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Editorial

ACP3-targeted PET imaging agents based on small-molecule ligands for prostate cancer diagnostics and theranostics

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Abstract: Prostate cancer (PCa) remains a leading cause of cancer-related morbidity and mortality worldwide, underscoring the need for improved molecular imaging strategies. Although prostate-specific membrane antigen (PSMA) positron emission tomography (PET) has changed prostate cancer imaging and treatment, its clinical utility is limited in some settings by heterogeneous tumor expression and substantial off-target uptake in organs such as the kidneys and salivary glands. Acid phosphatase 3 (ACP3), also known as prostatic acid phosphatase, has regained attention as an alternative prostate-associated target because of its abundant expression in prostate cancer and comparatively low expression in several normal tissues. Recent advances in high-affinity small-molecule ligands, including radiolabeled OncoACP3 derivatives, have enabled the development of ACP3-targeted PET radiopharmaceuticals. Preclinical studies and early clinical investigations demonstrate favorable biodistribution, high tumor-to-background contrast, and the capacity to detect lesions in PSMA-low or PSMA-negative disease. Moreover, ACP3-directed radioligand strategies highlight its potential in theranostic applications. Overall, ACP3 radiopharmaceuticals may provide a complementary approach for precision prostate cancer imaging and therapy.

Keywords: Acid phosphatase 3, prostatic acid phosphatase, PET imaging, prostate cancer, theranostics

Introduction

Prostate cancer (PCa) remains one of the most prevalent malignancies worldwide and continues to represent a major cause of cancer-related morbidity and mortality [1, 2]. Although significant advances have been made in screening, surgical management, systemic therapy, and radiotherapy, accurate detection of metastatic or recurrent disease remains a central clinical challenge [3, 4]. Conventional imaging modalities, including computed tomography (CT) and magnetic resonance imaging (MRI), are frequently limited by insufficient sensitivity for micrometastatic disease, particularly in patients with biochemical recurrence [5]. As precise staging increasingly guides treatment intensification or deescalation strategies, improved molecular imaging approaches are critically needed [6].

Positron emission tomography (PET) has substantially advanced prostate cancer imaging through radiotracers targeting prostate-specific membrane antigen (PSMA) [7]. Owing to its high expression in most prostate cancer cells, PSMA has become a validated diagnostic and theranostic target. PSMA PET provides high lesion detectability and has influenced clinical decision-making across multiple disease states. However, important limitations remain. PSMA expression can be heterogeneous, particularly in dedifferentiated, treatment-exposed, or advanced disease [8]. PSMA-low or PSMA-negative lesions may therefore escape detection. In addition, physiological uptake of PSMA-PET in kidneys and salivary glands is common, which not only complicates image interpretation but also constrains radioligand therapy (RLT) due to off-target toxicity [9].

These limitations have stimulated interest in additional molecular targets that may complement PSMA imaging. Acid phosphatase 3 (ACP3), also known as prostatic acid phosphatase (PAP), represents a biologically relevant prostate lineage marker with re-emerging clinical relevance [10]. ACP3 is abundantly expressed in prostate cancer cells, including metastatic lesions, while exhibiting comparatively low physiological distribution in kidneys and salivary glands [11]. This expression profile suggests that ACP3-targeted imaging and companion radioligand therapy may improve tumor-to-background contrast in selected clinical contexts, particularly in PSMA-low disease.

As illustrated in **Figure 1**, ACP3-targeted PET imaging is enabled by high-affinity small-molecule ligands such as OncoACP3, which can be radiolabeled via DOTA chelation with isotopes including Gallium-68. Following systemic administration, [^{68}Ga]Ga-OncoACP3-DOTA selectively binds ACP3-expressing prostate cancer cells, enabling noninvasive lesion visualization by PET (**Figure 1A**) [12]. Beyond its role as an imaging handle, ACP3 has been reported to intersect with tumor signaling programs, including pathways linked to ErbB-2/HER-2 phosphorylation states (**Figure 1B**), although the extent to which these processes influence tracer kinetics in patients

