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Platinum Priority – Editorial

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Tumour Heterogeneity and Resistance to Therapy in Prostate Cancer: A Fundamental Limitation of Prostate-specific Membrane Antigen Theranostics or a Key Strength?

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A major challenge to effective cancer treatment is the Darwinian evolution of tumours in response to their microenvironment and treatments, resulting in bewildering heterogeneity. Our ability to appreciate this heterogeneity is increasing with advances in analysis of tumour specimens. This includes analysis of individual tumour samples such as genetic interrogation using next-generation sequencing and noninvasive liquid biopsy for detection of circulating tumor cells or DNA. Equally valuable is our ability to image tumour heterogeneity using functional techniques that include positron emission tomography (PET) and single-photon emission computed tomography. While the resolution of these imaging technologies means that they are limited for discerning intratumoural heterogeneity, they provide powerful characterisation of intertumoural heterogeneity by visualising the spatial and organ distribution of different disease phenotypes on a whole-body scale. With the evolution of specific PET radiotracers such as small molecules that bind to prostate-specific membrane antigen (PSMA) we are now able to interrogate the whole body expression of specific targets and, consequently, predict the likelihood of response to particular therapies. The coupling of a tumour-specific imaging agent and therapy epitomises the realisation of precision oncology.

In this issue of *European Urology*, Paschalis et al. [1] report remarkable heterogeneous membranous expression of PSMA. In line with existing data, they report an association of PSMA expression with higher Gleason grade and prognosis. Surprisingly, however, they report higher levels of prostate cancer (PC) with no PSMA expression: 42% of castration-sensitive PC (CSPC) and 27% of metastatic castration-resistant PC (mCRPC) tissues sampled had no detectable PSMA. They further report marked intratumour heterogeneity, with no foci of detectable PSMA in all cases of CSPS and 84% of mCRPC. Furthermore, they identified for the first time specific PC phenotypes that may have higher PSMA expression, specifically tumours with defective DNA repair.

Evolving clinical experience suggests that <5–10% of primary PCs show negative PSMA PET findings. To date, however, PSMA PET has mainly been performed in patients with high-risk PC before surgery or radiotherapy or in patients with biochemical recurrence. Prospective randomised data from the upcoming proPSMA study will provide robust data on the positivity rate in the staging setting [2], with a high positive predictive value for PSMA confirmed in biochemical recurrence already demonstrated [3]. It is likely that positivity rates will be substantially lower among patients with Gleason <7 disease, reflective of the more aggressive nature of PCs with high PSMA expression. An interesting question is whether the uptake of PSMA in the screening setting might be useful in identifying patients who are unlikely to have clinically significant PC and should have active surveillance, and whether it is complementary or superior to multiparametric magnetic resonance imaging. Studies such as the PRIMARY trial (ACTRN 12618001640291 t) are under way to answer these questions.

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Paschalis et al demonstrated significant heterogeneity even for patients with high PSMA expression. This is not unexpected. Indeed, most cell-surface markers in advanced malignancy demonstrate similar heterogeneity. A central failure of personalised medicine has been the underestimation of tumour heterogeneity [4]. Highly targeted therapies inevitably lead to selective growth of cells not expressing the molecule being targeted over time.

A fundamental advantage of the theranostic approach is the ability to select the patients most likely to benefit from therapy via whole-body imaging. Our groups have adopted a highly personalised approach to selecting patients for PSMA-directed radionuclide therapy [5]. Using contemporaneous PSMA and FDG PET we are able to identify patients who have high PSMA expression at all sites of disease and are most likely to benefit. We have observed that sites with low PSMA expression but high FDG uptake are likely to progress (Fig. 1). Moreover, we found that patients who we did not treat on the basis of low expression or discordant FDG-avid disease had very poor prognosis [6] and demonstrated that the amount of radiation delivered to tumours correlated with the prostate-specific antigen (PSA) response [7]. Heterogeneous phenotypes of progressive disease can be identified via repeat PSMA imaging at PSA progression after PSMA-targeted therapy [8]. These nicely reflect the heterogeneous PSMA expression demonstrated on biopsy by Paschalis et al. A better understanding of the genetics underlying these variable PSMA phenotypes will help in determining subsequent and combination treatment options for PSMA-targeted treatments.

Paschalis et al found a significant association between high PSMA expression and DNA damage response (DDR) mutations in mCRPC and suggest that this may be because of an increased cellular demand for folate and glutamate to counter the DNA instability. They did not assess the association with DDR in hormone-sensitive PC specimens, but this is an important part of the puzzle. We know that there is a significant increase in PSMA expression levels between the hormone-sensitive and castrate-resistant states, in addition to an increase in the heterogeneity of expression shown in this study. Both PSMA mRNA expression and PSMA PET intensity levels increase with androgen blockade, particularly in the mCRPC setting. This PSMA upregulation in response to androgen blockade is probably an adaptive cellular response to the stress of losing the androgen growth driver. Refining and understanding these complex interactions among DDR, androgen blockade, and PSMA expression will be critical in determining how best to use PSMA-targeted therapies in the future.

