

Diagnosing prostate cancer: advances in radiopharmaceutical imaging

By G Mullen

Prostate cancer is an enormous global burden and one of the most prevalent cancers in men. Although the vast majority of men diagnosed with prostate cancer do not die of the disease, it still kills more than 300,000 men each year and in high- and middle-income countries it is considered to be the third most common cause of cancer-associated mortality in men [1].

Although there have been great strides in the management of prostate cancer over the last few decades, the prevalence of undiagnosed disease and the mortality rate lag behind some other types of cancer, raising the question as to why this should be. There are many factors at play, but among the most crucial are deficiencies in the diagnosis and accurate staging of prostate cancer.

DIAGNOSIS AND STAGING — CURRENT APPROACHES AND CHALLENGES

The initial presentation of prostate cancer patients is usually as a result of issues related to urination e.g. frequency, lack of or difficulty in urinating. The typical prostate cancer diagnostic pathway begins with measurement of prostate specific antigen (PSA) levels, followed by a digital rectal examination. These techniques can only indicate whether there might be a problem with the prostate and not the specific nature of that problem. PSA levels increase with age even in the absence of prostate cancer, and high levels are merely an indication that an issue may exist with the prostate gland [2]. A firm diagnosis of prostate cancer relies on sonography-guided needle biopsy, which of course is an invasive procedure, with a risk of bleeding and infection. Anterior tumors tend to be missed by transrectal ultrasound-guided biopsy until they grow to a substantial size and reach within 15–20 mm of the posterior margin

of the prostate [3]. A template biopsy might only sample a proportion of the lesions in a diseased prostate gland. The histology of each of these lesions is not necessarily the same, which can often lead to under- or over-staging of the disease. A further limitation of biopsy is that the histological findings may come back as negative, even though PSA levels are high. In intermediate- or high-risk patients imaging will then be used.

Imaging can be used to detect and visualize prostate lesions. MRI, especially multiparametric MRI (mpMRI) has greatly improved the diagnostic and staging pathway in prostate cancer patients, but it is only appropriate for detecting prostate and local lymph node lesions that are >5 mm in diameter. Lesions smaller than this may be missed.

When prostate cancer is confirmed histologically the patient is typically assigned a risk category, based on his initial rectal examination, histological findings and serum PSA level. After a risk category has been assigned, the guidelines recommend CT, MRI and bone scintigraphy for detecting primary tumors, recurrent and/or metastatic disease and monitoring treatment response [4,5]. Other imaging modalities, such as PET with choline-based tracers or fluorodeoxyglucose, have been investigated, but they do not always reliably identify local recurrence, lymph node involvement or visceral metastases, and arguably have low value in overall patient management [6].

The over-arching problems with this current approach for the detection and staging of prostate cancer are three-fold.

- Firstly, digital rectal examinations and PSA tests only reveal if there is a problem with the prostate gland, without specifically ruling out or ruling in cancer.
- Secondly, prostate cancer is very heterogeneous – some cancers are slow-growing and non-aggressive, while others are extremely malignant. The inability to resolve this heterogeneity is a serious shortcoming as it may lead to over-treatment in which many men receive treatment that they may not have needed, for a cancer that may not have harmed them. Under-treatment also occurs. [2].

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- Thirdly, moving through the disparate elements of the patient management pathway takes time; time to obtain a false negative, time to schedule further appointments and time for further procedures. In patients with aggressive disease this extended time scale is a luxury they simply do not have. In the weeks between an initial consultation and a firm diagnosis, the cancer may have already metastasized to distant parts of their body.

A NEW APPROACH: PSMA PET/CT IMAGING

A single, non-invasive imaging modality that improves diagnosis and disease staging and which can be used to assess disease progression and treatment response has the potential to transform the management of prostate cancer. Such an imaging modality is already available – PET/CT imaging with prostate cancer-specific tracers.