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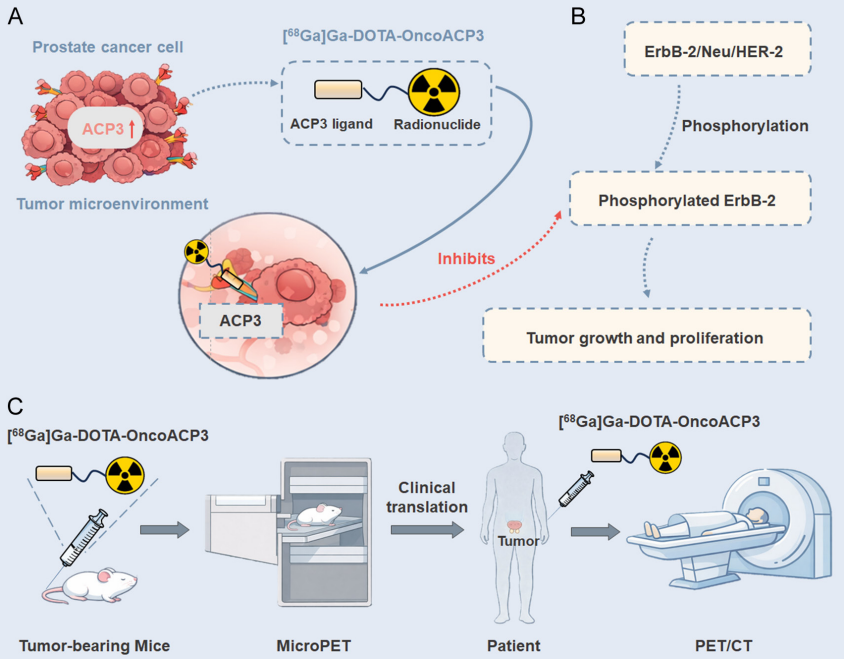

Figure 1. Schematic illustration of ACP3-targeted PET imaging and translational workflow in prostate cancer. A. Mechanism of tumor targeting by [^{68}Ga]Ga-DOTA-OncoACP3. ACP3 is overexpressed in prostate cancer cells within the tumor microenvironment. The small-molecule ACP3 ligand, radiolabeled with Gallium-68 via DOTA chelation, selectively binds to ACP3, enabling visualization of tumor lesions by PET imaging. B. Simplified signaling pathway involving ACP3 in prostate cancer cells. ACP3 modulates phosphorylation of ErbB-2/HER-2, thereby influencing downstream tumor growth and proliferation pathways. Target engagement may contribute to tumor-selective tracer retention. C. Preclinical evaluation and clinical translation of ACP3 PET imaging. Tumor-bearing mice are imaged by microPET following tracer administration, followed by clinical PET/CT imaging in patients with prostate cancer to assess tumor detection and biodistribution.

remains to be established [13]. Preclinical validation in tumor-bearing mouse models using microPET supported tumor-selective uptake, and early clinical translation has demonstrated feasibility in patients with prostate cancer (**Figure 1C**) [12].

Recent early-phase clinical studies of ACP3 PET tracers have shown promising tumor avidity and favorable biodistribution profiles [12, 13]. Together, these developments position ACP3 PET as a complementary molecular imaging strategy with potential diagnostic and theranostic applications. This paper summarizes current progress in ACP3-targeted PET imaging agents, evaluates emerging clinical data, and discusses their potential role alongside established PSMA-based approaches, particularly in biologically heterogeneous prostate cancer.

Literature highlight

Backhaus and coworkers reported the first-in-human evaluation of [^{68}Ga]Ga-OncoACP3-DOTA, a small-molecule ACP3-targeted PET tracer, in a head-to-head comparison with [^{18}F]PSMA-1007 for imaging prostate cancer [14]. **Figure 2A** illustrates representative maximum intensity projections and quantitative organ uptake comparisons between the two tracers. OncoACP3 was identified through DNA-encoded chemical library screening and subsequently optimized for radiolabeling using the chelator DOTA, enabling coordination with Gallium-68. The resulting tracer was synthesized with high radiochemical purity (>95%) and demonstrated strong binding affinity for ACP3-expressing prostate cancer cells in preclinical characterization studies [12].

