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The role of non-FDG agents in PET imaging of bladder cancer

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Bladder cancer (BC) poses significant diagnostic challenges for molecular imaging, as [^{18}F]FDG PET/CT demonstrates not only intense urinary excretion that obscures pelvic lesions but also inherently limited diagnostic accuracy in differentiating tumor from inflammation and in detecting small or low-grade lesions. These shortcomings have spurred the development of non-FDG PET tracers aimed at improving lesion detectability and providing more tumor-specific information. Early-generation tracers such as [^{11}C]acetate, [^{11}C]/[^{18}F]choline, [^{18}F]fluciclovine, [^{11}C]methionine, as well as PSMA-targeted agents demonstrated feasibility for imaging primary and recurrent disease but offered modest sensitivity for nodal or distant metastases, restricting their clinical impact. In contrast, novel molecularly targeted agents, including fibroblast activation protein (FAP) inhibitors and Nectin-4-directed ligands, have emerged as promising tracers with high tumor-to-background ratios, less urinary clearance, and strong correlation with histopathologic markers. [^{68}Ga]FAPI PET has shown superior lesion detection and staging performance compared with [^{18}F]FDG, while Nectin-4 PET offers potential for precision imaging and theranostic integration with antibody-drug conjugate therapies. Collectively, these advances signal a shift from conventional metabolic imaging toward receptor-targeted, biologically driven PET approaches that enable more accurate, personalized assessment of bladder cancer.
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Introduction

Bladder cancer (BC) is among the most frequently diagnosed urinary tract malignancies, with urothelial carcinoma (UC) accounting for over 90% of cases.[1] Clinically, BC is divided into non-muscle-invasive (NMIBC) and muscle-invasive (MIBC), with the latter requiring more aggressive treatment including radical cystectomy and systemic therapy.[2] While cystoscopy and biopsy remain the diagnostic gold standards for evaluating intraluminal lesions, imaging plays a crucial role in assessing local invasion, regional lymph node involvement, and distant metastatic spread. The current global standard for imaging in BC relies primarily on contrast-enhanced computed tomography (CECT) and magnetic resonance imaging (MRI). CT urography remains the modality of choice for evaluating hematuria and screening the upper urinary tracts, while CT of the chest, abdomen, and pelvis constitutes the cornerstone of systemic staging. MRI, particularly multiparametric MRI, offers superior soft-tissue contrast for local staging and helps assess detrusor invasion and perivesical extension.[3] Moreover, [^{18}F]FDG PET/CT provides a whole-body metabolic imaging

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approach and can detect occult nodal or distant disease not evident on CT or MRI. Current reports indicate that [^{18}F]FDG PET/CT may alter management in approximately 20-30% of cases.[4] Currently, according to the EAU-ESMO Consensus Statements, [^{18}F]FDG PET/CT is recommended for staging oligometastatic BC considered for curative or metastasis-directed therapy.[5] Nevertheless, it is not routinely advised for first-line staging, primarily due to practical constraints and the limited availability of robust prospective data. The diagnostic performance of [^{18}F]FDG PET/CT in BC is further limited by the tracer's intense urinary excretion, which generates high background activity within the bladder and ureters and may obscure intravesical or perivesical lesions. Although the use of diuretic protocols and bladder catheterization can partially mitigate this effect, residual urinary activity often persists.[6] Moreover, inflammatory or post-therapeutic changes can add further complexity to image interpretation. Overall, conventional imaging modalities remain essential in BC evaluation; however, their limitations, along with those specific to [^{18}F]FDG PET, have prompted growing interest in alternative non-FDG PET radiotracers to enhance diagnostic accuracy and patient management. Several non-FDG PET tracers, such [^{11}C]acetate, [^{11}C]/[^{18}F]choline, [^{18}F]fluciclovine, and [^{11}C]methionine and PSMA-based agents, have been explored over the past decade but have not entered routine clinical use, and while summarizing the available evidence on these earlier tracers, this review highlights the emerging innovations such as FAPI, Nectin-4, and novel theranostic compounds that are shaping the future of molecular imaging in BC (Fig. 1).

Preclinical data and first in human studies on the novel PET tracers

While numerous tracers have been investigated through the years, the majority have not achieved concrete clinical translation and the related literature appears dated. Those which are still the subject of active interest are the tracers based on