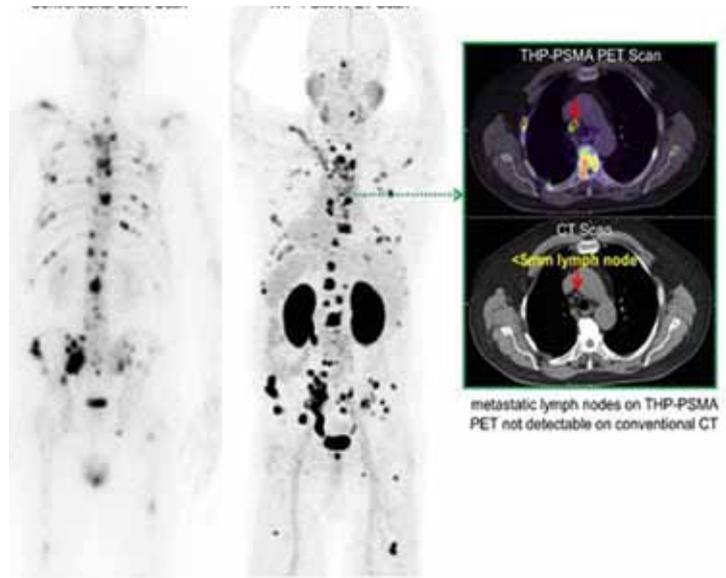
⁶⁸Ga-PSMA PET/CT is a rapidly emerging targeted imaging modality in the field and involves the use of an injectable ⁶⁸Ga-labeled urea-based small molecule, which binds with high affinity to the extra-cellular domain of the prostate-specific membrane antigen (PSMA). Increased PSMA expression is seen in a variety of malignancies, most notably in prostate cancer. Adenocarcinomas of the prostate demonstrate PSMA expression in the great majority of primary and metastatic lesions. ⁶⁸Ga-PSMA-PET/CT imaging has rapidly emerged as a practice-changing imaging modality with significant advantages compared to conventional imaging such as CT, MRI or bone scanning.

⁶⁸Ga-HBED-PSMA-11 PET/CT has demonstrated significant clinical utility in both the staging of newly diagnosed patients and restaging. More accurate staging of high-risk patients may enable better selection of the most appropriate management strategy and avoid futile locoregional surgery or radiotherapy in patients with metastatic disease. However, the cumbersome production of the ⁶⁸Ga-HBED-PSMA-11 tracer, which has to be performed at the hospital site because of the short half-life of the ⁶⁸Ga, is an impediment to its standard, widespread use.

⁶⁸Ga-THP-PSMA PET/CT Phase 1 study design

The results of a phase 1 study were recently published in the Journal of Nuclear Medicine [7]. The paper described a promising solution to overcoming some of the production challenges of existing technologies. The new approach is based on the use of a tris(hydroxypyridinone) (THP) chelator to form a novel ⁶⁸Ga PSMA PET tracer known as ⁶⁸Ga-THP-PSMA. This tracer can be produced quickly and on-demand in the clinic using a simple single step kit much in the same way as traditional nuclear medicine Tc-99m radiopharmaceuticals are produced [7].

“...The ⁶⁸Ga-THP-PSMA tracer can be produced quickly and on-demand in the clinic using a simple, single-step kit...”



Compared to conventional bone scans, ⁶⁸Ga-THP-PSMA-PET enables better visualisation of widespread bony metastases. ⁶⁸Ga-THP-PSMA-PET also allows the visualisation of metastatic lymph nodes not detectable with conventional CT. (Conventional Bone Scan on left; THP-PSMA PET on right)

In this Phase 1 study, fourteen patients with biopsy proven adenocarcinoma of the prostate were recruited; eight in Group A and six in Group B. Safety and biodistribution of ⁶⁸Ga-THP-PSMA were assessed in all patients. In Group A, additional aims were to define whole body radiation dose and plasma radiotracer clearance, and correlate the uptake with tumor PSMA expression on histopathology. In Group B, the aim was to compare physiologic and pathologic biodistribution in patients with PSMA-avid malignant disease on ⁶⁸Ga-HBED-PSMA-11 PET/CT.

In Group A, patients had no prior treatment for prostate carcinoma and were scheduled for prostatectomy. In Group B, inclusion criteria additionally mandated patients with prior clinical ⁶⁸Ga-HBED-PSMA-11 PET/CT demonstrating at least one unequivocal PSMA-avid focus considered to represent metastatic prostate cancer.

⁶⁸Ga-THP-PSMA PET/CT Phase 1 study results

This study is the first-in-human validation of ⁶⁸Ga-THP-PSMA, the first clinical tracer to utilise the novel THP chelator, which enables labelling to be carried out in less than five minutes at room temperature. In contrast, the DOTA chelator, incorporated in the widely used DOTATATE, requires pH adjustment, heating followed by cooling, and sometimes a purification step, necessitating either significant manual handling or the use of an automated synthesis device [7,8]. This increases expense and may not be compliant with Good Manufacturing Practices (GMP). Furthermore,

cartridge-based automated synthesis typically takes more than 45 minutes, which is suboptimal for a short half-life radionuclide such as ^{68}Ga . HBED chelation can be performed at room temperature but this produces a mixture of cis/trans geometric isomers [9]. ^{68}Ga -THP-PSMA has been developed as a single step kit-formulated GMP radiopharmaceutical, requiring only the addition of unprocessed, unfractionated generator eluate (with low Ge-68 breakthrough) to a single vial.