In preclinical evaluations, [^{68}Ga]Ga-OncoACP3-DOTA exhibited selective accumulation in ACP3-positive prostate cancer xenografts, with clear tumor delineation on microPET imaging. Tumor uptake increased over time, consistent with favorable retention kinetics. Specificity was supported by blocking experiments using excess unlabeled ligand, which significantly reduced tumor uptake, as well as by comparison with ACP3-negative tumor models that showed minimal tracer accumulation. These findings supported ACP3 as a feasible imaging target and justified clinical evaluation.

Following these preclinical data, a clinical study involving 25 patients with prostate cancer was conducted to compare [^{68}Ga]Ga-OncoACP3-DOTA PET/CT with [^{18}F]PSMA-1007 PET/CT. Imaging was performed approximately 64 ± 14 min post-injection for the ACP3 tracer and 116 ± 12 min for PSMA-1007. No tracer-related adverse events were observed, indicating favorable tolerability.

Biodistribution analysis revealed a distinct physiological uptake pattern for [^{68}Ga]Ga-OncoACP3-DOTA compared with [^{18}F]PSMA-1007. Notably, significantly lower uptake was observed in the salivary glands, lacrimal glands, kidneys, liver, spleen, pancreas, and small intestine for the ACP3 tracer (**Figure 2B**, **2C**). This reduced background activity in critical organs is relevant for image interpretation and may also matter for future radioligand therapy applications, where off-target uptake in kidneys and salivary glands remains a major limitation for PSMA-targeted agents. Conversely, [^{68}Ga]Ga-OncoACP3-DOTA demonstrated relatively higher blood-pool activity at early imaging time points, suggesting that delayed imaging may further improve tumor-to-background contrast. Indeed, additional delayed acquisitions in selected patients showed decreasing blood activity with sustained tumor uptake, resulting in improved lesion conspicuity at later time points.

Regarding tumor detection, [^{68}Ga]Ga-OncoACP3-DOTA achieved high lesion uptake across primary and meta-

