



⁶⁸Ga-dotatoc vs. ¹⁸F-FDG vs. radiolabelled PSMA PET/CT in renal cancer patients

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Most renal masses are diagnosed incidentally by imaging. Traditionally, conventional studies, in example ultrasonography (US), contrast enhanced computed tomography (ceCT) and magnetic resonance imaging (MRI) are employed for detecting and characterizing renal masses. International guidelines recommend the use of ceCT in order to assess the tumour extension, including the widespread of disease in the local and distant lymph nodes, the assessment of the surrounding and distant organs and the function of the contralateral kidney. MRI has a higher diagnostic performance for small cystic masses and tumour thrombus than CT. However, the major limitation of ceCT or MRI is the inability to distinguish benign tumours from malignant renal neoplasms (1-3). In case of indeterminate ceCT findings, ceUS represents an alternative method to further characterize small renal lesions, although the current guidelines recognize an indeterminate low level of evidence for its accuracy. Diffusion-weighted and perfusion-weighted techniques have been explored for the evaluation of renal masses, but they are still considered experimental (4).

The evaluation of lymph node involvement with conventional imaging is problematic, as well. Indeed, only the length of the smallest axis of the nodes, assessed by ceCT, is considered predictive of tumour spread. This may create, especially for small nodes, the intraoperative doubt for a role of lymph node dissection.

Similarly, the restaging with conventional imaging has

limitations. After a tumour focal ablation (i.e., cryoablation or thermoablation) or surgery, conventional imaging is not accurate for the evaluation of metabolic active tissue, especially in those areas with some artefacts due to previous therapies (i.e., necrotic areas/changes of normal tissue after focal therapy/presence of clips-stitches/fibrosis). Finally, the exclusion of metastatic renal carcinoma with bone scan or brain CT/MRI is routinely indicated by guidelines only in the case of symptoms at diagnosis with thus any possibility to recognize the disease in a very early stage.

The metabolic value of positron emission tomography (PET)/CT in kidney cancer, particularly renal clear cancer cells (RCC) remains to be determined (5,6). Based on literature evidences, ¹⁸F-FDG PET/CT has a low sensitivity for primary RCC (7) and the role in the staging process is not supported by international guidelines. The European Association of Urology (EAU) guidelines, in fact, recognizes a low level of evidence to PET/CT due to its limited diagnostic performance for the assessment of primary and metastatic renal masses, both in the staging and restaging phase.

However, in the clinical scenario, especially in selected patients with high risk for disease recurrence, it can be useful when conventional imaging findings are doubtful (8-10). Furthermore, the identification of prognostic variables, in RCC patients, is crucial for the risk stratification and in order to adapt a specific therapy. The American Urology Association (AUA) guidelines suggest

that ^{18}F -FDG PET/CT could play a role in advanced or aggressive kidney tumours (11). In a study conducted on 104 patients, ^{18}F -FDG PET/CT has shown to be a valuable tool both in treatment decision-making and predicting survival in patients affected by recurrent RCC (12). Furthermore, several articles using ^{18}F -FDG PET/CT confirmed a good performance (sensitivity and specificity: 63–88% and 75–100%, respectively) for metastatic RCC (12–14). Some authors suggest the use of maximum standardized uptake value (SUVmax) as a predictor of survival and clinical outcome in RCC, but its use remains unclear in daily practice (15–17).

The expression of Prostate Specific Membrane Antigen (PSMA) has been reported on the cell surface of the microvasculature of several solid tumours, also RCC (18,19). PET/CT with radiolabelled PSMA has been tested extensively in recurrent prostate cancer (20,21). However, PSMA is expressed also in the proximal tubules of the normal kidney and it has been associated with the neovasculature of primary and metastatic RCC (18). Therefore, PSMA PET/CT would be a promising technique for the detection of metastatic RCC.

The paper by Nakamoto *et al.* (22) discussed about the utility of ^{68}Ga -DOTATOC PET/CT for the detection of recurrent RCC. The authors assessed the accuracy of ^{68}Ga -DOTATOC PET/CT in 25 subjects and in comparison with ^{18}F -FDG PET/CT in 12 patients with kidney cancer. They found that ^{68}Ga -DOTATOC PET/CT has a high sensitivity for the assessment of soft tissue (true positive rate-TPR =100%), bone (TPR =97%) and brain metastasis (TPR =100%), but it fails for the identification of lymph node involvement (TPR =33%). At patient-based and lesion-based analysis, the sensitivity of ^{68}Ga -DOTATOC for the evaluation of recurrent RCC was higher than ^{18}F -FDG PET/CT (83% and 74% *vs.* 58% and 59%, respectively), although not statistically significant. Similarly, Siva *et al.* (23) demonstrated that ^{68}Ga -PSMA PET/CT has a higher performance than ^{18}F -FDG PET/CT for the detection of oligometastatic RCC (n=8 patients), particularly in lungs, adrenal glands and bone.

The different available radiopharmaceutical agents for RCC should be linked with the histopathology. ^{68}Ga -DOTATOC and radiolabelled PSMA are both receptorial tracers that are therefore correlated with a well-differentiated cancer cells. Conversely, FDG is associated with the glucose metabolism that is particularly increased in undifferentiated cancer cells (24). The choice between radiolabelled PSMA and ^{68}Ga -DOTATOC depends by

some conditions: (I) the availability of tracer (i.e., ^{18}F -PSMA would be simpler to obtain than ^{68}Ga -labelled agents); (II) the expression of somatostatin receptors in the renal cancer cells (evaluated by immunohistochemistry analysis) and (III) the effect on the therapeutic management (few data are now available). However, the choice between receptorial and metabolic agents is strongly associated with histopathological differentiation of the primary and metastatic lesions.

In our opinion, the suggested recommendations in patients with recurrent RCC would be to: (I) consider the histopathological features of the primary tumour (histology, grade, mitotic index and others); (II) evaluate the utility of ^{18}F -FDG in case of aggressive disease and doubtful conventional imaging findings; (III) assess the utility of a receptorial PET/CT scan (with ^{68}Ga -DOTATOC or radiolabelled PSMA) in case of a negative FDG PET/CT scan or in case of a potential target therapy with ^{177}Lu -PSMA or $^{90\text{Y}}$ / ^{177}Lu -DOTATOC.

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Footnote

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