

## Case report

# Metastatic clear cell renal cell carcinoma demonstrating intense uptake on $^{68}\text{Ga}$ -DOTATATE positron emission tomography: Three case reports and a review of the literature

## ABSTRACT

$^{68}\text{Ga}$ -DOTATATE positron emission tomography (PET) is a molecular imaging technology which has shown superiority over  $^{111}\text{In}$ -octreotide scanning for the detection and staging of neuroendocrine tumors. We report three patients with pancreatic masses that were ultimately diagnosed as clear cell renal cell carcinoma (ccRCC) metastases on histopathology. During their initial diagnostic assessment, the three patients underwent both  $^{18}\text{F}$ -fluorodeoxyglucose ( $^{18}\text{F}$ -FDG) and  $^{68}\text{Ga}$ -DOTATATE PET. While all three patients' lesions showed variable  $^{18}\text{F}$ -FDG avidity, uptake on  $^{68}\text{Ga}$ -DOTATATE PET was comparatively intense. The small case series illustrates the need to consider ccRCC in the differential diagnosis of  $^{68}\text{Ga}$ -DOTATATE avid lesions.

**Keywords:**  $^{68}\text{Ga}$ -DOTATATE, kidney neoplasms, positron emission tomography, renal cell carcinoma, somatostatin receptors

## INTRODUCTION

Clear cell is the most common phenotype of renal cell carcinoma (RCC) and has increased in incidence over recent decades. Current staging investigations are unfortunately less reliable than for many cancer subtypes, with variable uptake and limited sensitivity seen with both  $^{18}\text{F}$ -fluorodeoxyglucose ( $^{18}\text{F}$ -FDG) positron emission tomography (PET)<sup>[1]</sup> and  $^{111}\text{In}$ -octreotide studies.<sup>[2,3]</sup> Imaging of carbonic anhydrase IX inhibitor expression has shown potential utility in the diagnosis and prognostication of clear cell RCC (ccRCC);<sup>[4]</sup> however, its role in clinical management is yet to be fully defined.

## CASE REPORTS

### Patient one


The first patient was an 86-year-old woman who presented for assessment of central abdominal pain. This occurred in the context of prior RCC, which was in remission following

left nephrectomy 15 years prior. Ultrasound examination demonstrated a 3 cm hypervascular mass in the pancreatic body, considered suspicious for a neuroendocrine tumor. An  $^{18}\text{F}$ -FDG and  $^{68}\text{Ga}$ -DOTATATE PET were subsequently performed for characterization and staging. The pancreatic mass showed minimal  $^{18}\text{F}$ -FDG avidity [Figure 1a], however showed comparatively intense uptake on  $^{68}\text{Ga}$ -DOTATATE PET [Figure 1b]. No additional metastatic deposits were seen

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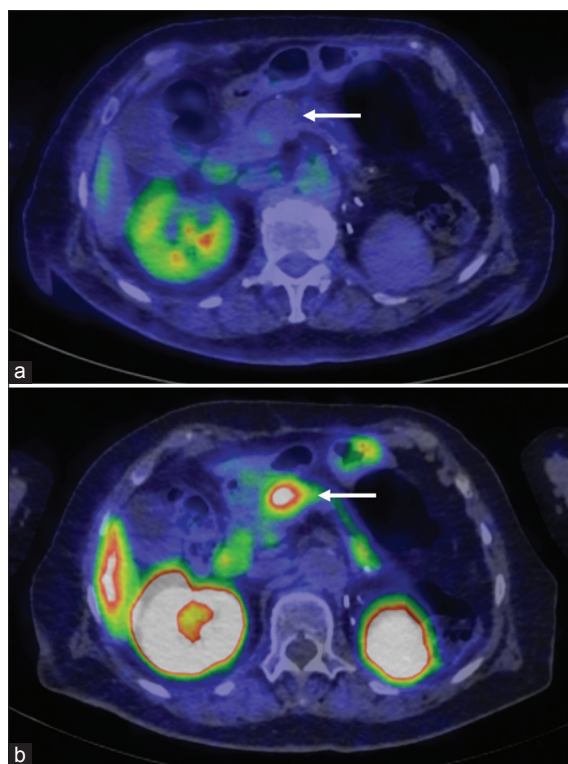
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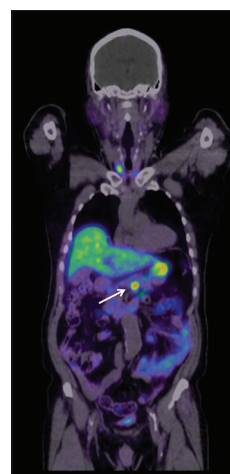


**Figure 1:** Transaxial positron emission tomography/computed tomography sections demonstrating differential radiotracer uptake within the pancreatic body lesion (arrowed). The mass was photopenic on <sup>18</sup>F-fluorodeoxyglucose positron emission tomography (a) but demonstrated intense <sup>68</sup>Ga-DOTATATE uptake (b)

throughout the remainder of the body on either scan. In view of the differential radiotracer uptake, the mass was felt to represent a well-differentiated neuroendocrine tumor. The patient subsequently underwent a central pancreatectomy and retroperitoneal lymph node dissection. Histopathology showed nests of polygonal cells with clear cytoplasm, which stained positive for CD10. The specimen was diagnosed as a ccRCC metastasis rather than a neuroendocrine tumor as initially suspected.