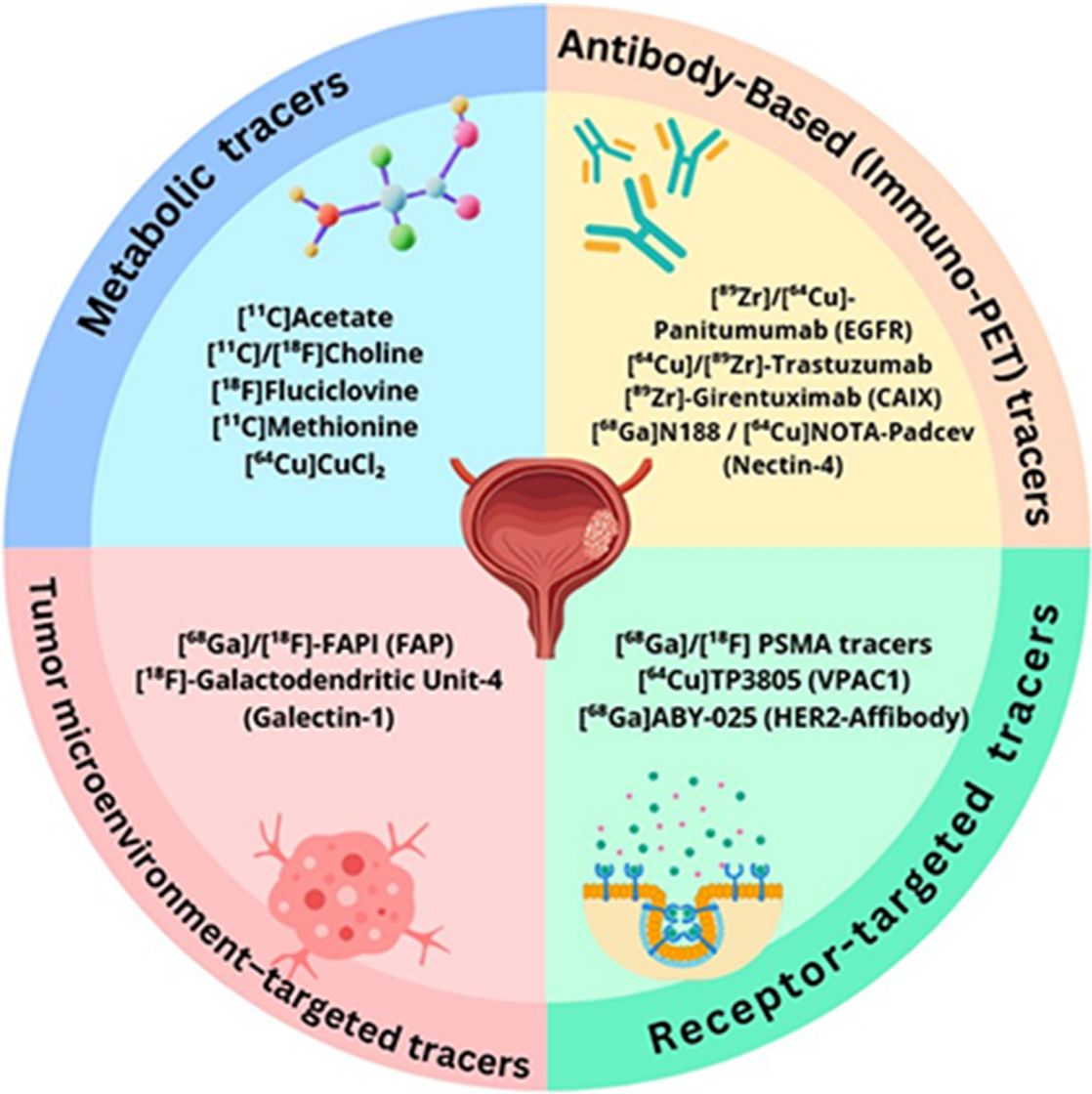


Fig. 1 Overview of major diagnostic non-FDG PET tracers in bladder cancer, grouped by different mechanisms

specific target molecules like Carbonic Anhydrase IX (CAIX) and Human Epidermal Growth Factor Receptor 2 (HER2). At the same time, monoclonal antibodies, long of interest to nuclear medicine, have seen their application in imaging historically constrained by available technologies.

Preclinical studies

Panitumumab

The primary radiotracers utilized are based on panitumumab, which binds with high affinity to the extracellular ligand-binding domain of Epidermal Growth Factor Receptor (EGFR), which is frequently overexpressed and sometimes mutated in various epithelial malignancies. Immuno-PET, which combines monoclonal antibodies with PET imaging to visualize and quantify target antigen expression in vivo, enables noninvasive assessment of receptor status across tumor sites.[7] The long pharmacological half-life of panitumumab (approximately 7.5 days) makes it particularly suitable for such applications, allowing time for clearance from non-target tissues and accumulation in tumors.[8] High EGFR expression is reported in up to 74% of BC tissues, making it an attractive target for both imaging and therapy.[9] Hoang et al. demonstrated specific binding of [^{89}Zr]Zr-DFO-Panitumumab to EGFR-expressing BC cells (UMUC3) in vitro and visualized both subcutaneous and orthotopic UMUC3 tumors using immuno-PET, with signal correlating to tumor volume in the orthotopic model.[10] In a preclinical study, Ku et al. demonstrated that PET imaging with [^{64}Cu]Cu-DOTA-panitumumab F(ab')$_2$ can non-invasively identify EGFR-positive head and neck squamous cell carcinoma and predict radiation dosimetry for [^{177}Lu]Lu-DOTA-panitumumab F(ab')$_2$ therapy, indicating that it may represent a feasible theranostic strategy.[11] The literature further supports the use of [^{89}Zr]Zr- and [^{64}Cu]Cu-panitumumab as promising probes for non-invasive imaging of EGFR-expression, with potential utility in patient selection, therapy monitoring, and understanding drug biodistribution.[12]

Galactodendritic unit

The radiotracer is [^{18}F] galactodendritic-unit-4. Galectins are carbohydrate-binding proteins often overexpressed in malignancies. Specifically, galectin-1 expression correlates with histologic grade and pathologic tumoral stage in BC. Physiological sites of uptake, when administered intravenously, include excretory and metabolic organs, such as the liver and urinary system, with accumulated activity in the bladder obscuring tumor delineation. However, when administered intravesically, the tracer was not found to accumulate in healthy, non-tumoral murine bladders. In vivo studies, indeed, utilized an orthotopic BC model. Quantitative analysis showed a high SUVmean of 43.5 in tumors compared to an SUVmean of 2.0 in non-tumoral control bladders.[13]

First in human studies

Girentuximab

Girentuximab is a radiopharmaceutical agent based on a chimeric monoclonal antibody targeting CAIX, which is a highly specific transmembrane enzyme overexpressed under hypoxic conditions. It is found in over 90% of clear−cell renal cell carcinomas (ccRCC) and in approximately 70-90% of BCs, while being nearly absent in normal urothelial tissue. CAIX expression is also evident on the membrane of NMIBC cells. A fundamental clinical advantage of girentuximab, particularly when labeled with ^{89}Zr, lies in its pharmacokinetic profile, undergoing hepatic clearance. This translates to low background activity in the urine, improving the visualization of renal and bladder lesions. Human clinical data have confirmed the agent's high diagnostic accuracy (Fig. 2).[14] The ZIRCON Phase 3 clinical trial evaluated [^{89}Zr]Zr-girentuximab PET/CT in patients with indeterminate renal masses, demonstrating that the study met its primary endpoints. In 300 patients, the modality reported a sensitivity of 86% and a specificity of 87% for the identification of ccRCC, with a positive predictive value of 93%, all validated histologically with a very high inter-reader agreement.[15] For UC, the proof-of-concept PERTINENCE study (NCT04897763) investigated the intravesical administration of [^{89}Zr]Zr-girentuximab PET/CT in NMIBC, demonstrating that the procedure was feasible and well-tolerated. Minimal to no systemic absorption was observed, confirming the safety of the intravesical approach. [^{89}Zr]Zr-girentuximab PET/CT identified intravesical foci corresponding to either recurrent tumor or post-TURB inflammatory changes, with uptake showing correlation to CAIX expression on immunohistochemistry

