Eur J Nucl Med Mol Imaging (2007) 34:884–888
DOI 10.1007/s00259-006-0362-5

SHORT COMMUNICATION

[1-^{11}C]Acetate uptake is not increased in renal cell carcinoma

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Received: 8 September 2006 / Accepted: 15 December 2006 / Published online: 30 January 2007

Abstract
Purpose The purpose of this study was to investigate the potential of [1-^{11}C]acetate (AC) as a metabolic tracer for renal cell cancer in human subjects.
Methods Twenty-one patients with suspected kidney tumours were investigated with AC and dynamic PET. AC uptake was scored on a five-step scale. Tumour localisation was known from CT/MRI. Histology was available in 18/21 patients. The results in these 18 patients are reported.
Results AC uptake by the tumour was less than (n=11), equal to (n=5) or higher than (n=2) uptake in the surrounding renal parenchyma. Histological tumour types showed a typical distribution, with a predominance of clear cell carcinomas (n=14) and only a small number of papillary cell carcinomas (n=2) and oncocytomas (n=2). Only the benign oncocytomas were highly positive with AC.
Conclusion In most kidney tumours the AC accumulation was not higher than in normal kidney parenchyma. Therefore, AC PET cannot be recommend for the characterisation of a renal mass.

Keywords [1-^{11}C]acetate · Kidney tumour · Positron emission tomography

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Introduction

Renal cell carcinoma (RCC) accounts for approximately 3% of all cancers in adults. With the increased use of ultrasound and computed tomography (CT) for the evaluation of abdominal disease, the number of incidentally discovered RCCs has increased significantly. CT is the standard imaging test for evaluation of patients with renal masses [1]. Fluorodeoxyglucose (FDG) positron emission tomography (PET) is of proven potential in the majority of tumours but has limited value in the evaluation of kidney tumours because of inconsistent intratumoral FDG uptake and reduced tumour to background contrast due to renal tracer elimination [1]. However, the latter limitation may be expected not to apply when using other radiotracers like acetate or choline, for which renal tracer elimination is absent [2]. In tumour imaging, [1-^{11}C]acetate (AC) is mainly used in prostate cancer but it is also applied in hepatocellular and nasopharyngeal carcinoma and lung cancer [3–5]. Shreve et al. reported high AC uptake in RCC in three patients [6]. However, more data are lacking, especially on AC tumour uptake compared with histology. Therefore, we investigated suspected RCC and compared AC-PET with histological results.

Table 1 Patient characteristics

Patient no.	Age (yrs)	Sex	Size (mm)	AC score	Histology	Creatinine (μmol/l)
1	59	m	17	1	Clear cell	60
2	46	f	70	2	Clear cell	92
3	73	m	45	4	Oncocytoma	116
4	83	m	25	4	Oncocytoma	172
5	66	f	60	2	Clear cell	107
6	63	m	110	0	Papillary	74
7	64	m	40	3	Clear cell	114
8	42	m	35	2	Clear cell	161
9	70	m	33	1	Clear cell	95
10	81	m	40	0	Clear cell	127
11	48	f	150	1	Clear cell	112
12	72	m	55	1	Clear cell	134
13	54	f	30	0	Papillary	55
14	67	m	58	1	Clear cell	104
15	67	m	20	2	Clear cell	103
16	69	m	20	1	Clear cell	134
17	70	m	65	1	Clear cell	139
18	45	f	70	0	Clear cell	94

m male, *f* female, *AC score* [1-^{11} C]acetate uptake score (for details see text)

Materials and methods

Patient population

Twenty-one patients (16 male, 5 female, mean age 62 years, range 42–83) with suspected kidney tumour were investigated after providing written informed consent, as part of an individualised therapy management protocol (Table 1). Conventional imaging indicated that neither lymph node involvement nor distant metastases were present. In 18 patients, histology after PET imaging was available. In three males no surgery was performed, and these patients were removed from the analysis. The analysis was performed with the approval of the local ethical committee and complied with current German law.