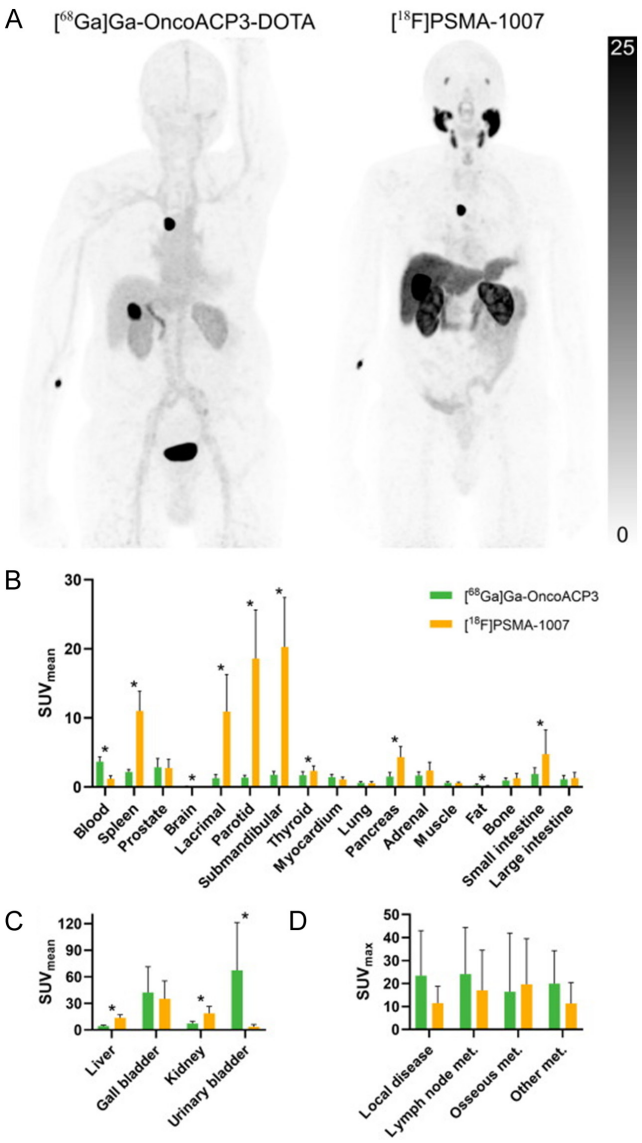

Figure 2. Head-to-head comparison of [^{68}Ga]Ga-OncoACP3-DOTA and [^{18}F]PSMA-1007 PET/CT imaging in patients with prostate cancer. A. Representative maximum intensity projection (MIP) images illustrating tumor uptake and physiological biodistribution for both tracers. B. Quantitative analysis of organ uptake (SUV_{mean}) showing significantly lower physiological accumulation of [^{68}Ga]Ga-OncoACP3-DOTA in salivary glands, kidneys, liver, spleen, pancreas, and small intestine compared with [^{18}F]PSMA-1007; lesion uptake (SUV_{max}) was comparable between tracers. C. Comparison of SUV_{mean} values across excretory organs within the same cohort. D. SUV_{max} values were compared across 25 paired scans using [^{68}Ga]Ga-OncoACP3-DOTA and [^{18}F]PSMA-1007 for primary lesions and various metastatic sites. No statistically significant differences were identified under the Bonferroni-corrected threshold for four lesion categories. Reproduced with permission from Backhaus et al. Eur. Urol. 2025. © Elsevier.

static sites, with SUV_{max} values reaching up to approximately 210 in certain lesions (**Figure 2D**). Overall tumor uptake did not significantly differ from that of [^{18}F]PSMA-1007, indicating comparable tumor avidity. Importantly, in several clinical scenarios - including biochemical recurrence and metastatic disease - ACP3 PET identified lesions that were less conspicuous or undetected on PSMA imaging. Representative matched cases are shown in **Figure 3**. In these examples, ACP3 PET demonstrated clearer visualization of osseous and nodal metastases, and in some cases revealed additional lesions that influenced therapeutic decision-making, including modification of radiation fields or initiation of systemic therapy.

A subgroup analysis suggested that ACP3 PET may provide particular benefit in patients with heterogeneous or low PSMA expression, as well as in those previously treated with PSMA-targeted radioligand therapy. In these settings, discordant uptake patterns between the two tracers were observed. While PSMA PET remains highly effective in many patients, the complementary detection profile of ACP3 PET supports its role as an adjunct molecular imaging modality rather than a direct replacement.

The authors acknowledged several limitations. The study was retrospective and included heterogeneous patient populations and imaging intervals, which may introduce bias in tracer comparison. Additionally, the higher early blood retention of [^{68}Ga]Ga-OncoACP3-DOTA warrants optimization of imaging protocols to maximize contrast. Nevertheless, the study provided the first clinical evidence that ACP3-targeted PET imaging can achieve tumor uptake comparable to PSMA PET while offering reduced off-target accumulation in organs commonly limiting PSMA-based imaging and therapy.

In summary, these findings support the translational value of ACP3-targeted PET imaging. By combining high tumor avidity with a cleaner physiological background in critical organs, [^{68}Ga]Ga-OncoACP3-DOTA establishes ACP3 as a clinically relevant molecular target in prostate cancer. Larger prospective studies are needed to validate its diagnostic performance, define optimal imaging protocols, and clarify its role in staging, restaging, and theranostic patient selection.

Perspectives

The clinical trajectory of ACP3 PET should be guided by lessons learned from the PSMA paradigm: meaningful adoption in prostate cancer care depends not on incremental imaging metrics alone, but on demonstration of clear clinical utility within well-defined decision pathways. Rather than positioning ACP3 PET as a replacement for PSMA imaging, its development is more appropriately framed as complementary - addressing biological heterogeneity, particularly in PSMA-low or treatment-exposed disease [15].