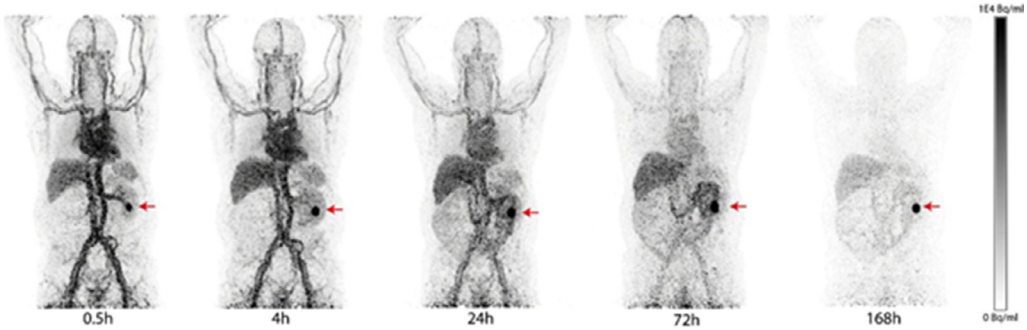


Fig. 2 Whole-body biodistribution of [^{89}Zr]Zr-girentuximab showing high uptake in CAIX-expressing renal tumors and physiologic distribution in liver, spleen, and kidneys. Adapted from Merkx RIJ et al., Eur J Nucl Med Mol Imaging 2021; 48(10): 3277−3285. CC BY 4.0.

(IHC).[16] Moreover, the preliminary results of the ZIPUP trial indicate that [^{89}Zr]Zr-girentuximab is effective in identifying both primary tumors and lymph node metastases in UC. In some cases, it even demonstrated superiority in detecting a greater number of lesions compared to [^{18}F]FDG, reaffirming the advantage of low urinary activity for more accurate local staging.[17] Beyond imaging, radiopharmaceuticals targeting CAIX have also been developed for therapy, notably [^{211}At]At-anti-CAIX (ATO-101^{TM}), which demonstrated high binding affinity, potent cytotoxicity, and favorable biodistribution in preclinical models compared with [^{177}Lu]Lu-girentuximab. These findings support the feasibility of intravesical α-therapy for NMIBC.[16]

Human epidermal growth factor receptor 2

HER2 is a transmembrane tyrosine kinase receptor that promotes tumor cell proliferation and survival. Its overexpression or gene amplification has been demonstrated in UC of the bladder, particularly in high-grade and muscle-invasive tumors, where it is associated with more aggressive disease and poorer prognosis. HER2 expression rates vary widely depending on technique and cohort, with overexpression reported in up to 60% of high-grade lesions, highlighting its potential as an imaging and therapeutic target.[18,19] For PET imaging, the main vectors evaluated clinically are trastuzumab-based monoclonal antibodies (e.g., [^{64}Cu]Cu-DOTA-trastuzumab, [^{89}Zr]Zr-DFO-trastuzumab) [20] (Fig. 3) and smaller engineered affinity proteins known as Affibody molecules, such as [^{68}Ga]Ga-ABY-025. Full-length antibodies are eliminated slowly via reticuloendothelial and hepatic catabolism with minimal renal excretion, whereas Affibody tracers are rapidly cleared through the kidneys, enabling high-contrast imaging within 2-4 hours. Clinical studies with [^{68}Ga]Ga-ABY-025 have shown strong correlation with biopsy-derived HER2 status and good reproducibility.[18,21,22] Although most clinical data originate from breast cancer, these pharmacokinetic features and the documented prevalence of HER2 expression in bladder tumors indicate strong translational potential for HER2-targeted PET and theranostic applications in HER2-positive BC.

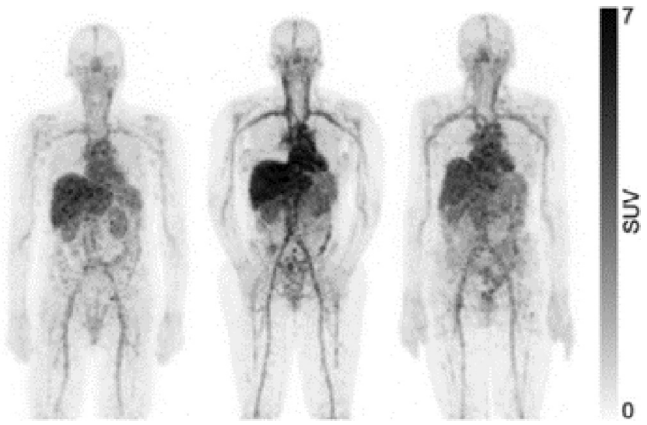


Fig. 3 Biodistribution of [^{89}Zr]Zr-trastuzumab showing physiologic tracer distribution and uptake in three different patients. Adapted from Mansur A et al., J Nucl Med 2025; 66(7): 1018–1026. CC BY 4.0.

$CuCL_2$

[^{64}Cu]$CuCl_2$ is a PET radiotracer that reflects cellular copper metabolism. Increased cellular uptake is mediated by the human copper transporter 1 (hCTR1), which is frequently overexpressed on the membrane of cancer cells. Copper is essential for cancer cell proliferation and tumor angiogenesis. Human studies consistently demonstrate negligible urinary clearance. The primary route of elimination is via the hepatobiliary system, resulting in significant physiological tracer accumulation in the liver followed by excretion into the bowels and ultimately via feces. Its low physiological uptake in the brain also supports its potential use for detecting brain metastases from copper-avid primary tumors. [^{64}Cu]$CuCl_2$ PET has been primarily investigated in humans for imaging prostate cancer, both primary staging and biochemical recurrence, urothelial BC, and penile cancer. A phase IIa study encompassing various urological malignancies reported detection rates as high as 85.7% for prostate and BC, and 83.3% for penile cancer, with significantly higher tracer uptake in malignant tissues compared to corresponding healthy organs.[23]