The study demonstrated that ^{68}Ga -THP-PSMA is comparable with ^{68}Ga -HBED-PSMA-11 in terms of safety, biodistribution and visualization of malignant tissue. Indeed, ^{68}Ga -THP-PSMA had significantly lower background physiologic uptake compared to ^{68}Ga -HBED-PSMA-11. Specifically, uptake in the salivary (parotid and submandibular) and tear glands (lacrimal), liver, spleen, duodenum and small bowel was significantly lower for ^{68}Ga -THP-PSMA.

THE FUTURE OF PSMA PET/CT IMAGING

The recent study has a number of important implications for the detection and management of prostate cancer. First and foremost is the fact that ^{68}Ga -THP-PSMA can be produced simply, quickly and on demand in the clinic, thus offers significant efficiencies (e.g. days instead of months of validation and a few minutes instead of hours of preparation and production time) when compared with the production of ^{68}Ga -HBED-PSMA-11. This advance could facilitate and underpin a more widespread use of PSMA-PET imaging for prostate cancer patients. Combining ^{68}Ga -THP-PSMA-PET with mpMRI instead of CT also promises to improve the detection, localization or exclusion of malignant foci within the prostate, owing to the excellent anatomical and zonal resolution of the prostate obtained by MRI [10]. A further possibility is the use of this modality to detect and localise suspicious lesions and PSMA-positive tissue. This ability would be extremely useful, especially in those patients who have undergone several biopsies, all of which have been negative on inspection. Imaging with ^{68}Ga -THP-PSMA-PET in these patients could be used to pinpoint the area a

biopsy must target to collect cancerous tissue.

^{68}Ga -THP-PSMA-PET may also improve the evaluation of the metastatic spread of the disease to lymph nodes, bone or viscera in patients with primary intermediate/high risk disease [10]. In this setting, ^{68}Ga -THP-PSMA-PET imaging enables a whole staging procedure to be performed in a single examination, therefore obviating the need for further cross-sectional imaging or bone scintigraphy [10]. This potential is in line with ^{68}Ga -PSMA-PET imaging generally, as recent results have shown that this approach increases the diagnostic accuracy in primary staging, which might influence the subsequent management of the disease [10]. This is particularly relevant to surgical treatment. Often, the prostate gland is removed unnecessarily when the cancer has already spread to distant parts of the body although surgical removal offers no benefit. In this scenario, the patient would be better treated with androgen deprivation therapy (ADT) chemotherapy/radiotherapy. Removing the prostate gland is an invasive procedure that can result in bleeding, infection, incontinence and erectile dysfunction, so any modality that can inform the most appropriate treatment decision would be a step forward. Conversely, PSMA-PET imaging could underpin new salvage treatment options in those patients with oligometastatic disease who are suitable for PSMA-radioguided surgery. In castration-resistant prostate cancer it is possible to envisage an approach where radionuclide-tagged PSMA inhibitors could be used to treat the lesions [10].

To date, the majority of PSMA-PET data have come from studies on patients with recurrent prostate cancer. In this setting, PSMA-PET improves the detection of metastatic prostate cancer compared with conventional, cross-sectional imaging or bone scintigraphy [10]. Moreover, PSMA-PET increases the detection of lesions (even at very low serum PSA values) compared with conventional imaging or PET using different tracers [10]. This has important implications for salvage

radiotherapy as this treatment is most effective at low serum PSA values. PSMA-PET imaging could therefore be used to optimize and guide radiotherapy.

CONCLUSIONS

The ^{68}Ga -THP-PSMA PET/CT modality offers a significant step forward in the management of prostate cancer. PSMA-PET scanning is fast becoming the imaging modality of choice in high-risk and recurrent prostate cancer because of the simplicity of its preparation. The advance promises to make this imaging technique more widely available to men with prostate cancer. Pending further data and regulatory approval, ^{68}Ga -THP-PSMA PET/CT can make a real difference in the management of this disease.

ACKNOWLEDGMENTS

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