European Journal of Nuclear Medicine and Molecular Imaging (2024) 51:2442–2443
https://doi.org/10.1007/s00259-024-06757-z

EDITORIAL

# Biological characterization of renal masses using immuno-PET

**Fabrizia Gelardi[1,2] · Alessandro Larcher[1,2] · Lidija Antunovic[2] · Umberto Capitanio[1,2] · Andrea Salonia[1,2] · Arturo Chiti[1,2]**

Published online: 11 May 2024


Classifying solid renal masses is a complex task that significantly challenges clinical decision making. The expanding diversity of renal neoplasms complicates accurate diagnosis and management, as different subtypes exhibit a wide range of clinical behaviour, from indolent to highly aggressive. Approximately 20% of patients with suspicious renal masses who undergo surgery have benign or indolent lesions, most commonly oncocytomas, angiomyolipomas and renal cysts [1]. Given these challenges, there is a growing need within the urology community to develop improved tools to correctly identify specific renal cell carcinoma histotypes [2].

Imaging is of paramount importance in the pre-surgical assessment of renal lesions. However, accurately characterizing solid renal masses using conventional imaging poses a major challenge. A significant difficulty is distinguishing clear cell renal cell carcinoma (ccRCC), which is typically associated with a poor outcome, from other non-ccRCC types with a better prognosis. Although the difference in enhancement patterns between ccRCC and papillary RCC is remarkable and helps in effective differentiation, distinguishing ccRCC from chromophobe RCC is more complex [3]. In addition, conventional imaging may underestimate the spread of disease, particularly in the detection of lymph node micro-metastases [4]. Similarly, bone scintigraphy may miss occult bone metastases due to the lytic nature of the lesions [5].

In this context, molecular imaging with radiopharmaceuticals targeting specific sites is becoming increasingly important, thanks to the ability to design effective molecules for peculiar tasks.

Carbonic anhydrase IX (CAIX) is overexpressed in ccRCC, making it an ideal diagnostic and therapeutic target. CAIX-targeted PET/CT is emerging as a promising tool for the precise characterisation and staging of renal masses suspicious for ccRCC. This technique provides critical information to guide treatment strategies, thereby improving overall clinical management. The high specificity of CAIX targeting may allow for preoperative identification of ccRCC, potentially sparing patients with benign renal masses from unnecessary surgery [6, 7]. CAIX-targeted PET/CT offers not only primary tumor characterization of ccRCC but also whole-body assessment for locoregional and distant metastases. In the growing field of theranostics, the development of lutetium-177-labelled CAIX-targeted radiopharmaceuticals is opening new treatment options for these patients.

Several CAIX-binding radiopharmaceuticals are under investigation, including [$^{89}$Zr]Zr-DFO-girentuximab and [$^{68}$Ga]Ga-DPI-4452 [8, 9]. The main limitation of the zircon-labelled antibody is principally related to the long uptake time and radionuclide half-life. This requires prolonged imaging and specific radioprotective measures [8]. An attempt has been made to overcome this problem by developing a gallium-labelled small molecule, but without achieving the same target-to background performance [9].

Beyond CAIX, research is ongoing to identify specific ccRCC targets for the development of new radiopharmaceuticals both for diagnosis and treatment.

The study published in this issue of the European Journal of Nuclear Medicine on the first-in-human use of [18 F] RCCB6 marks a significant milestone in molecular imaging and oncology [10]. The paper focuses on the development and clinical application of novel single-domain antibodies (sdAbs) labelled with fluorine-18, targeting CD70 specifically.

The CD70-CD27 axis represents an attractive target for molecular imaging. We know that CD70 can facilitate immune escape and tumour development by binding to CD27 in the tumour microenvironment. CD70 is overexpressed in both primary and metastatic ccRCC lesions, as well as in other solid tumours. Its expression in ccRCC is related with the accumulation of hypoxia-inducible factor

✉ Fabrizia Gelardi
gelardi.fabrizia@hsr.it

[1] Università Vita-Salute San Raffaele, Milan, Italy

[2] Nuclear Medicine Department, IRCCS San Raffaele, Via Olgettina 60, Milano 20132, Italy

due to the mutation of Von Hippel-Lindau, and its high rate of positivity—over 85% in ccRCC without expression in normal kidney tissue—makes CD70 a promising biomarker for ccRCC diagnosis and even treatment.

In the early clinical trial published in this issue of the EJNMMI, six patients with pathologically confirmed ccRCC were studied with [$^{18}$F]RCCB6 PET/CT. The results showed that [18F]RCCB6 provided a high tumor-to-background ratio and demonstrated diagnostic potential by identifying metastases with superior performance, due to specific lesion targeting and better imaging contrast, revealing a higher number of tumour sites compared to conventional methods. In addition, labelling these small antibody fractions with fluorine-18 may lead to more easy and practical clinical applications of these new tracers.

The advent of these new radiopharmaceuticals might mark a significant shift in the imaging of renal cell carcinoma. The high tumor-to-background ratio and specificity for ccRCC may enable earlier and more precise detection of primary and metastatic lesions, which is particularly valuable given ccRCC's variable presentation and progression patterns that might escape detection until metastasis occurs.

While the results are promising, the small sample size and preliminary nature of the findings warrant a cautious interpretation. Subsequent Phase II and III trials, as well as comparisons with other radiopharmaceuticals for ccRCC, are essential to validate these results, further understand the dynamics of CD70 expression in ccRCC, and establish standardized protocols for the use of [$^{18}$F]RCCB6 in clinical practice.

The paper by Wu et al. represents a significant advancement in ongoing research and development of targeted radiopharmaceuticals and emphasizes the importance of incorporating innovative diagnostic tools in oncology to enhance patient outcomes through precision medicine.

In line with the successful application of PSMA-based radiopharmaceuticals in prostate cancer, the role of PET in urology is going to further develop in the near future.

## Declarations

**Ethical approval** Institutional review board approval was not required because the paper is an editorial.

**Consent to participate** Not applicable.

**Conflict of interest** Arturo Chiti serves as the Editor in Chief of the EJNMMI; Lidija Antunovic is an Editorial Board Member of the EJNMMI.

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