TP3805

The radiotracer [^{64}Cu]Cu-TP3805 targets the VPAC1 receptor, a G-protein-coupled receptor that binds both Vasoactive Intestinal Peptide (VIP) and Pituitary Adenylate Cyclase Activating Peptide (PACAP) and is involved in the cell proliferation regulation and immunomodulation. Crucially, it is expressed at high density on several cancer cell types, including prostate cancer and urothelial BC, often from the onset of oncogenesis before morphological changes occur.[12] In contrast, their expression is minimal on normal stromal cells and benign tissues like benign prostatic hyperplasia. Normal bladder tissue also shows negligible uptake.[12] Preclinical studies in mice and subsequent human imaging have consistently shown negligible urinary excretion. This minimal urinary activity is a particularly advantageous characteristic for imaging pelvic malignancies. The primary route of clearance appears to be hepatobiliary. Uptake in the lungs was observed in a significant number of patients, particularly correlating strongly with smoking history or underlying conditions like granuloma or emphysema, possibly due to VPAC1 expression on alveolar cells. In a first-in-human study of 19 patients with urothelial BC scheduled for radical cystectomy, PET imaging with ^{64}Cu-TP3805 demonstrated minimal urinary excretion, rapid blood clearance, and the ability to detect residual disease with 79% sensitivity and 80% specificity compared with surgical pathology. These findings support further exploration of VPAC-targeted PET for staging and therapeutic guidance.[24]

Novel tumor-targeted PET tracers

Nectin-4-radioligands

Nectin cell adhesion molecule 4 (Nectin-4), also known as poliovirus receptor-like protein 4 (PVRL4), is a calcium-independent, immunoglobulin-like transmembrane protein.[25,26] This cell adhesion molecule plays a key role in cell−cell junction formation, maintaining epithelial integrity, and signal transduction in normal tissues. It is minimally expressed in healthy adult tissues but is markedly overexpressed in various cancer types. Significant Nectin-4 expression has been observed in UC of the bladder as well as in triple-negative breast cancer, colorectal, gallbladder, gastric, and non-small cell lung cancers.[27,28]

Molecular and biological background of Nectin-4

Several studies have demonstrated that Nectin-4 is expressed in over 60-80% of malignant cases, as detected by immunohistochemistry, with a similar distribution across low, moderate, and strong staining intensities.[29-31] This widespread expression supports the role of Nectin-4 as both a prognostic biomarker and a promising molecular target for imaging and therapy.[32] The clinical significance of Nectin-4 has increased substantially following the approval of enfortumab vedotin (EV) by the U.S. Food and Drug Administration (FDA). EV is an antibody−drug conjugate (ADC) that targets Nectin-4 in patients with advanced UC.[33] In bladder cancer, ADCs have shown promising therapeutic efficacy by binding to tumor-associated antigens such as Nectin-4, inducing tumor cell apoptosis, and inhibiting further tumor growth.[25] The clinical effectiveness of Nectin-4-targeted therapies reinforces its biological relevance and accessibility on tumor cells, making it a compelling target not only for treatment but also for molecular imaging.[34] Multiple studies have reported positive outcomes with EV, demonstrating improved overall survival (OS) compared to chemotherapy. For instance, EV therapy achieved a median OS of 12.9 months, compared to 9.0 months with standard chemotherapy.[25,26,35] However, despite its therapeutic benefits, EV is associated with high treatment costs and the emergence of drug-resistant lesions. To address these challenges, radiolabeled Nectin-4 antibodies offer a promising approach in molecular imaging. PET imaging using such tracers enables non-invasive, quantitative visualization of Nectin-4 expression. This technique can improve patient selection and stratification prior to the initiation of ADC therapy and facilitate therapy monitoring.[26,36]

Nectin-4-targeted PET imaging

The biodistribution of Nectin-4-targeted radiotracers has shown specific accumulation within tumors, as well as in the liver and spleen, while non-specific uptake in other organs remains minimal [37] (Fig. 4). Non-invasive PET imaging targeting Nectin-4 is emerging as a valuable tool for quantifying in vivo expression, assessing intra-patient heterogeneity, and potentially predicting or monitoring therapeutic response.[36] One promising radioligand, [^{68}Ga]N188, is a bicyclic peptide-based compound developed to bind Nectin-4 with high affinity. Its uptake has been shown to correlate with Nectin-4 expression levels, as confirmed by IHC in patients with advanced UC.[34] In a first-in-human pilot study including both healthy volunteers and patients with advanced disease, [^{68}Ga]N188 successfully visualized Nectin-4-positive lesions. Standardized uptake value (SUV) measurements were in agreement with IHC-derived Nectin-4 expression in biopsy samples.[25,38] Preclinical and clinical studies have further