A further advantage of the theranostic approach is the cross-fire effect. The most common β-emitting radioisotope currently used, lutetium-177, has a mean and maximum path length of 0.7 mm and 1.8 mm, respectively. This means it has a “cluster bomb” effect, with deposition of ionising radiation in a sphere surrounding the actual PSMA-expressing cell. In a tumour mass, this means that adjacent non–PSMA-expressing cells receive similar doses of radiation. There is also growing interest in the use of α-emitters such as actinium-225, thorium-232, and lead-208. These have linear energy transfer—a measure of the amount of energy deposited per μm—that is two orders of magnitude greater, resulting in double-stranded DNA breaks even in radioresistant tissues. Their short path lengths in the range <0.01 mm provide precise tumour targeting, but there may

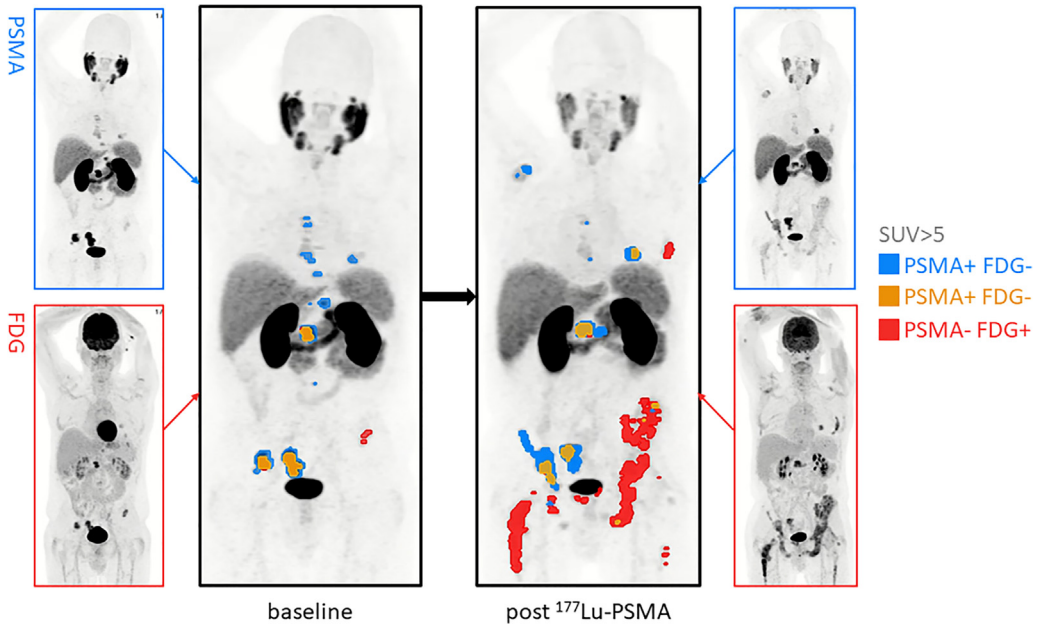

Fig. 1 – Paired PSMA and FDG PET before and after ^{177}Lu-PSMA-617 therapy demonstrating tumour heterogeneity with progression of FDG-positive, low-PSMA–expressing disease. The patient had metastatic castration-resistant prostate cancer after docetaxel and enzalutamide. He was deemed suitable for ^{177}Lu-PSMA on the basis of high PSMA expression. A single small site of disease with low PSMA expression and high FDG uptake is seen in the left pelvis. Over the course of four cycles of ^{177}Lu-PSMA-617, the patient developed increasing left hip pain without any change evident on post-therapy single-positron emission computed tomography/computed tomography to explain the pain. Following treatment, FDG/PSMA PET revealed a mixed response, with a dominant pattern of progression in the disease site with low PSMA expression in the left pelvis. FDG = fluorodeoxyglucose; PET = positron emission tomography; PSMA = prostate-specific membrane antigen.

be significant limitations given the spatial heterogeneity demonstrated by Paschalis et al, who reported a distance of 2 mm between PSMA-expressing cells. Given these findings, the use of longer-range β-emitters such as yttrium-90, with a maximum path length of 11 mm, may warrant further investigation. This approach might also be beneficial for the treatment of tumours that are poorly vascularised.

Exceptional responses with PSMA theranostics do occur but they are not the most common type of response to this new class of therapy. Paschalis et al have revealed that phenotypes with mutations in DNA repair pathways might have particularly high PSMA expression, which, because of their inherent radiosensitivity, may be subtypes that merit particular attention for theranostic targeting. It remains to be seen whether these preclinical findings translate to clinical outcomes. Translational substudies, particularly those embedded in prospective studies, will be key to identifying and validating these findings. As the number of effective therapies for prostate cancer continues to increase, data from multiple sources will need to be combined to allow optimal selection of treatment for an individual patient. We believe that deep analysis of PET imaging data will also play a critical role.

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