PET imaging

[1-^{11}C]Acetate was produced from carbon dioxide by Grignard's reaction [7]. PET imaging was performed with an ECAT EXACT HR+ (Siemens/CTI, Knoxville, TN, USA), with an axial field of view of 15.5 cm and image resolution of 4.5 mm in all three dimensions. Patients fasted for at least 6 h (serum glucose 4.7±0.8 mmol/l). After a 10-min transmission scan with rotating ^{68}Ga/^{68}Ge rod sources, a dynamic emission scan of the kidneys over 30 min (12× 10 s, 2×30 s, 2×60 s, 2×150 s, 4×300 s) was started with the injection of 0.84±0.44 (range 0.4–1.8) GBq AC intravenously.

The PET scans were reviewed independently by two board-certified nuclear medicine physicians (B.B.-B., J.K.). AC uptake in tumour was scored using a five-step classification, from 0=photopenic to 4=intense tumour uptake on summed images from 5 to 30 min. Time-activity curves were calculated when the RCC could be delineated from surrounding kidney parenchyma.

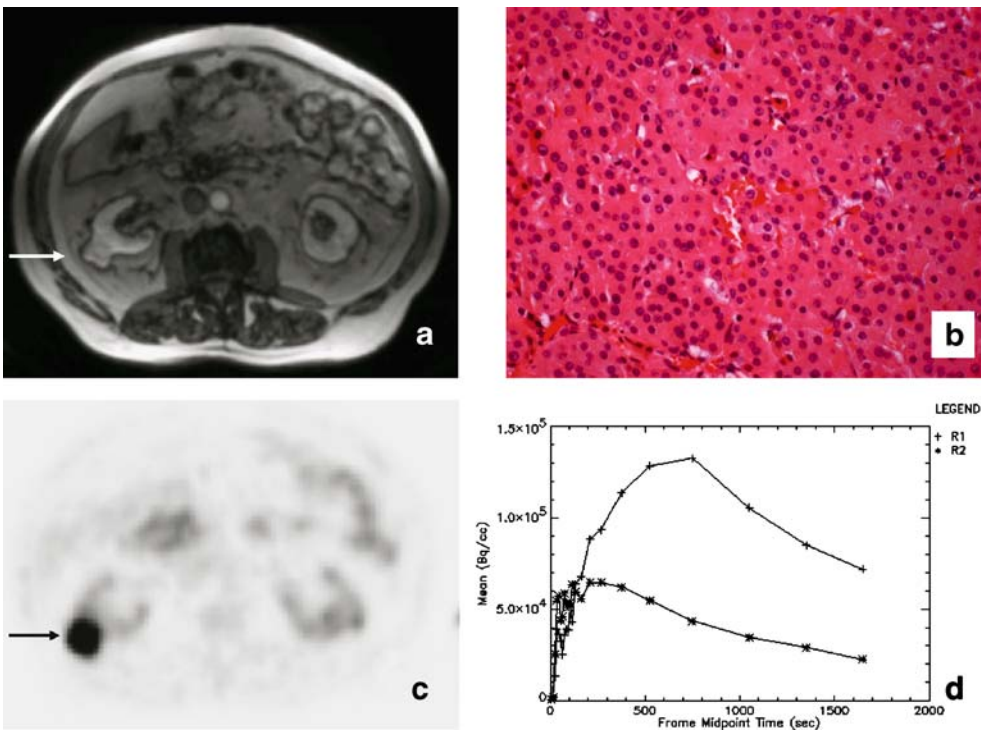

Fig. 1 PET in an 83-year-old male (Table 1, patient no. 4) revealed a lesion of 25 mm in diameter in the right kidney (*white and black arrows*) with intense AC uptake (score=4). Time-activity curve of the lesion (*R1*) yielded a peak activity at 12 min p.i. and a contrast ratio in relation to normal kidney parenchyma (*R2*) of 2.0–3.0 from 10 to 30 min p.i. Contrast-enhanced T1-weighted magnetic resonance imaging (MRI; gradient echo sequence) in breath hold demonstrated reduced contrast uptake as compared with the normal renal parenchyma. Histology revealed an oncocytoma composed of large cells with intensely granular eosinophilic cytoplasm and small, uniform and vesicular nuclei (H&E staining, ×200). **a** Morphological imaging, **b** histology, **c** AC PET, **d** time-activity curves