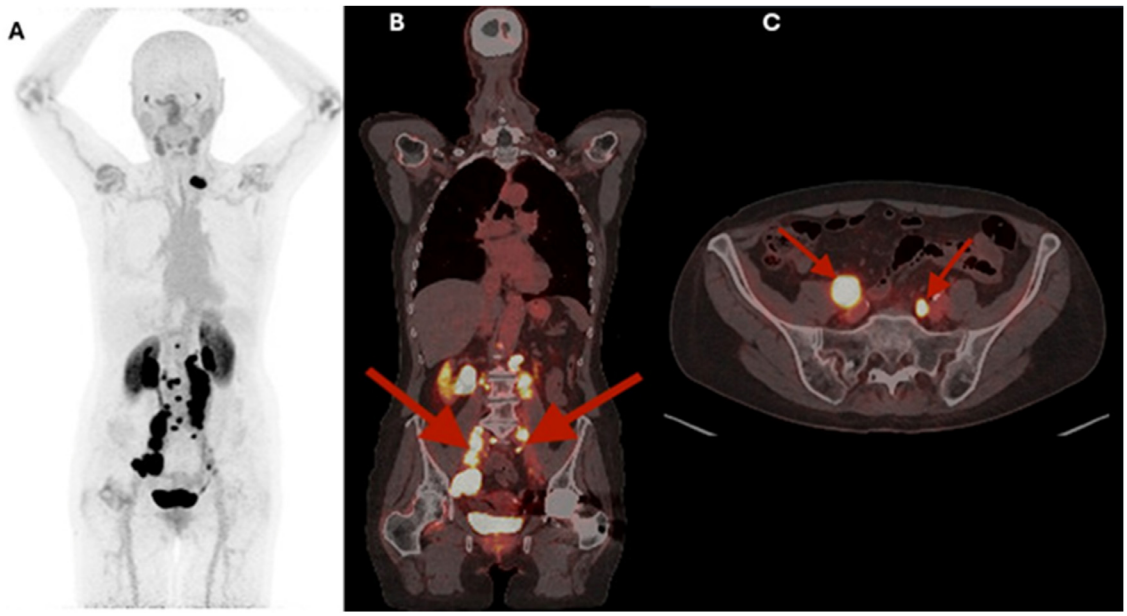


Fig. 4 Female patient, 77 years old, with metastatic urothelial carcinoma of the urinary bladder (carcinoma in situ). Nectin-4−expressing lymph node lesions in the left supraclavicular region (histologically verified) as well as bilaterally in the retroperitoneal and parailiac regions (red arrows). (A) Maximum-intensity projection, (B) coronal fused PET/CT, and (C) axial fused PET/CT images.

demonstrated the feasibility and potential clinical utility of Nectin-4 PET tracers in UC. Compared to [^{18}F]FDG PET/CT, Nectin-4-targeted imaging may offer improved specificity. While [^{18}F]FDG PET/CT is widely used in oncology, it is prone to false-positive results due to uptake in inflammatory or benign lesions; limitations that are particularly relevant in the setting of UC.[39] Nectin-4 PET imaging, by contrast, benefits from tumor-specific targeting, improving the differentiation between malignant and non-malignant lesions.[40] Importantly, Nectin-4 expression visualized through PET imaging has been shown to correlate with immunohistochemical staining, confirming the biological specificity of tracer uptake. In a prospective study, Miederer et al. assessed Nectin-4 expression in patients with metastatic UC using [^{68}Ga]N188 PET/CT. The study revealed both inter- and intratumoral heterogeneity in Nectin-4 expression across metastatic lesions. Notably, lymph node and visceral metastases exhibited divergent tracer uptake, indicating that single-site biopsies may not fully reflect the molecular landscape of the disease.[36] Tumor heterogeneity poses a clinical challenge, as some metastatic lesions may exhibit partial or complete loss of Nectin-4 expression, potentially leading to false-negative imaging findings or resistance to Nectin-4-targeted therapies such as EV. These findings support the use of molecular imaging as a complementary diagnostic approach to improve therapeutic decision-making and patient selection for targeted treatments. Furthermore, it remains unclear whether Nectin-4 expression is modulated during disease progression or in response to ADC therapy, an area warranting further investigation.[41]

While further research and larger clinical trials are needed to define its role as a standard imaging modality in BC, PET imaging with radiolabeled Nectin-4 represents a novel approach in disease management. It combines precise molecular diagnostics with the potential for personalized targeted radionuclide therapy, offering a comprehensive tool for improved patient care.[42] Through enhanced diagnostic precision, Nectin-4-targeted imaging may facilitate earlier detection of UC, optimize therapeutic strategies, and ultimately contribute to more personalized and effective patient management.

FAPI-/FAP-radioligands

The fibroblast activation protein (FAP) which is expressed on activated fibroblasts in proliferating tissue has gained interest as highly promising molecular target in oncological as well as non-oncological diseases.[43] FAP as type II transmembrane serine protease is expressed not only by normal activated fibroblasts but especially by cancer-associated fibroblasts (CAFs) that are part of the tumor microenvironment and are involved in tumor progression.[44,45] Given its limited expression in normal tissues, FAP represents an attractive target for both, imaging and therapeutic applications.[44] In recent years, different FAP inhibitors (FAPIs) have been developed that have shown significant uptakes in a variety of FAP-positive tumors and often outperform [^{18}F]FDG PET/CT in its diagnostic accuracy.[44,45]

Preoperative lymph node staging currently relies on conventional imaging, but these methods have a low accuracy in comparison to intra-operatively selected pathological specimens.[46] Consequently, PET imaging with novel tracers for pretherapeutic staging may be beneficial, especially since up to 20% of patients with clinically localized muscle-invasive UC of the bladder already present with lymph node metastases at the time of radical cystectomy.[47,48] As IHC studies have demonstrated high FAP expression in UC combined with low expression in normal urothelial tissue and a favourable signal-to-background expression,[49,50] FAPI radioligands may represent a promising novel tracer. First studies have already aimed at assessing the value of FAP-based PET imaging in UC. Novruzov et al. analyzed a small patient cohort and reported that [^{68}Ga]FAPI PET/CT demonstrates significantly higher tracer uptake in tumor lesions compared to [^{18}F]FDG PET in patients with BC.[51] In comparison with [^{18}F]FDG PET or stand-alone CT, multiple studies have demonstrated the superior diagnostic performance of [^{68}Ga]FAPI PET in the detection of metastatic sites.[47,52-55] (Fig. 5). Additionally, Unterrainer et al. demonstrated that [^{68}Ga]FAPI PET, prior to radical cystectomy, has a significantly higher sensitivity for the detection of locoregional lymph node metastases than CT.[52,53] Ongoing analyses are currently addressing the potential value of [^{68}Ga]FAPI PET as a response assessment tool under systemic therapies such as EV with pembrolizumab or chemotherapy.[56] Beyond its diagnostic utility, first studies have also shown the potential of radiolabeled FAPIs such as [^{177}Lu]Lu-FAPI, [^{90}Y]Y-FAPI, and [^{225}Ac]Ac-FAPI for radioligand therapy in different tumor entities.[44,57-60] Li et al. reported a patient with recurrent BC that underwent [^{177}Lu]Lu-FAP-2286 therapy and showed radiological remission on imaging after 1 cycle of treatment.[49] This case is encouraging further assessment of therapeutic-FAP-targeting agents in patients after failure of approved systemic therapies. Prospective trials are needed to further evaluate FAP-targeting ligands in urothelial carcinoma for staging, response assessment, and potential therapeutic use.

Other PET tracers

Among the key limitations of [^{18}F]FDG PET in BC is its intense urinary excretion, which obscures bladder wall and pelvic lesions. To address this and other diagnostic challenges, alternative tracers such as [^{11}C]acetate, [^{11}C]/[^{18}F]choline, [^{18}F]fluciclovine, [^{11}C]methionine and [^{18}F]/[^{68}Ga]-PSMA have been investigated, targeting pathways beyond glucose metabolism. Most evidence arises from small, early-phase studies, and research remains limited as focus has shifted toward newer, receptor-specific agents. The following sections summarize the available clinical data and diagnostic performance of these tracers in BC.

