by the superior characteristics of these ligands. A head-to-head comparison between these tracers and ^{124}I MIBG would likely address this issue.

Estrogen receptor-based imaging

Estrogen receptors (ERs) are intracellular mediators targeted by the hormone estrogen that are highly expressed in the most common forms of breast cancer. Therefore, ERs are prime targets for the molecular imaging and noninvasive evaluation of breast cancer using the ^{18}F-labeled PET tracer fluoroestradiol (^{18}F-FES).

Accepted applications of ^{18}F-FES include: (1) assessing ER status in lesions that are difficult to biopsy or when biopsy is nondiagnostic, resulting in a pooled sensitivity and specificity in the pretherapy setting of 82% and 95%, respectively, as demonstrated by Evangelista et al.[72]; (2) at diagnosis or after progression of metastatic disease to guide antiestrogen therapy, thanks to its ability to evaluate biomarker expression in all metastatic lesions with greater safety profile compared with tissue biopsy; and (3) to solve clinical dilemmas arising with other imaging modalities, including FDG PET, showing equivocal or inconclusive findings, provided that the ^{18}F-FES PET results could lead to treatment modification.[10] Furthermore, its diagnostic performance in the staging of ER-positive breast cancer was identified as comparable to, if not better than, the standard of care with FDG PET/CT.[73]

^{18}F-FES PET is particularly useful in patients with known invasive lobular breast cancer, in which substantial numbers of metastatic lesions are not FDG-avid.[74] In one head-to-head comparison study by Ulaner et al. in seven patients, staging ^{18}F-FES PET detected more metastatic invasive lobular breast cancer bone lesions than FDG PET (254 ^{18}F-FES–avid lesions vs. 111 ^{18}F-FDG–avid lesions) and showed overall greater uptake within disease sites. However, in one patient, liver metastases were evident on FDG PET but not on ^{18}F-FES PET.[75] It has been demonstrated that FDG PET and ^{18}F-FES PET successfully complement each other in the setting of metastatic invasive lobular breast cancer. In one study involving 20 patients who underwent imaging with both tracers, ^{18}F-FES PET was identified as more sensitive than FDG PET in the detection of bone metastases (43 vs. 37 of 53 skeletal anatomic regions involved with superior detection of bone metastasis in nine versus four patients; $p = .05$); whereas FDG PET was more sensitive in the detection of nonbone metastases (57 vs. 37 lesions; $p < .001$).[76] The inferiority of ^{18}F-FES PET in the liver because of its high physiologic uptake was demonstrated by Boers et al., who observed that ^{18}F-FES PET had only 18% sensitivity when using visual assessment alone.[77] Taken together, these results suggest that both ^{18}F-FES PET and FDG PET should be performed in the evaluation of metastatic invasive lobular breast cancer.[76]

Finally, in the setting of ER-positive brain metastasis, ^{18}F-FES PET may play an adjunct role for radiotherapy response assessment, distinguishing normal from recurrent or residual disease from radiotherapy sequalae.[78]

Beyond breast cancer, potential uses of ^{18}F-FES PET that have been evaluated include the diagnosis, prognostication, and therapy response assessment of endometrial and ovarian cancers.[79–82] When used with FDG PET/CT, ^{18}F-FES PET may have a role in distinguishing benign from malignant uterine tumors.[82] Moreover, in a prospective study by Yamada et al., low ^{18}F-FES uptake of the primary tumor in patients with endometrial cancer at staging was strongly predictive of lymph node metastasis and was an independent predictor of poor PFS and OS.[79] Furthermore, Roze et al. demonstrated in a small cohort of six patients that ^{18}F-FES PET/CT potentially could be used to determine eligibility of patients with granulosa cell tumors of the ovary for hormonal therapy and to predict treatment response.[80]

Proliferation-based molecular imaging

Cell proliferation is another hallmark of cancer and has been successfully imaged in vivo by tracking cell nucleoside metabolism and DNA synthesis. The most studied proliferation tracer is ^{18}F-fluorothymidine (FLT), mostly used for therapy response assessment.[11–14,83,84] Other agents that have been used include ^{11}C-labeled thymidine analogs and ^{18}F-fluoromethylarabinofuranosyluracil.[85,86]