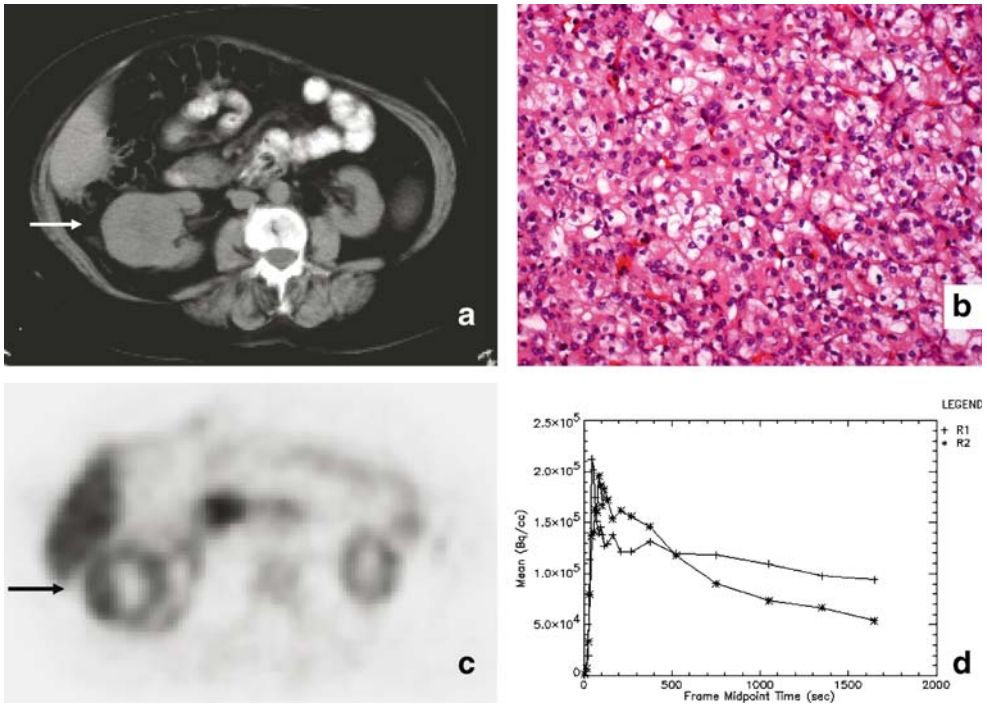

Fig. 2 PET in a 66-year-old female (Table 1, patient no. 5) revealed a lesion of 60 mm in diameter in the right kidney (*white and black arrows*) with an AC uptake comparable to that in surrounding kidney parenchyma (score=2). Time-activity curve of the lesion (*R1*) yielded an initial peak and fast clearance comparable to normal kidney parenchyma (*R2*). Plain CT revealed a slightly inhomogeneous tumour with central hypodensity corresponding to the photopenic area not included in R1. Histology (H&E staining, ×200) demonstrated large cells with clear cytoplasm and medium-sized, rounded nuclei with granular chromatin (clear cell carcinoma). The high prevertebral AC uptake was due to tracer accumulation in the pancreas. **a** Morphological imaging, **b** histology, **c** AC PET, **d** time-activity curves

Histology

In 18 patients the kidney tumour was removed without evidence of metastatic disease. The specimens were formalin fixed and paraffin embedded. Histological workup included the examination of three to six different areas of each tumour. H&E sections were examined by two pathologists. Diagnosis was made by H&E histology alone in all cases using the established criteria [8, 9]. All carcinomas were graded according to the criteria of Thoenes et al. [8].

Results

AC PET imaging

Two patients demonstrated intense AC uptake in the kidney tumour (Table 1, Fig. 1). Histologically, both AC-positive tumours were oncocytomas. In five patients, AC uptake by the tumour was similar to that in surrounding kidney parenchyma but the lesion could be defined by virtue of its shape (Fig. 2). In seven patients, tumour presented lower uptake than normal kidney parenchyma, and a photopenic area could be detected in four patients (Fig. 3). No systematic influence of renal function, indicated by current creatinine levels, on the AC uptake by the RCCs was detectable (Table 1).

Time-activity curves from the lesions with high AC uptake revealed maximum activity in the tumours approximately 10 min after injection, followed by prolonged washout compared with normal kidney parenchyma (Fig. 1). In tumours with AC uptake comparable to that in normal kidney parenchyma, similar uptake and washout kinetics were observed for benign and malignant tissue regions (Fig. 2).

Histology

Histological examination of the 18 tumours removed showed clear cell RCC in 14 cases, papillary RCC in two cases and benign oncocytomas in two cases (Table 1).