^{11}C-acetate

To overcome the challenge of intense urinary excretion that limits [^{18}F]FDG PET in BC, [^{11}C]acetate was explored as a non-glycolytic tracer with negligible urinary clearance, enabling clearer visualization of the bladder wall and

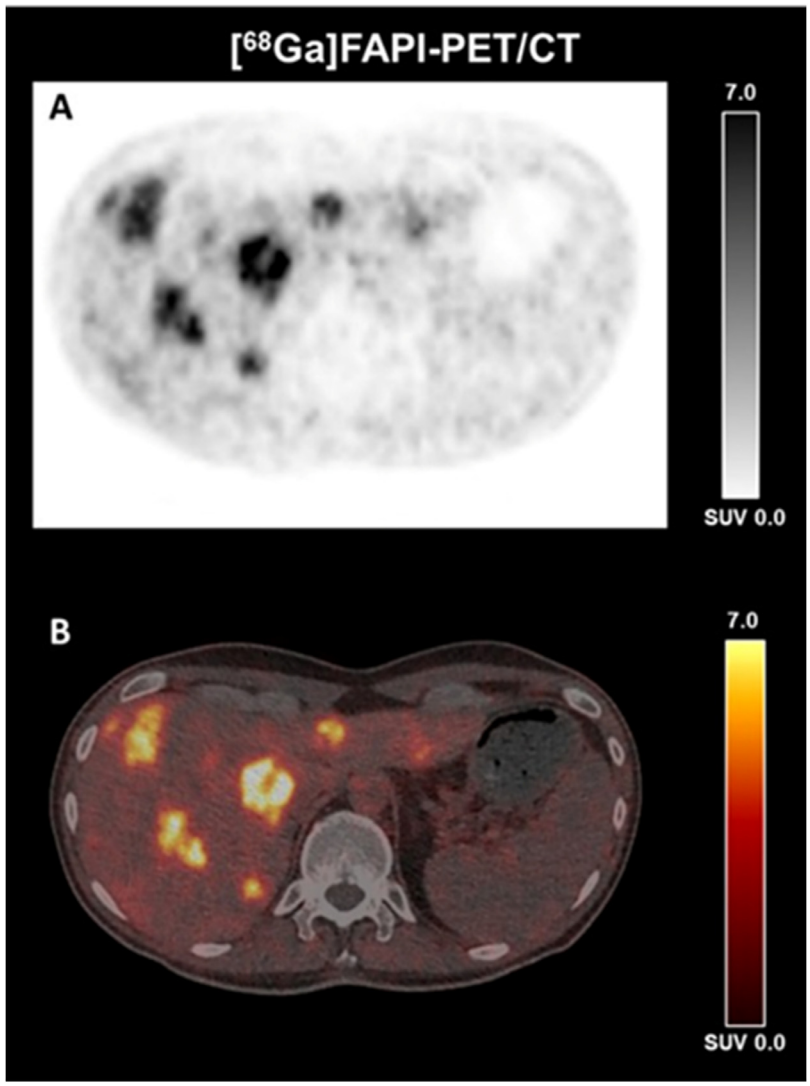


Fig. 5 Patient with metastatic urothelial carcinoma and a significantly increased FAPI uptake in multiple hepatic metastases. (A) Axial PET image and (B) corresponding fused PET/CT image demonstrate markedly elevated FAPI avidity (SUVmax = 11.1).

perivesical abnormalities. Early studies established its feasibility and sensitivity for local tumor detection. In a pre-cystectomy cohort of 17 men with transitional cell carcinoma, [^{11}C]acetate PET detected 8 of 10 residual tumors (80%), with false negatives confined to carcinoma in situ, whereas false positives were mainly due to post-BCG inflammation.[61] Similarly, in 16 patients, [^{11}C]acetate PET/CT identified bladder wall uptake in 7/9 true-positive cases, showing comparable accuracy to MRI and CT, although affected by prior therapies.[62] Furthermore, the ACEBIB PET/MRI trial by Salminen et al. confirmed tracer uptake in all primary tumors among 15 treatment-naïve patients with urothelial tumors, yielding 100% sensitivity, 69% specificity, and 73% overall accuracy for detecting MIBC.[63] These findings indicate that [^{11}C]acetate PET enables reliable visualization of bladder wall lesions without urinary interference, though sensitivity for in-situ disease remains limited. The previously mentioned studies also evaluated nodal staging, but with variable results. In the series by Schöder et al., [^{11}C]acetate PET/CT achieved 100% sensitivity for pelvic lymph node metastases but about 87% specificity, largely due to granulomatous inflammation after intravesical BCG therapy.[61] Vargas et al. reported both false-positive and false-negative findings in nodal assessment,[62] whereas the ACEBIB trial demonstrated low regional sensitivity (20%) but high specificity (96%). Overall, a PET-positive node suggests malignancy, whereas a negative scan cannot exclude microscopic disease.[63] These observations are consistent with a meta-analysis by Kim et al. combining 10 studies (282 patients) using [^{11}C]acetate and [^{11}C]choline PET/CT, which reported pooled sensitivity and specificity of 66% and 89%, respectively, for lymph node staging, representing the modest sensitivity but reasonable specificity of these tracers.[64] Interest has also explored the use of [^{11}C]acetate PET as a biomarker of therapeutic response. In the trial mentioned above, a subset of five patients with MIBC underwent [^{11}C]acetate PET/MRI after treatment. Imaging correctly identified pathological stage in three patients, overstaged one, and understaged one,

demonstrating partial concordance between imaging and histologic response; however, the small sample size precluded clinical relevance.[63]