The potential role of FLT PET lies in therapy response assessment for cancer, including B-cell lymphoma,[11] head and neck squamous cell carcinoma,[83] mesothelioma,[84] lung cancer,[12] and breast cancer,[13] as well as in the evaluation of brain tumors.[14] Minamimoto et al. demonstrated that, in patients with diffuse large B-cell lymphoma who received either rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone or rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin, interim FLT PET/CT performed after two cycles of chemoimmunotherapy was a superior independent predictor of outcome compared with interim FDG PET/CT performed in the same patients.[11] Christensen et al. found added value in the use FLT PET/CT for the diagnosis of lung cancer relapse postradiotherapy, distinguishing it from benign radiation sequelae with greater specificity than FDG PET/CT.[12] In addition, FLT PET/CT has potential use in the planning and monitoring of radiotherapy to minimize bone marrow toxicity by evaluating baseline FLT bone marrow uptake and radiotherapy-induced uptake changes.[87,88]

Unfortunately, FLT has not been adopted for routine use because of its scarce availability and lack of approval by the FDA at the time of this writing. This has also likely hindered clinical research on its use in cancer assessment; therefore, and it has not yet been officially incorporated into cancer management guidelines. Moreover, it has not been demonstrated that FLT is consistently superior or of added value to FDG in disease staging of lymphoma, breast cancer, lung cancer, and other cancers and thus cannot be recommended for cancer staging.[89–91] However, it could be used to assess response to cyclin-dependent kinase 4 and 6 inhibition therapy in various cancers, such as breast cancer and mantle cell lymphoma.[92,93] In fact, this was tested in a clinical trial in patients with mantle cell lymphoma[94] and is currently under investigation in patients with breast cancer (ClinicalTrials.gov identifier NCT02608216).

Cell membrane synthesis-based molecular imaging

Along with an increased proliferation rate, an elevated rate of cell membrane synthesis accompanied by an increased metabolism of its phospholipid components, such as choline, is a hallmark of neoplasms. Molecular imaging of cell membrane synthesis is predominantly based on the labeling of choline with ^{11}C or ^{18}F radionuclides. However, ^{18}F-fluorocholine is preferred because it overcomes the logistical challenges associated with the short physical half-life of ^{11}C of only 20 minutes.

Both ^{11}C-choline and ^{18}F-fluorocholine have established roles in the evaluation of prostate cancer, including in the setting of biochemical recurrence.[7] However, the use of choline PET seems limited primarily by its reduced sensitivity for small regional lymph node detection,[95] and its use is controversial when PSA values are <1 ng/mL.[96–98] Accordingly, choline PET, even using ^{18}F-fluorocholine, has been almost completely replaced by PSMA PET because of the overall higher sensitivity and detection rate of the latter in the setting of biochemical recurrence, as demonstrated in randomized clinical trials comparing both tracers.[99,100] Consequently, choline PET is arguably reserved for the evaluation of biochemical recurrence only when PSMA PET is unavailable.[7]

^{18}F-fluorocholine PET has potential application in the setting of intrahepatic well differentiated hepatocellular carcinoma (HCC) in pretreatment and post-treatment settings in part because of its relatively low liver uptake.[101,102]

Amino acid-based molecular imaging

A few amino acids (AAs) have been radiolabeled over the years for the purpose of molecular imaging of AA metabolism in specific cancer types, based on the upregulation of AA transport and the consequent increased AA uptake compared with normal tissue. Examples of AAs labeled with positron emitters include ^{11}C-methionine (^{11}C-MET), ^{18}F-fluroethyltyrosine (^{18}F-FET), ^{18}F-fluorodihydroxyphenylalanine (^{18}F-FDOPA) and ^{18}F-fluorocyclobutanecarboxylic acid (^{18}F-FACBC; also known as ^{18}F-fluciclovine or Axumin [Blue Earth Diagnostics]). An example of an AA tracer available for SPECT imaging is ^{123}I-iodomethyltyrosine (^{123}I-IMT). ^{18}F-FDOPA and ^{18}F-fluciclovine are FDA-approved, while ^{18}F-FET is undergoing evaluation for approval by the FDA.