Discussion

In this study, high AC uptake in kidney tumour was observed in only two out of 18 patients for whom histology was available. Among these 18 patients, histology confirmed a normal distribution of histological subtypes of

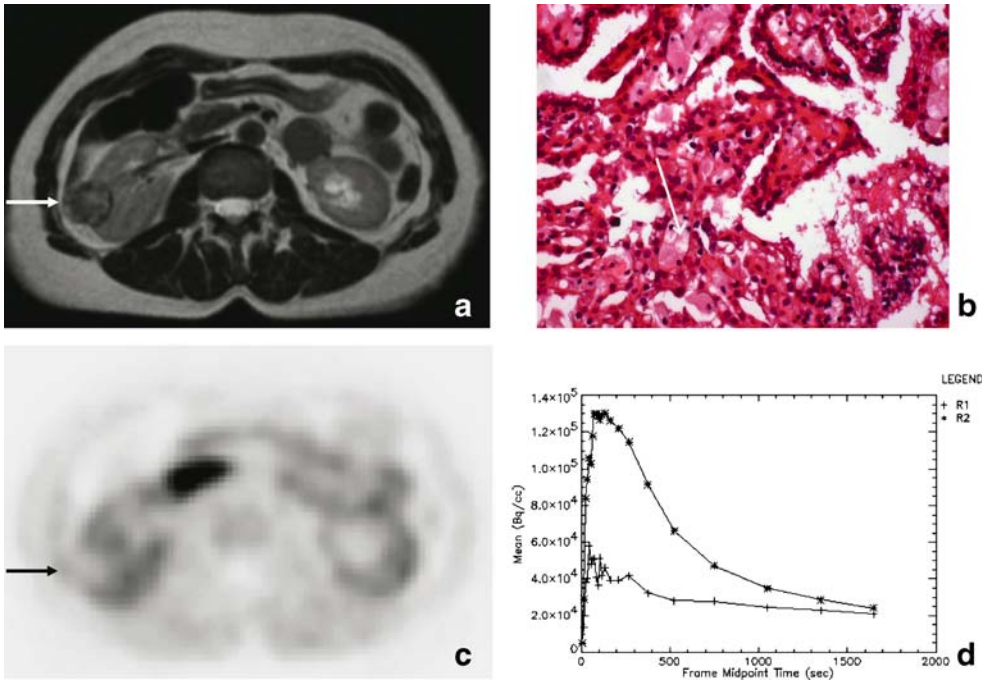

Fig. 3 PET in a 54-year-old female (Table 1, patient no. 13) revealed a lesion of 30 mm in diameter in the right kidney (*white and black arrows*) without AC uptake (score=0). Time-activity curve of the lesion (*R1*) demonstrated no specific uptake of the lesion and washout kinetics comparable to normal kidney parenchyma (*R2*). T2-weighted MRI (turbo spin echo sequence) using a breath-hold technique visualised a slightly hypointense lesion as compared with the normal renal parenchyma. Histology (H&E staining, ×200) demonstrated a papillary structure, eosinophilic cytoplasm and small and uniform nuclei (*arrow*, typical foamy cells) from papillary RCC. The high prevertebral AC uptake was due to tracer accumulation in the pancreas. **a** Morphological imaging, **b** histology, **c** AC PET, **d** time-activity curves

RCC, with a predominance of clear cell carcinomas [8]. High tumour uptake only occurred in the two cases of oncocytoma. Clear cell carcinoma, the most common histological subtype, demonstrated equal or less AC uptake compared with normal kidney parenchyma. These findings are in contrast to those reported by Shreve et al., who observed high AC uptake in three of three patients with RCC [6], suggesting that AC might be a useful radiotracer for tumour imaging in renal cancer. Recently, a kidney tumour with high AC uptake was detected during AC PET whole-body imaging for staging of prostate cancer [10]; histopathological analysis again revealed an oncocytoma. Interestingly, one other publication reported increased uptake of FDG in an oncocytoma [11].

The accumulation of AC in malignant cells is related to the highly active lipid metabolism in the cell membrane associated with tumour growth. AC is channeled into the tricarboxylic acid cycle via acetyl coenzyme A and then incorporated via phosphatidylcholine into the cell membrane's phopholipids. AC uptake may be increased in slowly growing, well-differentiated tumours, as has been demonstrated in hepatocellular carcinomas showing a low FDG metabolism [3]. In agreement with this hypothesis, oncocytoma, a benign neoplasm, showed the highest AC uptake.