Choline-based tracers

Like acetate, choline tracers were investigated in BC for their minimal urinary interference to improve pelvic lesion visualization. Choline PET reflects membrane phospholipid synthesis via the choline kinase pathway; however, [^{11}C]choline is limited by a short half-life, while ^{18}F-labeled analogs (e.g., [^{18}F]fluoromethylcholine, [^{18}F]fluoroethylcholine) offer extended imaging availability and facilitate broader distribution. Early clinical experience by de Jong et al. showed avid [^{11}C]choline uptake in bladder tumors with minimal background.[65] Picchio et al. evaluated 27 patients prior to cystectomy and reported detection of viable tumor in 24 of 25 cases (96%) compared with 84% on CT, confirming high sensitivity for primary tumor visualization.[66] The performance of [^{11}C]choline PET/CT in lymph node staging has been moderately consistent across studies, with sensitivity typically ranging from 40–60% and specificity from 80–90%.[67,68] A meta-analysis of 362 patients found pooled sensitivities of 59% (patient-based) and 51% (node-based) and specificities of 92% and 99%, respectively, superior to MRI in specificity and accuracy but limited by modest sensitivity.[68] These findings indicate that while choline PET can confirm metastatic nodes with good specificity, it cannot replace histologic staging because of frequent false negatives. In the context of distant metastases, a head-to-head comparison showed that [^{18}F]FDG PET/CT detected a number of extravesical lesions missed by [^{11}C]choline also yielding higher positive predictive values overall (90.7% vs 84.7%) and for extravesical sites (88.2% vs 79.4%), highlighting FDG's superior performance beyond the bladder.[69] However, choline PET has demonstrated encouraging results in restaging and recurrence assessment. Graziani et al. evaluated 25 patients after curative-intent therapy and reported sensitivity and specificity of 66.7% and 84.6% for local relapse, and 90% and 93.3% for nodal or distant recurrence, respectively, confirming good performance for detecting disease relapse.[70] These findings demonstrate that choline PET/CT has potential to detect systemic recurrence, especially in bones and distant lymph nodes that may be occult on CT or MRI. Nonetheless, its prognostic significance in BC has not been clearly established. In a prospective cohort of 44 patients staged before radical cystectomy, Maurer et al. found no significant correlation between PET/CT findings and overall or cancer-specific survival, with results comparable to CT. Although modest hazard ratios suggested possible trends, neither modality reliably predicted outcome.[71] Evidence specific to [^{18}F]choline remains scarce, but consistent with findings from [^{11}C]choline. Parekh et al. described a case of incidental papillary bladder carcinoma identified on [^{18}F]fluoromethylcholine PET/CT performed for prostate cancer evaluation, demonstrating the tracer's ability to detect urothelial lesions.[72] Owing to its longer half-life, [^{18}F]choline is more widely available; however, large-scale bladder-specific data remain limited, and its use in clinical decision-making is still exploratory.

[^{18}F]Fluciclovine

[^{18}F]fluciclovine (FACBC) is a synthetic amino acid tracer, originally approved for imaging recurrent prostate cancer, but has also gained attention as a promising PET radiotracer for BC because of its minimal urinary excretion, only about 3% within four hours, allowing clearer visualization of pelvic and bladder lesions that are often obscured with FDG or PSMA tracers.[73] Despite this pharmacokinetic advantage, publications or clinical cohorts specifically addressing BC remain sparse. The most substantial human evidence comes from a recent prospective pilot study by Ng et al. in patients with MIBC undergoing cystectomy.[74] [^{18}F]fluciclovine PET/CT detected the primary tumor with a sensitivity of 89%, although specificity was modest at 39%. Dynamic kinetic analysis showed that the tracer influx (k_1) and blood volume (v_b) parameters were significantly higher in tumors of pathologic stage $\geq$ pT2 ($p<0.05$), suggesting that [^{18}F]fluciclovine uptake may reflect tumor aggressiveness. For nodal staging, specificity was high (91%) but sensitivity low (13%), indicating that while positive nodes are generally reliable, negative scans cannot exclude small or microscopic metastases. Evidence regarding detection of recurrent disease is currently limited to individual case reports and incidental findings. Surasi et al. described an 82-year-old man with prior prostate and bladder cancer in whom [^{18}F]fluciclovine PET/CT incidentally revealed focal urethral uptake, subsequently confirmed as recurrent high-grade UC.[75] Larger prostate cancer imaging series have also documented incidental uptake leading to the diagnosis of previously unrecognized urothelial primaries, supporting the biological avidity of this tracer for such lesions.[76] Taken together, current evidence on [^{18}F]fluciclovine PET in BC remains preliminary. The tracer shows potential for detecting primary tumors and offers high specificity for nodal disease, but evidence is limited to small studies and case reports.

[^{11}C]Methionine

The amino acid tracer [^{11}C]methionine attracted interest as an alternative to [^{18}F]FDG as well, however, evidence on its use in bladder UC remains limited. In the early prospective series, Ahlström et al. showed that [^{11}C]methionine PET can detect bladder tumors >1 cm but offers no staging advantage over conventional imaging.[77] In a comparative case series, [^{11}C]methionine and [^{18}F]FDG PET were compared in four cancer cases, including a patient with recurrent bladder carcinoma. In that case, [^{11}C]methionine PET clearly detected the ureteral orifice recurrence that [^{18}F]FDG PET failed to visualize [78] (Fig. 6). Similarly, Kubota et al. demonstrated that [^{11}C]methionine PET provided higher lesion contrast than [^{18}F]FDG PET across several cancer types, including bladder carcinoma. The evidence was limited to case-level observations but they indicate potential diagnostic advantages.[79] Isolated case reports have also illustrated potential applications of [^{11}C]methionine PET in metastatic disease. In one such report, a patient with BC and brain metastasis in the parietal