Early clinical data suggest that ACP3-targeted imaging combines preserved tumor avidity with reduced physiological uptake in salivary glands and kidneys. If confirmed in larger prospective cohorts, this biodistribution profile may have implications beyond diagnosis, particularly for theranostic development where off-target toxicity remains a limiting factor. However, several critical questions

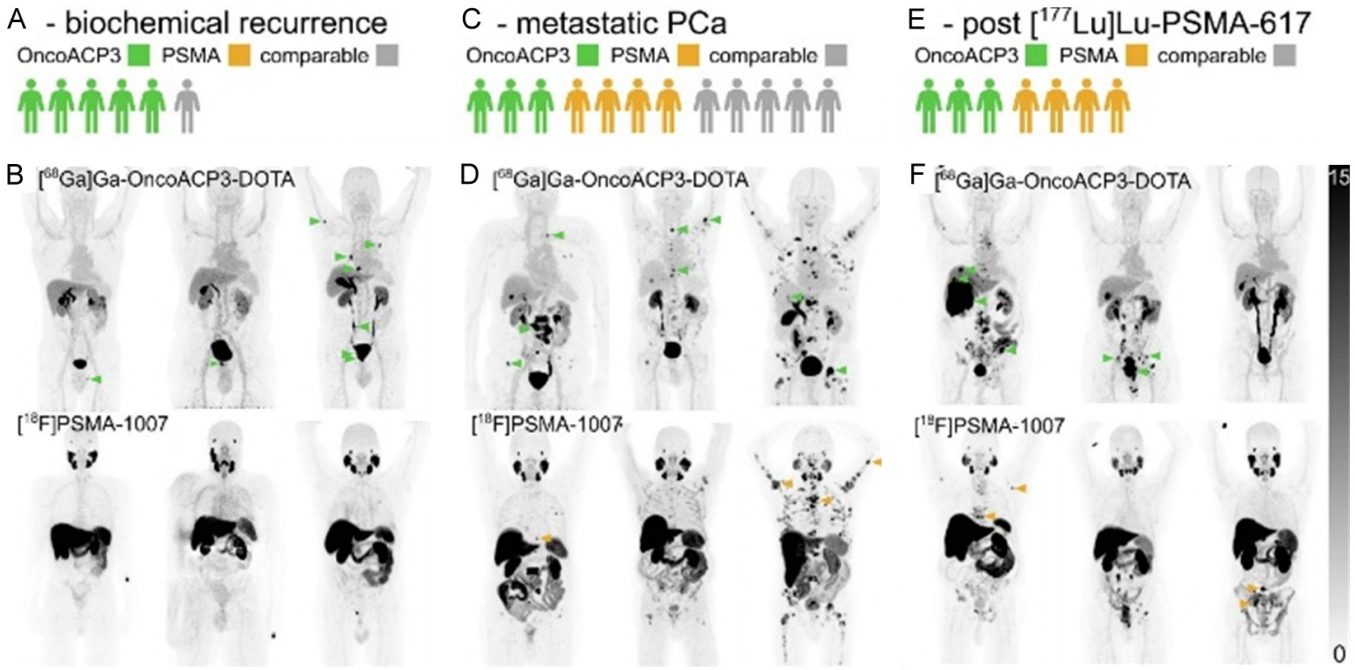

Figure 3. Diagnostic performance of [^{68}Ga]Ga-OncoACP3-DOTA PET/CT in different clinical scenarios. A. Comparative lesion detection between [^{68}Ga]Ga-OncoACP3-DOTA and [^{18}F]PSMA-1007 in patients with biochemical recurrence or metastatic disease. B-F. Representative matched PET/CT images illustrating lesions that were more conspicuous or uniquely detected on ACP3 PET, including nodal and osseous metastases. In selected cases, ACP3 PET findings contributed to changes in clinical management. Reproduced with permission from Backhaus et al. Eur. Urol. 2025. © Elsevier.

remain. The biological determinants of ACP3 PET signal across disease stages and treatment contexts require systematic evaluation, and standardized imaging protocols will be necessary to optimize timing and reproducibility. Importantly, future studies should prioritize clinically meaningful endpoints - including management change, therapeutic selection, and patient outcomes - rather than lesion detection rates alone [16, 17].

As the field advances, multidisciplinary collaboration and well-designed prospective trials will be essential to define the precise role of ACP3 PET in prostate cancer staging, restaging, and radioligand therapy selection. With evidence-driven development, ACP3-targeted imaging may expand the molecular toolbox for precision prostate cancer management.

Disclosure of conflict of interest

None.

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