Molecular imaging and prostate cancer: unmet clinical needs and future perspectives

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Despite the fact that prostate cancer (PC) is the most common malignancy and cause of death of elderly men in Europe and USA, imaging procedures for PC have been unsatisfactory so far.

PC workup requires clinical evaluation, including digital rectal examination, prostate-specific antigen levels assay and transrectal ultrasound (TRUS); however, the final diagnosis of PC is eventually achieved, in most cases, by ultrasound (US)-guided random sampling biopsy. Nonetheless, there is no certainty that the needle will actually collect a sample of in the malignant tissue, but there is the expectation that multi-parametric MRI/US fusion-guided prostate biopsy can improve PC detection following TRUS.

Also, an improvement of the accuracy of staging is being pursued by a number of methods, that have superior sensitivity than bone scanning and X-ray computed tomography, and some of them, including PET/CT and wbMRI, have higher specificity, with fewer indeterminate lesions. The combination of PET/CT, in particular using different radiopharmaceuticals, and mpMRI is likely to improve the results of staging even further [1, 2].

Concurrently to advances in early diagnosis and accurate staging, the management of advanced PC has also developed quickly over the last few years thanks to the approval of several drugs in the castration-resistant state of the disease (abiraterone acetate, enzalutamide, docetaxel, cabazitaxel, radium-223). Thus, tumour response monitoring has also become an urgent and relevant need.

Bone is frequently the unique or the dominant site of metastatic disease in PC; however, the evolution of bone metastases is not measurable by standard response criteria (RECIST). Thus, there is currently no accepted imaging-based criterion to assess tumour response to therapy. The issue of bone imaging with either wbMRI and/or nuclear medicine procedures, including choline PET/CT, suggests a potential role for nuclear medicine imaging in this setting.

Several clinical conditions have been scrutinized for choline PET/CT, the most relevant consisting in the evaluation of patients with biochemical relapse after radical prostatectomy [3]. In such setting, the use of choline PET/CT has finally been recognized in international guidelines, in spite of the poor sensitivity at low PSA values. Nonetheless, choline PET/CT certainly holds a role in selected clinical scenarios, such as radiotherapy planning and salvage surgery and/or radiotherapy.

Beyond choline PET/CT, in the last 5 years, exciting results have been obtained with gallium-68-labelled small molecule inhibitors of prostate-specific membrane antigen (PSMA), and several groups have reported high accuracy for detection of recurrent PC in a large number of patients, as well as for proper staging of high-risk patients with PC. Based on these data, the capability of PSMA PET to identify the site of recurrence in patients with rising PSA is likely to be superior to all other clinically available imaging tests: therefore, PSMA PET is regarded, at

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present, as the most promising nuclear medicine imaging method for PC.

In addition to choline and PSMA inhibitors, there are several other promising radiopharmaceuticals for the detection and biological characterization of PC, including some tracers developed more than a decade ago, such as ^{11}C -acetate, androgen receptor ligand, 16-beta- ^{18}F -fluoro-5-alpha-dihydrotestosterone and a synthetic L-leucine analogue, ^{18}F -fluciclovine. The potential of PET/CT imaging, however, goes beyond the identification of the presence or absence of disease. The biological characterization of PC is also a possible and future application that may be used to personalize treatment plans based on disease biology. Kijar and colleagues introduced, for this purpose, the use of PET imaging of urokinase-type plasminogen activator receptor (uPAR), and some preliminary data on this innovative approach are now available [4]. PSMA-based therapy of PC is clearly at its early stages, but very impressive responses have been reported in patients with only very limited therapeutic options. Indeed, PSMA is an ideal membrane-bound molecule for imaging and also for targeted radionuclide therapy. Upon positive image findings, the same molecule can be used for therapy by alpha- or beta-particle emitter labelling. The most widely used radiopharmaceutical has been, so far, ^{177}Lu -PSMA, a significant promise for treatment of advanced metastatic PC.

Conclusion

Imaging of prostate cancer has rapidly become one of the hottest topics in molecular imaging. In recent years, we have witnessed the introduction of several imaging radiopharmaceuticals, and the proposal of several clinical

indications for their use. The literature and the data have grown rapidly, making sometime uneasy to establish the appropriate use of the various methods, by taking into account their diagnostic accuracy, the costs, availability, and effective clinical impact. Some of the unmet needs are being addressed with upcoming satisfactory results.

However, there are still a number of unmet clinical needs, including increasing the accuracy of an early and timely diagnosis, optimizing the methods for staging, identifying imaging approach to monitor tumour response to therapy. Molecular imaging by means of PET/CT and MRI will surely play a major role, especially with the introduction of new PET tracers and mpMRI.

Compliance with ethical standards

Conflict of interest The following conflicts of interest have to be reported: SF advisory boards/speakers' bureau: Bayer, Sanofi, GE Healthcare, Novartis, BlueEarth Dx. Research support: BlueEarth Dx, Movember.

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

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