# Molecular Imaging and Precision Medicine in Prostate Cancer

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**KEYWORDS**

• $^{68}$Ga-PSMA PET/CT • Prostate cancer • Biochemical relapse • Castrate resistant prostate cancer • Androgen receptor

**KEY POINTS**

- PET/computed tomography (CT) with prostate-specific membrane antigen gallium 68 ($^{68}$Ga-PSMA PET/CT) is valuable diagnostic tool with promising performance to detect the site of relapse in prostate cancer patients.
- $^{68}$Ga-PSMA, as theranostics agent, will be effective in delivering high doses for systemic radionuclide therapy, offering a new therapeutic approach to patients with resistance to castration in PCa (CRPC).
- Molecular biomarkers are expected to become in the future robust test to predict appropriateness of the new second-generation antiandrogen agents in CRPC patients.

## INTRODUCTION

Prostate cancer (PCa) is the most common solid neoplasm and the third leading cause of cancer-related death in men in Europe and the United States.[1,2] Although primary treatment of clinically localized PCa is associated with excellent oncologic results, up to 50% of the patients treated with radical prostatectomy or external-beam radiotherapy (EBRT) experience biochemical recurrence (BCR) during follow-up.[3–7] Nowadays, several tools evaluating clinical and pathologic parameters (prostate-specific antigen [PSA], PSA doubling time [PSAdt], PSA velocity, pathologic Gleason score [GS], pathologic T, lymph node [LN] invasion, and distant metastases) are available to assess the probability of harboring local versus systemic recurrence after radical prostatectomy or EBRT.[8–10] Although these models are characterized by a relatively good accuracy in distinguishing between local and distant relapse, they are not able to provide precise and individual information about the site of relapse (visceral vs bone metastases, pelvic vs extrapelvic lesions) and/or the number of metastases.

As a consequence, clinicians are currently not able to target individualized and precise salvage therapies according to the information provided by these tools only. Thus, individuals experiencing BCR are generally referred for salvage radiotherapy (S-RT) to the prostate bed versus systemic androgen deprivation therapy (ADT) when a local versus systemic relapse is suspected, respectively. In this context, patients are generally treated without any efforts to detect the real sites of the disease. Metastases-directed therapy might play a role in the management of these patients[11,12] if

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an imaging modality that accurately identifies number and site(s) of metastases were available.

Conventional imaging techniques, including computed tomography (CT), bone scintigraphy, and MR imaging, are characterized by low sensitivity for detecting the sites of PCa recurrence.[10] Functional imaging, in particular PET, demonstrated to be a useful imaging procedure showing molecular function and metabolic activity information not available with other diagnostic modalities, in a single-step examination.[13] Over the last decade, PET/CT with $^{11}$C-choline and/or $^{18}$F-choline has proven its role for investigating PCa.[10,14] Particularly, choline PET/CT proved to be a better diagnostic tool for restaging PCa patients presenting BCR, as compared with conventional imaging.[10,14] This modality allows for differentiating between an early relapse limited to the pelvis and a systemic progression[14] and already proved its impact on the management of patients with recurrent PCa.[15]

Moreover, despite some limitations including the presence of nodal micrometastases, functional molecular imaging could provide valuable information also for staging PCa, in selected cases, before primary therapies (radical prostatectomy or EBRT).[16] In patients with high risk of extraprostatic involvement (high PSA values and/or high GS), PET/CT imaging could show the presence of nodal metastases in uncommon sites (eg, presacral and retroperitoneal LNs). Thus, an image-guided treatment strategy including PET-positive findings, such as an extended pelvic lymph-node dissection or an EBRT performed with an enlarged planned target volume, could be performed. In contrast, choline-PET/CT may lead to exclude the patient from a radical therapy owing to the assessment of a systemic metastatic spread–diffusion.[16] Nevertheless, the main application of PET imaging in PCa remain the restaging of the disease, with the detection of the site(s) of relapse in case of BCR as the main purpose. In this context, choline-PET/CT still holds relatively low sensitivity, especially in patients with low PSA levels at the time of imaging.[14] Unfortunately, the optimal timing for salvage treatments to obtain the best chance of cure in case of PCa recurrence would be when the PSA level is low, which reflect a still limited cancer burden.[17–19]

Several efforts have been made over the last years to develop new probes able to provide better performances when compared with the choline-PET/CT, particularly in case of low PSA levels during BCR.[20] The development of radiotracers designed to specifically target the extracellular domains of substrates overexpressed in PCa cells, could lead to the development of theranostics tracers, valuable both for diagnostic and therapeutic purposes.[21] Finally, understanding the molecular mechanisms underlying resistance to castration in PCa (CRPC) and the maintenance of active androgen receptor (AR) would be of interest, because they may represent predictive biomarkers for response to antiandrogen therapy.

## PROSTATE-SPECIFIC MEMBRANE ANTIGEN–BASED PET AND COMPUTED TOMOGRAPHY IMAGING

A new molecular probe targeting the prostate-specific membrane antigen (PSMA) has been developed recently.[22] PSMA, the glutamate carboxypeptidase II (GCPII), is a membrane-bound metallopeptidase expressed in several tissues, including the prostate, brain, small intestine, and kidney. Although the function of GCPII in prostate remains unclear, it is well-known that this protein is overexpressed in PCa. Hence, GCPII is a putative target for PCa diagnosis and treatment.[23] The precise localization of the catalytic site of PSMA in the extracellular domain allowed for the development of small, highly specific inhibitors that are internalized inside the cell after ligand binding.[24] Molecular imaging, precisely targeting the GCPII, has seen an unprecedentedly rapid adoption in PCa imaging in the last few years.[25,26] There is a broad range of GCPII enzyme activities as represented by the biodistribution of gallium 68 ($^{68}$Ga-PSMA).[27] In normal organs, high uptake of $^{68}$Ga-PSMA was demonstrated in the kidney cortex and the duodenum, as well as in the lachrymal and salivary glands. The liver and spleen showed moderate uptake. Regarding the prostate, it was observed a significantly higher median uptake in primary prostate tumors as compared with the normal prostate stroma. Considering metastatic tumor lesions, LNs and bone metastases were easily detectable owing to their high tracer uptake.[27] The agent mostly used in clinical studies (Glu-NH-CO-NH-Lys-(Ahx)-[68Ga(HBED-CC)]) is labeled with $^{68}$Ga ($^{68}$Ga-PSMA).[28] However, it is important to mention that the different available probes, including $^{68}$Ga-PSMA-I&T, $^{18}$F-DCFBC, and $^{18}$F-DCFPyL, seem to show equivalent efficacy for evaluating PCa. Although no direct comparisons have been performed yet, advantages of $^{18}$F over $^{68}$Ga are mostly owing to a higher feasibility of these compounds and possibly to higher quality standards of fluorinated isotopes.[28]

The first investigations reported a higher tumor to background ratio for $^{68}$Ga-PSMA PET/CT for the detection of suspected PCa metastases when compared with $^{18}$F-choline PET/CT[29] and very promising performances also at very low PSA levels.[25,26] Morigi and colleagues[30] performed a prospective comparative study between