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Brief Correspondence

Positron Emission Tomography/Computed Tomography with ^{89}Zr-girentuximab Can Aid in Diagnostic Dilemmas of Clear Cell Renal Cell Carcinoma Suspicion

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Abstract

Based on the high expression of carbonic anhydrase IX (CAIX) in 95% of clear cell renal cell carcinoma (ccRCC), the anti-CAIX monoclonal antibody girentuximab can be used for the detection of ccRCC. This clinical study explores the value of ^{89}Zr-labeled girentuximab positron emission tomography/computed tomography (PET/CT) imaging in diagnostic challenges regarding ccRCC. PET/CT imaging was performed 4 or 5 d after injection of ^{89}Zr-girentuximab in patients with a primary renal mass (n = 16) or a history of ccRCC (n = 14). Scans were used for decision making (surgery/active surveillance) in case of indistinct renal masses. All resected PET-positive primary lesions proved to be ccRCC, while no lesion progression was seen in PET-negative masses. In patients suspected of recurrent/metastatic ccRCC, PET/CT with ^{89}Zr-girentuximab was useful to confirm or exclude ccRCC, evaluate the extent of the disease, and differentiate from other cancers. In this group, ^{89}Zr-girentuximab PET/CT resulted in a major change in clinical management in five patients (36%), while in three patients (21%) repeat biopsies could be avoided. We conclude that ^{89}Zr-girentuximab PET/CT is a valuable diagnostic tool that can guide clinical decision making in case of diagnostic dilemmas concerning ccRCC suspicion.

Patient summary: Positron emission tomography/computed tomography imaging with ^{89}Zr-girentuximab can be a valuable diagnostic tool to identify clear cell renal cell carcinoma.

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Noninvasive confirmation of the presence or absence of clear cell renal cell carcinoma (ccRCC) can be useful to guide clinical decision making in patients with indistinct primary renal tumors or in those suspected of recurrent or metastatic ccRCC. The high expression of carbonic anhydrase IX (CAIX) in 95% of ccRCC allows detection with the anti-CAIX monoclonal antibody girentuximab [1]. Multiple studies have confirmed the high accuracy of radionuclide imaging using radiolabeled girentuximab [2–4]. A positron emission tomography (PET) tracer, such

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as ^{89}Zr-girentuximab, allows better contrast and spatial resolution compared with single-photon emission computed tomography (SPECT) tracers. Furthermore, animal studies have demonstrated that ^{89}Zr-girentuximab outperforms ^{124}I-girentuximab in terms of tumor-to-normal tissue ratios [5,6].

This phase I/II study aims to evaluate the value of ^{89}Zr-labeled girentuximab PET/computed tomography (CT) imaging in 30 patients suspected of ccRCC in whom the clinician faced a diagnostic dilemma defined as uncertainty about the best medical treatment despite conventional diagnostics. Two subgroups were distinguished: (1) patients with an indistinct renal mass, and (2) patients suspected of recurrent/metastatic ccRCC. Whole-body PET/CT images were obtained 4–5 d after injection of 5 mg ^{89}Zr-girentuximab (37 MBq). Lesions of interest were considered PET positive or PET negative based on a visual scale, taking into account the background signal in surrounding organs and blood pool. Patient management was discussed in a multidisciplinary meeting before and after PET/CT results. A major change in management was defined as a change in one of the next-step strategies: surgery (including surgical strategy), surveillance, or systemic therapy. The study was approved by the Regional Internal Review Board (clinicaltrials.gov; NCT02883153). All patients signed informed consent.

In group 1 (n = 16), ^{89}Zr-girentuximab PET/CT imaging was used in the decision to perform either surgery or active surveillance. In all cases, follow-up data supported the decision (Supplementary Table 1). In six patients, tumors were PET positive and five of them underwent surgery confirming ccRCC (Supplementary Fig. 1). In the sixth patient (Supplementary Fig. 2), with Von Hippel Lindau (VHL) syndrome, PET/CT revealed additional PET-positive lesions compared with magnetic resonance imaging, and the largest lesion was treated by cryoablation for debulking purposes. In patient #12, active surveillance of a 0.9-cm PET-positive lesion (follow-up: stable disease) and a 4-cm PET-negative lesion (follow-up: shrinking) was initiated due to extensive previous abdominal surgery. In nine patients, tumors were PET negative and they were followed by active surveillance. None of the PET-negative tumors progressed during follow-up (mean 13.0 ± 4.9 mo), and these lesions are considered most likely to be benign or indolent non-ccRCC. However, longer follow-up is needed since average growth of renal tumors is 3 mm/yr [7].

