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EDITORIAL

Performance of ^{18}F-fluciclovine PET/MR in the evaluation of osseous metastases from castration-resistant prostate cancer

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With a propensity for prostate cancer to spread to the skeleton and the recognised shortcomings of conventional imaging, such as computed tomography (CT) and bone scintigraphy (BS) in detecting skeletal metastases, there is a need for more sensitive detection of bone metastases, both at diagnosis and at biochemical recurrence (BCR). The need for more sensitive imaging is now of greater importance with the introduction of several novel therapeutics for metastatic prostate cancer that can improve morbidity and prolong survival, as well as the introduction of potentially curative treatment strategies for those with oligometastatic disease.

^{18}F-fluciclovine is a synthetic amino acid analogue with affinity for prostate cancer that is approved in Europe and the USA for investigation of BCR of prostate cancer. ^{18}F-fluciclovine positron emission tomography/computed tomography (PET/CT) has been shown to change management in approximately 60% of patients in this indication in prospective US and UK trials [1, 2].

Despite normal diffuse ^{18}F-fluciclovine metabolic activity in the bone marrow [3], there are preclinical and clinical data describing successful detection of skeletal metastases in prostate cancer [4, 5]. The preclinical data showed, in a rat osteoblastic bone metastasis model, that ^{14}C-fluciclovine had a similar distribution to other metabolic tracers, including ^{3}H-FDG and ^{3}H-choline, but not the bone-specific tracer ^{99m}Tc-HMDP, in keeping with detection of metabolically active tumour cells rather than osteoblastic bone mineralisation [4]. Clinical data have shown a greater sensitivity for detecting prostate cancer bone metastases with ^{18}F-fluciclovine (100%) compared with BS (79%) [5].

In this issue, Amorim et al. describe a comparison of bone scintigraphy (BS), ^{18}F-fluciclovine PET alone and ^{18}F-fluciclovine PET/magnetic resonance imaging (MRI) in 8 patients (347 bone lesions) with castrate-resistant prostate cancer (CRPC), 5 of whom also had a follow-up ^{18}F-fluciclovine PET/MRI scan [6]. ^{18}F-fluciclovine PET/MRI was equivalent to MRI alone (347 and 344 lesions detected, respectively), and detection was lower for BS (286/347) and ^{18}F-fluciclovine PET alone (238/347), inferring that ^{18}F-fluciclovine confers no significant incremental benefit in lesion detection compared with MRI (apart from 3 lesions where prosthetic metallic artefact impaired MRI lesion conspicuity).

Of particular note, it was reported that only 25/112 densely sclerotic lesions were ^{18}F-fluciclovine-positive. The authors hypothesised that sclerotic lesions were more likely to have scanty tumour cells and resultant low uptake that may be inconspicuous against background physiological bone marrow activity.

All patients were receiving androgen deprivation therapy with a GnRH agonist at the time of imaging, and although all were considered to be castrate-resistant and being considered for radium-223 therapy, it is not possible to determine if some metastases that were visible on MRI had been previously rendered metabolically quiescent and inactive (i.e. ^{18}F-fluciclovine-negative), given that heterogeneity of response between skeletal metastases may exist [7]. There was no metabolic comparator in this study and the standard of reference only relied on osteoblastic or morphologic criteria (BS/CT/MRI). To support this point, there is evidence that successfully treated metastases become more sclerotic [8] and less metabolically active as shown with other tracers such as ^{18}F-FDG and ^{18}F-choline

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[9, 10]. Changes in metabolic activity and lesion detection in the 4 patients that received radium-223 in this study were not reported.

A comparison of sensitivity between metabolic and morphologic imaging modalities in patients who have had prior treatment will always be biased towards the morphologic (e.g. MRI–bone marrow, CT–bone) or bone-specific (BS, ^{18}F-fluoride PET–osteoblastic bone mineralisation) methods that cannot distinguish between viable tumour and treated "scar" or reactive osteoblastic healing, respectively.

In conclusion, the study by Amorim et al. suggests that ^{18}F-fluciclovine does not confer a significant increase in sensitivity over MRI alone. However, the possibility of a treatment effect causing some lesions to be metabolically inactive, and therefore revealing important metabolic information, remains a possible explanation for some of the reported discordance noted between MRI and ^{18}F-fluciclovine PET. Further work will be required to determine if ^{18}F-fluciclovine, as a tumour metabolic tracer, will be able provide incremental knowledge to morphologic (e.g. CT or MRI) or bone-specific (e.g. BS or ^{18}F-fluoride PET) information on the viability of individual metastases. The possibility that viable sclerotic metastases are truly false negative with this tracer will also need to be carefully determined, preferably in a longitudinal study with comparison to another direct measure of tumour viability.

Compliance with ethical standards

Conflict of interest GC is a coinvestigator in the The FALCON trial (NCT02578940). GC receives research funding from Theragnostics Ltd and NanoMab Technology Ltd.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

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