Despite inconsistent findings in the literature, primary RCC and its metastases can be detected by FDG imaging [1]. In the largest study investigating primary tumours, 20 out of 26 histologically confirmed RCCs took up FDG [12]. Assuming that the behaviour of RCCs resembles that of hepatocellular carcinomas, high FDG uptake should be accompanied by low AC uptake.

Low AC uptake was not an artefact of late static imaging. Dynamic imaging was performed which demonstrated that the RCCs did not have high initial uptake and faster washout kinetics than surrounding kidney but rather showed reduced initial AC uptake and renal-like washout kinetics. Even very delayed imaging did not improve contrast substantially.

The AC uptake was not compromised by impaired renal function (cf. Table 1), which was close to normal in most of the patients. In addition, Shreve et al. observed that renal AC uptake is prompt and high even in the presence of markedly reduced renal function [6]. Two of the three patients with the lowest AC tumour uptake demonstrated normal serum creatinine values (74 and

94 μmol/l, normal <97 μmol/l; the value was 127 μmol/l in the remaining patient).

Conclusion

The majority of RCCs accumulated AC to a lesser or similar extent compared with normal kidney parenchyma. The exceptions were two oncocytomas with very high AC uptake as demonstrated by PET. The observation of Shreve et al. [6] that all RCCs accumulate more AC than normal kidney parenchyma could not be confirmed in this larger series. Therefore, AC PET cannot be recommended for the characterisation of a renal mass.

References

1. Schoder H, Larson SM. Positron emission tomography for prostate, bladder, and renal cancer. Semin Nucl Med 2004;34:274–92.
2. Seltzer MA, Jahan SA, Sparks R, Stout DB, Satyamurthy N, Dahlbom M, et al. Radiation dose estimates in humans for ^{11}C-acetate whole-body PET. J Nucl Med 2004;45:1233–6.
3. Ho CL, Yu SC, Yeung DW. ^{11}C-acetate PET imaging in hepatocellular carcinoma and other liver masses. J Nucl Med 2003;44:213–21.
4. Yeh SH, Liu RS, Wu LC, Yen SH, Chang CW, Chen KY. ^{11}C-acetate clearance in nasopharyngeal carcinoma. Nucl Med Commun 1999;20:131–4.
5. Higashi K, Ueda Y, Matsunari I, Kodama Y, Ikeda R, Miura K, et al. ^{11}C-acetate PET imaging of lung cancer: comparison with ^{18}F-FDG PET and ^{99m}Tc-MIBI SPET. Eur J Nucl Med Mol Imaging 2004;31:13–21.
6. Shreve P, Chiao PC, Humes HD, Schwaiger M, Gross MD. Carbon-11-acetate PET imaging in renal disease. J Nucl Med 1995;36:1595–601.
7. Kotzerke J, Volkmer BG, Neumaier B, Gschwend JE, Hautmann RE, Reske SN. Carbon-11 acetate positron emission tomography can detect local recurrence of prostate cancer. Eur J Nucl Med Mol Imaging 2002;29:1380–4.
8. Thoenes W, Storkel S, Rumpelt HJ. Histopathology and classification of renal cell tumors (adenomas, oncocytomas and carcinomas). The basic cytological and histopathological elements and their use for diagnostics. Pathol Res Pract 1986;181:125–43.
9. Storkel S, Eble JN, Adlakha K, Amin M, Blute ML, Bostwick DG, et al. Classification of renal cell carcinoma: Workgroup No. 1. Union Internationale Contre le Cancer (UICC) and the American Joint Committee on Cancer (AJCC). Cancer 1997;80:987–9.
10. Shriki J, Murthy V, Brown J. Renal oncocytoma on 1-^{11}C acetate positron emission tomography: case report and literature review. Mol Imaging Biol 2006;8:208–11.
11. Blake MA, McKernan M, Setty B, Fischman AJ, Mueller PR. Renal oncocytoma displaying intense activity on ^{18}F-FDG PET. AJR Am J Roentgenol 2006;186:269–70.
12. Bachor R, Kotzerke J, Gottfried HW, Brandle E, Reske SN, Hautmann R. Positron emission tomography in diagnosis of renal cell carcinoma. Urologe A 1996;35:146–50.