Each of these radiolabeled AAs has found specific indications in various oncological settings. ^{11}C-MET, ^{18}F-FET and ^{18}F-FDOPA have been extensively used for the evaluation of brain tumors.[15,103,104] Although ^{11}C-MET was frequently used in early PET studies exploiting the upregulated AA metabolism, it was later largely replaced by ^{18}F-labeled AA tracers, such as ^{18}F-FET and ^{18}F-FDOPA.[105] In general, all radiolabeled AAs show relatively low uptake by normal brain tissue,

and brain tumors can be distinguished from the surrounding normal brain tissue by increased AA uptake with high contrast. This altered metabolic activity underpins the rationale for several diagnostic aims: (1) to guide needle biopsy at diagnosis, (2) to differentiate neoplastic from nonneoplastic lesions, (3) to delineate tumor extent, (4) to distinguish tumor relapse from treatment-related changes, and (5) to assess treatment response.[15] For example, in the ARTE trial (ClinicalTrials.gov identifier NCT01443676), patients aged 65 years or older with glioblastoma who received bevacizumab with or without radiotherapy performed poorly, with inferior OS when pretherapy and/or post-therapy ^{18}F-FET uptake was elevated.[106] Moreover, several studies have demonstrated disagreement between pretherapy MRI and AA PET tumor volumes, which, if not taken into consideration, could lead to undertreatment using either modality alone.[107–109] Consequently, radiolabeled AAs have become the preferred PET tracers in patients with brain tumors, and the use of AA PET as a supplement to MRI is recommended.[15,110–112]

^{18}F-FDOPA PET/CT is also useful in the detection and localization of pheochromocytoma and paraganglioma, with diagnostic performance varying considerably between the two entities and according to the different genetic mutation associated.[113,114] In two meta-analyses, the pooled sensitivity at initial diagnosis was 79% for paraganglioma and 97% for pheochromocytoma.[115,116] ^{18}F-FDOPA PET is further recommended by the European Society of Medical Oncology in the preoperative evaluation of medullary thyroid carcinoma with a calcitonin level >500 pg/mL or when metastasis is suspected.[16]

With regard to ^{18}F-fluciclovine, its recommended clinical use is in the evaluation of biochemical recurrence in prostate cancer as a second-choice imaging modality when PSMA PET is unavailable.[7] Its use for radiotherapy planning in the setting of postsurgical biochemical recurrence has been found useful, as seen in the EMPIRE-1 trial (ClinicalTrials.gov identifier NCT01666808) in which there was an improvement in 3-year biochemical failure-free survival when used with conventional imaging versus conventional imaging alone to guide radiotherapy (75.5% vs. 63.0%, respectively; $p = .0028$).[117]

Emerging biologic targets for molecular imaging

There are multiple biologic targets that have been more recently investigated, showing considerable promise in cancer molecular imaging. Table 2 shows some of the emerging biologic targets and their respective radiotracers along with suggested clinical applications.[118–124]

Among the most promising is the radiolabeled fibroblast-activating protein inhibitor (FAPI) imaging targeting fibroblasts recruited into the TME, thereby enabling cancer imaging. FAPI PET is proving to be a valuable alternative to FDG PET in the evaluation of various cancers in which FDG performance is suboptimal because of low FDG avidity or relatively high background uptake. Examples include sarcomas, gastrointestinal carcinomas, pancreatic adenocarcinomas, hepatocellular carcinomas, cholangiocarcinomas, and lung adenocarcinomas as well as breast, bladder, ovarian, and head and neck cancers.[118] Several, mostly retrospective studies comparing the performance of FAPI PET/CT versus FDG PET/CT in the same cancers are currently available. In ovarian cancer, Liu et al. observed that ^{68}Ga-FAPI PET/CT detected more metastatic peritoneal lesions in both lesion-based and patient-based analyses compared with FDG PET/CT at initial diagnosis and for recurrence, leading to a change in management for about 14% of patients.[125] More impressive changes in management (47.8%) were reported by Zhang et al. in HCC when staging FAPI and staging FDG were prospectively compared, with the former showing significantly superior intrahepatic and lymph node lesion detection.[126] Figure 5 illustrates the difference between FAPI PET and FDG PET performed in the same patient with HCC. In a retrospective study by Metzger et al., restaging FAPI PET for locally advanced or recurrent pancreatic adenocarcinoma resulted in a major change in planned radiotherapy in 52% of patients compared with contrast-enhanced CT alone.[127] Thus FAPI PET as a TME-centric probe may be used for staging, restaging, and response assessment instead of or in addition to the mainly cancer cell-centric FDG PET. Larger randomized clinical trials are needed to clearly establish a role for FAPI PET in the various settings and to determine whether its use improves patient outcome.