The confirmation of the presence or absence of ccRCC by ^{89}Zr-girentuxumab PET/CT imaging results provided valuable information for clinical decision making in challenging cases, such as patients with a relative contraindication for surgery. ^{89}Zr-girentuximab is not nephrotoxic and can be used in patients with renal insufficiency. Owing to highly specific CAIX targeting, ^{89}Zr-girentuximab does not target other RCC subtypes. However, a negative ^{89}Zr-girentuximab PET/CT reduces the a priori chance of lesions with a high malignant potential, which also aids in clinical decision making.

Group 2 contained 14 patients suspected of recurrent or metastatic ccRCC (Supplementary Table 2). In case of oligometastatic disease, surgery with curative intent can be considered, whereas in case of extensive metastatic disease, there are only systemic treatment options with a palliative effect. Confirmation of oligometastases prior to metastasectomy is of utmost importance to avoid futile surgery. Eight patients (#17–24) were considered for surgery with curative intent. In three of them, high uptake in the lesion of interest was seen and surgery was performed confirming ccRCC (Fig. 1). In patient #17, surgery

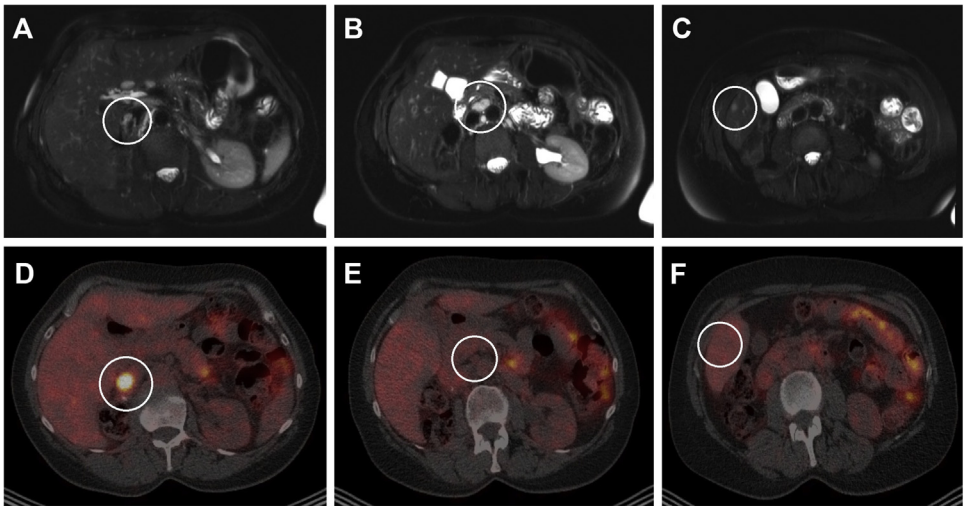

Fig. 1 – Patient #18 presented with a suspicious lesion in the inferior caval vein (ICV; 10 mm) 6 mo after nephrectomy (pT3a ccRCC with a positive surgical margin at the renal vein). CT and mpMRI (A) could not distinguish with certainty between tumor thrombus and a blood clot, and furthermore mpMRI revealed (B) several enlarged lymph nodes (short axis up to 12 mm) and (C) a liver lesion (7 mm). (D) ^{89}Zr-girentuximab PET/CT imaging showed uptake of ^{89}Zr-girentuximab in the inferior caval vein, thereby noninvasively confirming the presence of recurrent ccRCC. No uptake of ^{89}Zr-girentuximab in (E) the lymph nodes or (F) the liver lesion was seen, making ccRCC metastases less likely. Surgery was performed with resection of the lesion in the ICV (ccRCC) and several enlarged lymph nodes (benign). No change of the liver lesion was seen over 15 mo. The value of the ^{89}Zr-girentuximab PET/CT was to confirm the local recurrence and, prior to metastasectomy, provide more certainty about the enlarged lymph nodes and the liver lesion. ccRCC = clear cell renal cell carcinoma; CT = computed tomography; mpMRI = multiparametric magnetic resonance imaging; PET = positron emission tomography.

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