### Patient two

The second patient was a 76-year-old man who was diagnosed with a pancreatic lesion during the investigation of abnormal liver function tests. This was on a background of low-grade ccRCC, treated with a partial right nephrectomy 5 years prior. The pancreatic lesion was multifocal, with up to ten rounded enhancing masses seen within the pancreatic body on computed tomography (CT). <sup>18</sup>F-FDG PET showed only mild uptake within the pancreatic mass, in both adrenal glands and the L5 vertebral lamina; the intensity of uptake being considered nondiagnostic and equivocal for malignant disease. In contrast, <sup>68</sup>Ga-DOTATATE PET demonstrated relatively intense uptake throughout all four identified lesions [Figure 2]. A fine needle aspirate of the



**Figure 2:** Fused positron emission tomography/computed tomography coronal section demonstrating intense <sup>68</sup>Ga-DOTATATE uptake within case two's multifocal pancreatic lesion, which was subsequently diagnosed as metastatic clear cell renal cell carcinoma

pancreatic mass subsequently confirmed the diagnosis of recurrent ccRCC.

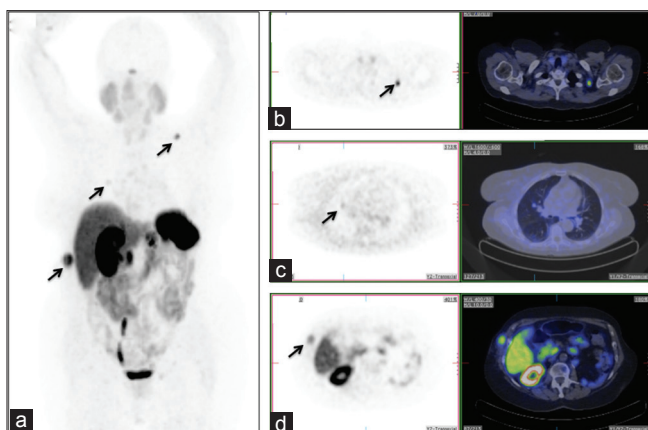
### Patient three

The third patient was an 84-year-old woman who presented after noting a superficial lump overlying her right lower ribs. Diagnostic CT showed a 33 mm subcutaneous mass in the right lower chest wall and multiple pancreatic lesions considered suspicious for metastases. <sup>18</sup>F-FDG PET showed minimal activity in the pancreatic lesion, moderate uptake in the right lower chest wall lesion, and faint uptake in a left infraclavicular lymph node. In contrast, the <sup>68</sup>Ga-DOTATATE PET study showed intense uptake in all of the lesions listed above, as well as additional uptake in a 1 cm pulmonary nodule [Figure 3]. Excisional biopsy of the subcutaneous mass showed rounded epithelial cells with prominent clear cytoplasm that were CD10 positive on immunohistochemistry. Following the diagnosis of metastatic ccRCC, the patient was referred for systemic therapy.

## DISCUSSION

We describe a case series of three patients with metastatic ccRCC, who all showed focal uptake on <sup>68</sup>Ga-DOTATATE PET. This finding has had limited description in existing literature, with single case reports of RCC avidity being published for <sup>68</sup>Ga-DOTATATE PET<sup>[5]</sup> and the related radiotracer <sup>68</sup>Ga-DOTATOC.<sup>[6]</sup>

While information surrounding <sup>68</sup>Gallium-DOTA-labeled somatostatin analogs in RCC remains limited, the expression of somatostatin receptors (SSTRs) by ccRCC is well recognized. Early investigations by Reubi and Kvolcs analyzed tissue



**Figure 3: Maximum intensity projection image (a) and three transaxial positron emission tomography and fused slices (b-d) demonstrating <sup>68</sup>Ga-DOTATATE avid clear cell renal cell carcinoma metastases involving the left infraclavicular region (b), right lung (c), and lower right chest wall (d)**

samples from 39 patients with RCC using autoradiography techniques.<sup>[7]</sup> They not only found SSTR to be expressed in 72% of tumor specimens but also found the receptors to be associated with poor prognosis and metastatic disease. A number of trials have followed, which have assessed the somatostatin analog, octreotide, as both a therapeutic and diagnostic target in ccRCC.<sup>[2,3,8,9]</sup> While <sup>111</sup>In-pentetreotide has shown some utility as a potential staging tool in ccRCC, the variable octreotide avidity and limited sensitivity have prevented the technique being translated into clinical practice.<sup>[2,3,9]</sup>

<sup>68</sup>Ga-DOTATATE PET is a more recent molecular imaging technology, which has shown superiority to <sup>111</sup>In-pentetreotide scanning for the staging of neuroendocrine tumors.<sup>[10]</sup> By replacing <sup>111</sup>Indium with the positron emitter <sup>68</sup>Gallium, <sup>68</sup>Ga-DOTATATE PET provides superior imaging characteristics compared to conventional single-photon emission CT. <sup>68</sup>Ga-DOTATATE also utilizes octreotate rather than octreotide, an analogous ligand which shows preferential affinity for subtype two of the SSTR2. ccRCC predominantly expresses the SSTR2 receptor subtype,<sup>[11]</sup> which may further explain the intensity of <sup>68</sup>Ga-DOTATATE uptake observed in the above cases.

Our case series provides further reminder that <sup>68</sup>Ga-DOTATATE uptake is not pathognomonic of neuroendocrine tumors and that metastatic ccRCC needs to be considered as a differential

diagnosis in the appropriate clinical scenario. Histopathologic confirmation significantly influenced the future management of all three patients, which underscores the value of biopsy in the evaluation of <sup>68</sup>Ga-DOTATATE avid lesions.

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#### Conflicts of interest

There are no conflicts of interest.

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