Another probe is the C-X-C chemokine receptor type 4 (CXCR4) ligand labeled with ^{68}Ga (e.g., ^{68}Ga-pentixafor and ^{68}Ga-pentixather), ^{64}Cu, and ^{18}F, which is potentially useful in patients with non-Hodgkin lymphoma, lung cancer, breast cancer, HCC, and other solid tumors.[119] The body of evidence supporting the clinical use of CXCR4 is less impressive compared with FAPI. However, ^{68}Ga-pentixafor has been compared with FDG in several studies, including a prospective one by Mayerhoefer et al. indicating superior performance of the former tracer in the pretherapy evaluation of mantle cell lymphoma.[128] Conversely, when applied for nasopharyngeal carcinoma staging and recurrence detection, no significant difference was reported between the two radiotracers.[129] Larger studies are needed to fully elucidate the potential of CXCR4 PET in various clinical scenarios.

Other agents include the glucagon-like peptide-1 receptor agonist exendin-4,[120] gastrin-releasing peptide receptor ligands (e.g., bombesin),[121] carbohydrate antigen 19-9 antibody 5B1,[128] carbohydrate antigen IX antibody girentuximab,[122] poly(adenosine diphosphate-ribose) polymerase inhibitors,[123] and tumor hypoxia-targeting agents (e.g., nitroimidazoles).[124] The tumor hypoxia tracers, such as ^{18}F-fluoromisonidazole (FMISO), show promise in guiding radiotherapy planning to maximize efficacy and minimize risk as well as predicting response by determining baseline tumor hypoxia for head and neck and nonsmall cell lung cancer.[130,131] One phase 2 clinical trial investigating radiotherapy dose escalation in head and neck cancer using ^{18}F-FMISO PET demonstrated a significantly better response among nonhypoxic tumors (no ^{18}F-FMISO uptake) and a 25% improvement in 5-year local disease control among patients with hypoxic tumors receiving dose-escalated radiotherapy compared with standard radiotherapy.[130] Other promising agents are monoclonal antibodies targeting receptor tyrosine kinases, including human epidermal growth factor receptor 2-targeting zirconium-89–trastuzumab for the assessment of human epidermal growth factor

TABLE 2 Biologic targets and associated radiotracers with promising applications in cancer molecular imaging.