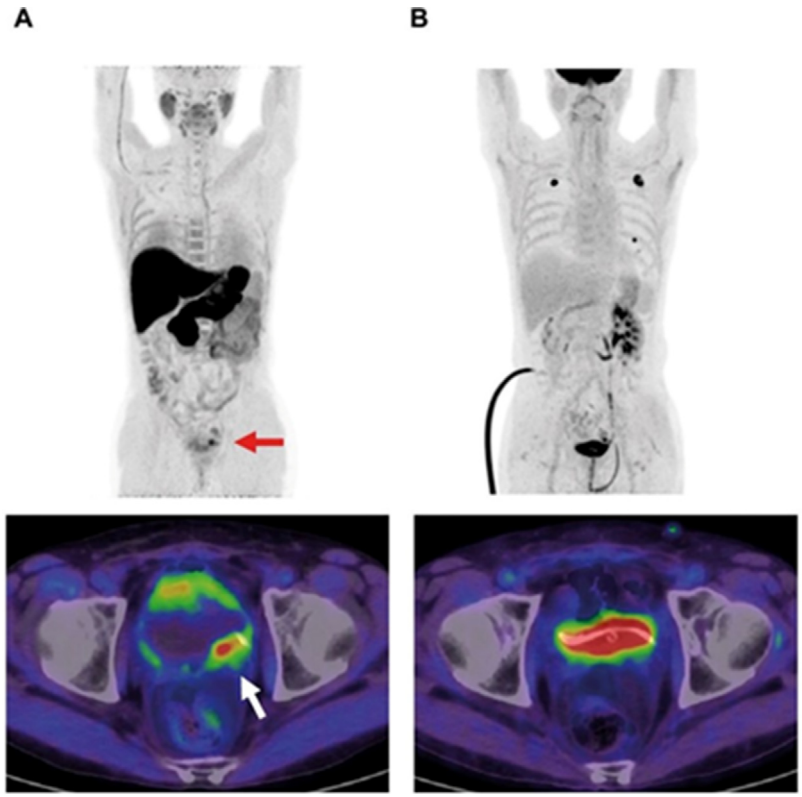


Fig. 6 Local recurrence of bladder cancer in a 67-year-old man with known pulmonary metastases. (A) [^{11}C]methionine PET and (B) [^{18}F]FDG PET (FDG-PET) images. Arrows indicate recurrent bladder tumor. Adapted from Sato M et al., Anticancer Res 2024; 44:3891–3898. CC BY 4.0.

lobe, showed clear tracer uptake in the lesion, supporting its malignant characterization on imaging.[80]

PSMA tracers

Prostate-specific membrane antigen (PSMA) has emerged as a molecular target for PET imaging beyond prostate cancer, as it is expressed not only on prostate carcinoma cells but also on the neovasculature of many solid tumors. In UC of the bladder, PSMA expression is almost exclusively confined to the tumor-associated neovasculature, even in carcinoma in situ, with minimal or absent expression in normal urothelium.[81] This provides the biological rationale for exploring PSMA-targeted PET tracers in BC. Although direct visualization of bladder tumors is hindered by tracer excretion, the use of agents such as [^{18}F]-PSMA-1007 (which has minimal urinary clearance compared with [^{68}Ga]PSMA-11 or [^{18}F]DCFPyL) offers a theoretical advantage by reducing bladder-background uptake and improving lesion detectability. Nonetheless, available clinical data specifically in BC remain limited and heterogeneous. In the most comprehensive systematic review to date, encompassing 11 reports and 18 patients, PSMA PET was positive in 17 of 18 UC cases, demonstrating that PSMA expression can occur in UC lesions, though the evidence is limited in scope and largely retrospective.[82] Consistent with these findings, individual case reports have further illustrated the variable degree of PSMA uptake in UC. In one example, a distal ureter tumor incidentally detected on [^{68}Ga]PSMA PET showed focal uptake, with histology confirming low-grade non-invasive papillary urothelial carcinoma.[83] Conversely, in a small series of patients with metastatic UC imaged using [^{18}F]DCFPyL, lesions were detectable but demonstrated only modest tracer accumulation, and the authors concluded that low PSMA expression likely limits clinical utility.[84] Although the affinity of PSMA tracers for skeletal metastases is well established in prostate cancer, similar imaging characteristics have occasionally been observed in UC. In one reported case with extensive bone involvement, [^{68}Ga]PSMA-11 PET/MRI demonstrated moderate-to-intense tracer accumulation, delineating osseous lesions more clearly than [^{18}F]FDG PET/CT and suggesting potential value for assessing skeletal disease.[85]

Conclusion

While early investigations with amino acid and metabolic tracers such as [^{11}C]methionine, [^{11}C]choline, and [^{11}C]acetate provided valuable proof-of-concept insights, their clinical relevance has since diminished. In contrast, novel molecularly targeted agents, particularly FAP-based tracers and Nectin-4-targeted radiopharmaceuticals, are emerging as highly promising tools for noninvasive tumor characterization in BC. Early clinical data indicate that these tracers can delineate viable tumor tissue with high contrast and may serve as theranostic biomarkers for personalized treatment. Moreover, ongoing development of agents targeting CAIX

and HER2 further expands the scope of precision molecular imaging. As these radiopharmaceuticals progress through clinical validation, they are poised to redefine the diagnostic, prognostic, and therapeutic landscape of BC beyond the limits of [^{18}F]FDG PET/CT.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Mohsen Beheshti reports a relationship with Novartis Pharma GmbH, Telix Pharmaceuticals Limited and Blue Earth Diagnostics Ltd. that includes: board membership and consulting or advisory. Christian Pirich reports a relationship with Novartis Pharma GmbH that includes: board membership and consulting or advisory. Matthias Eiber reports fees from Blue Earth Diagnostics Ltd. (consultant, research funding), Novartis/AAA (consultant, speaker), Telix (consultant), Bayer (consultant, research funding), RayzeBio (consultant), Point Biopharma (consultant), Eckert-Ziegler (speaker), Urotrials (speaker) and Janssen Pharmaceuticals (consultant, speakers bureau), Parexel (image review) and Bioclinica (image review) outside the submitted work and a patent application for rhPSMA. He and other inventors are entitled to royalties on sales of POSLUMA® . ME serves on advisory boards and/or steering committees for Novartis, Blue Earth Diagnostics and Telix. Lena M. Unterrainer reports funding from Bayerisches Zentrum für Krebsforschung (BZKF) and from the Munich Clinician Scientist Program (MCSP). She reports fees from Novartis (speaker), Telix (consultant) and Astellas Pharma Inc. (speaker) outside of the submitted work. Francesco Ceci is a consultant, on the speaker's bureau, and on the advisory board and steering committee for Novartis and Curium; is a consultant and on the speaker's bureau for Bayer, GE HealthCare, and Telix; is a consultant and has received grants from Hermes; is a consultant for NucsAI; and is a consultant and has investment interest in Radiantis Research.

CRediT authorship contribution statement

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