Biologic target	Radiotracer(s)	Prospective cancer imaging applications
Fibroblast-activating protein (FAP) expressed in the tumor microenvironment	^{68}Ga-labeled, ^{18}F-labeled, and ^{99m}Tc-labeled FAP inhibitors, such as FAPI-04 and FAPI-46	Sarcomas, gastrointestinal carcinomas, liver and biliary tract cancers, lung and pancreatic adenocarcinomas, and breast, bladder, ovarian, and head and neck cancers (Yang 2024[118])
C-X-C motif chemokine receptor type 4 (CXCR4)	^{68}Ga-labeled, ^{64}Cu-labeled, ^{18}F-labeled, and ^{99m}Tc-labeled CXCR4 ligands, such as pentixafor and pentixather	Non-Hodgkin lymphoma, lung cancer, breast cancer, hepatocellular carcinoma, and other solid tumors (Cheng 2024[119])
Glucagon-like peptide-1 receptor (GLP-1R)	^{68}Ga-labeled, ^{18}F-labeled, ^{99m}Tc-labeled, and ^{111}In-labeled GLP-1R agonist (exendin-4)	Insulinomas (Boss 2024[120])
Gastrin-releasing peptide receptor (GRPR)	^{68}Ga-labeled, ^{64}Cu-labeled, ^{18}F-labeled, ^{111}In-labeled, and ^{99m}Tc-labeled GRPR ligands (e.g., bombesin)	Prostate and breast cancer (Chernov 2023[121])
Receptor tyrosine kinases (RTKs), immune checkpoints and immune cell receptors	^{64}Cu-labeled and ^{89}Zr-labeled receptor tyrosine kinase antibodies (e.g., trastuzumab, bevacizumab, pembrolizumab)	Breast, gastric, ovarian, nonsmall cell lung, colorectal, and esophageal cancer as well as melanoma and squamous cell carcinoma of the head and neck (Manafi-Farid 2022[122])
	^{89}Zr-labeled antibodies against CD4 and CD8 expressed on tumor-infiltrating lymphocytes (e.g., IAB22M2C)	Lung cancer (Manafi-Farid 2022[122])
	^{64}Cu-labeled polyglucose nanoparticles for tumor-associated macrophages (e.g., macrin)	Lung cancer (Manafi-Farid 2022[122])
	^{89}Zr-labeled antibodies targeting cancer stem cell biomarkers (e.g., bstrongomab, anti-CD133, anti-LGR5)	Prostate cancer, colorectal cancer, and central nervous system tumors (Manafi-Farid 2022[122])
Carbohydrate antigen 19-9 (CA 19-9)	^{89}Zr-5B1	Pancreatic ductal adenocarcinoma (Manafi-Farid 2022[122])
Carbohydrate antigen IX	^{124}I-girentuximab and ^{89}Zr-girentuximab	Renal cell carcinoma (Manafi-Farid 2022[122])
Poly(adenosine diphosphate-ribose) polymerase (PARP)	^{18}F-labeled and ^{123}I-labeled PARP inhibitors (e.g., olaparib)	Prostate and breast cancer (Xu 2022[123])
Tumor hypoxia	^{18}F-labeled nitroimidazoles, including FMISO, FAZA, FETNIM, and EF5, as well as ^{64}Cu-ATSM	Glioma, breast, head and neck, cervical, esophageal, and lung cancer and rhabdomyosarcoma (Perez 2023[124])

Abbreviations: ^{18}F, fluorine-18; ^{64}Cu, copper-64; ^{68}Ga, gallium-68; ^{89}Zr, zirconium-89; ^{99}Tc, technetium-99 isomer; ^{111}In, indium-111; ^{123}I, iodine-123; ^{124}I, iodine-124; ^{177}Lu, lutetium-177; ATSM, diacetyl-bis(N4-methylthiosemicarbazozne); DOTA, dodecane tetraacetic acid; DOTATATE, DOTA-octreotate; DOTATOC, DOTA-octreotide; FAZA, fluoroazomycin arabinoside; FETNIM, fluoroerythronitroimidazole; FMISO, fluoromisonidazole; LGR5, leucine-rich repeat-containing G-protein–coupled receptor 5 precursor.

receptor 2-positive malignancies and predicting response to targeted therapy,[132] as well as antibodies targeting immune checkpoints, immune cells in the TME, such as CD4-positive or CD8-positive tumor-infiltrating lymphocytes, and tumor-associated macrophages as well as cancer stem cell biomarkers. These tracers are particularly useful for characterizing the TME and predicting response to immunotherapy for which there are ongoing clinical trials (e.g., ClinicalTrials.gov identifier NCT04168528).[122,133]

CONCLUSION AND PROSPECTS

By radiolabeling appropriate probes capable of targeting various aspects of cancer biology, molecular imaging provides a noninvasive method of cancer evaluation relevant for patient-specific (individualized) precision medicine. Molecular imaging with nuclear probes alongside advanced PET technology is spearheading the growing significance of this imaging approach in the personalization of cancer care. Multiple nuclear probes beyond FDG, primarily PET tracers discussed in this review, are currently used against specific biologic targets addressing specific clinical scenarios and guiding therapy. Some of these probes are already approved by the FDA and the European Medicines Agency and are now recognized as part of the standard of care, such as PSMA for prostate cancer, somatostatin analogs for NETs, and ^{18}F-FES for breast cancer (particularly invasive lobular breast cancer). Others, especially those targeting the TME, such as FAPI and CXCR4 ligands, are being investigated and validated by prospective clinical trials to evaluate their potential and impact on patient management.

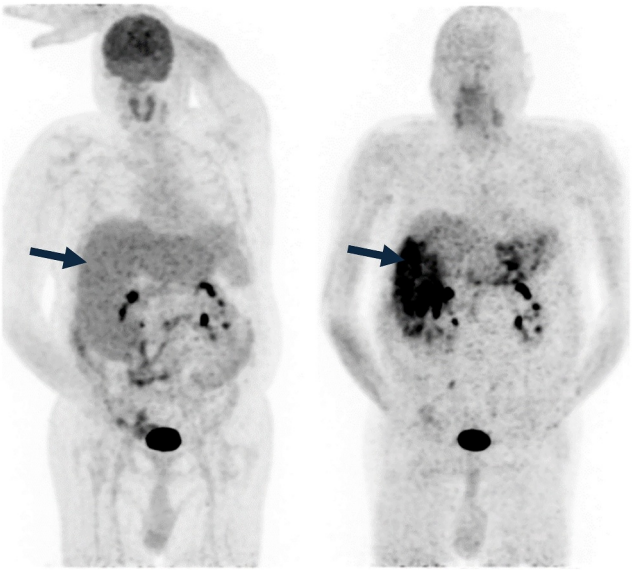

FIGURE 5 A case of biopsy-proven hepatocellular carcinoma in which (*Left*) FDG PET was first performed for evaluation before biopsy followed by (*Right*) FAPI PET when results on FDG, MRI, and CT were inconclusive. FAPI was positive for multifocal liver involvement (arrow), whereas FDG was not suggestive. CT indicates computed tomography; FAPI, fibroblast-activating protein inhibitor; FDG, fluorodeoxyglucose; MRI, magnetic resonance imaging; PET, positron emission tomography.

Additional ligands with different targets are expected to be discovered and evaluated. The combination of molecular imaging with advanced translational techniques, such as single-cell sequencing, spatial transcriptomics, or proteomics that can uncover surface-associated and tumor-specific molecular targets, enables the development of highly specific imaging probes that might even be adapted to the evolving tumor biology. A recent study by Wang and colleagues demonstrates the potential of such a data-driven approach to identify molecular targets.[134] Spatial transcriptomics and proteomics of human surgical samples from patients with pancreatic ductal adenocarcinoma were used to select appropriate targets, which led to the development of a peptide-based molecular imaging agent for PET imaging of tight junction protein expression. These developments, in combination with bimodal molecular imaging probes that are currently under investigation and combine radiolabels with fluorescence, are highly promising.[135] To this end, bimodal molecular agents could be used for concomitant PET imaging, optical surgical navigation, and targeted radiopharmaceutical therapy, guiding precision oncology strategies and opening new avenues for diagnostic and theranostic applications.

Finally, by interrogating various mechanisms involved at the level of both the cancer cell and the TME, cancer molecular imaging can also provide insights to improve current understanding of tumor growth and response to treatment.

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CONFLICT OF INTEREST STATEMENT

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ORCID

Malik E. Juweid https://orcid.org/0000-0002-6294-8118
Soud F. Al-Qasem https://orcid.org/0000-0002-6921-7748
Fadlo R. Khuri https://orcid.org/0000-0002-8638-7618
Andrea Gallamini https://orcid.org/0000-0002-2054-7412
Philipp Lohmann https://orcid.org/0000-0002-5360-046X
Felix M. Mottaghy https://orcid.org/0000-0002-7212-6521

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