

# Positron emission tomography (PET), immuno-PET and radioimmunotherapy in renal cell carcinoma: a developing diagnostic and therapeutic relationship

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## INTRODUCTION

Of primary adult renal tumours, 90% are RCC, with more being diagnosed incidentally using modern imaging methods [1]. However, RCC is often locally advanced and unresectable at diagnosis, with 25–30% of patients having metastatic disease [2]. Such patients are usually not curable and the 5-year survival rates for patients with metastatic RCC are <5%. Clearly, more accurate and reliable methods of diagnosing, staging and treating the disease are needed. The role of positron emission tomography (PET) is still developing in this regard. At present, the primary diagnosis and staging of RCC are conducted with CT and ultrasonography. PET with  $^{18}\text{F}$ -fluorodeoxyglucose ( $^{18}\text{F}$ -FDG) has been useful for re-staging RCC and in cases where conventional studies are inconclusive.

## PET IN ONCOLOGY

PET studies supply unique information on the metabolic activity of a tissue by tagging radioisotopes to natural substances in the body (Table 1) [3]. The most commonly used radionuclide in PET combines the radioisotope fluorine-18 with the D-glucose analogue 2 fluoro-2-deoxy-D-glucose ( $^{18}\text{F}$ -FDG). Tumour imaging with  $^{18}\text{F}$ -FDG is based on the fact that tumours are more metabolically active than their normal surrounding tissues and thus will metabolize more glucose. Tumour cells actively take up and shuttle  $^{18}\text{F}$ -FDG into glycolysis [3]. Once cycling has commenced, glucose is phosphorylated to

$^{18}\text{F}$ -FDG-6-phosphate. This metabolite becomes trapped and cannot proceed along the normal pathway of glucose metabolism. Eventually, increased amounts accumulate within malignant cells. This abnormal concentration of  $^{18}\text{F}$ -FDG in tumour cells produces a detectable signal greater than the background, allowing the isolation of tumour deposits [3]. The signal detected by the PET camera arises from the emission of radiation in the form of  $\gamma$ -photons when a positron collides with an electron within the radioisotope. Quantitative analysis of accumulated radioisotope within different tissues forms the basis of reporting PET studies. A standardized uptake value for normal tissue is established based on radioisotope uptake, and areas of interest within the same tissue are compared to this index for reduced or increased uptake. Tumours typically have a greater standardized uptake value than normal, indicating radioisotope accumulation.

## LIMITATIONS OF $^{18}\text{F}$ -FDG

PET offers an advantage over other methods as no allergy to  $^{18}\text{F}$ -FDG is known and implants are not contraindicated. However, previously there may have been limitations with oncological imaging, including a reduced ability to visualize very small tumours (<0.5 cm), and there may have been difficulty in differentiating between malignancy and chronic inflammation [4]. Fortunately, many of these perceived limitations have been addressed and resolved with the development of combined PET and CT.

## COMBINED PET AND CT

PET is a functional rather than anatomical method; as such, it previously relied on software-based image fusion for the

alignment of functional and anatomical images. Hence data from CT or MRI taken on a different machine at another time to the acquisition of the PET data was used to identify sites of abnormal  $^{18}\text{F}$ -FDG uptake. Image registration could not account for differences in patient positioning, scanner bed profiles and involuntary movement of internal organs. An alternative approach is a scanner acquiring both function and anatomy during one session, i.e. a fusion of technologies rather than a fusion of the images *post hoc* [5]. Commercially available scanners with clinical CT and PET scanners mounted together in a single gantry, known as PET/CT, have overcome image registration problems (Fig. 1). At this stage, non-contrast CT images are taken using helical, multislice protocols, but contrast studies may be used in the future.

## PET IN RCC USING $^{18}\text{F}$ -FDG

$^{18}\text{F}$ -FDG is the most commonly used radioisotope in oncological imaging. Several factors make interpretation of radiotracer activity in the kidney (particularly  $^{18}\text{F}$ -FDG) with PET challenging. First, most radiotracers are excreted through glomeruli but are not reabsorbed by tubules, and so accumulate in the renal collecting system. This may make identifying small parenchymal lesions difficult, even with hydration and diuretics. Furthermore, previous studies of  $^{18}\text{F}$ -FDG at our institution indicate that radiotracer uptake is only moderate in most primary renal tumours, but may vary. The uptake in metastatic disease is far greater [6].

Thus, new PET tracers are being developed to overcome these difficulties (see below). Despite limitations, 14 studies have been published using  $^{18}\text{F}$ -FDG to detect RCC (Table 2) [6,7–20]. The first series (four patients) was published in 1991, whilst the most recent series in 2004 is the largest (66 patients).

**TABLE 1** Commonly used isotopes in PET studies and their half-life

Radioisotope	Half-life
Fluorine-18	110 min
Carbon-11	20 min
Bromine-75	98 min
Oxygen-15	2 min
Nitrogen-13	10 min
Zirconium-89	78 h
Iodine-124	100 h
Yttrium-86	15 h

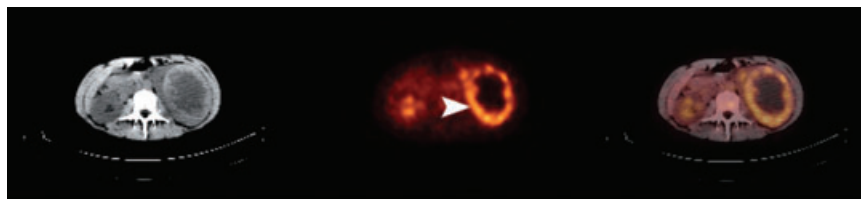
**DIAGNOSIS OF RCC**

The major methods for diagnosing RCC are CT or ultrasonography, with MRI having a specific role in evaluating tumour thrombus extension [21]. The major difficulty with diagnosing lesions with <sup>18</sup>F-FDG-PET is false-negative results due to difficulties with urinary excretion, leading to the variable detection of primary tumours, at 60–90% (Table 2). No imaging method has ideal specificity and ≈10% of lesions thought to be RCC are benign (e.g. oncocytomas) [22]. The role of PET in diagnosing primary renal tumours is likely to remain limited in the near future. However, this may change when PET/CT (Fig. 1) is standard, and cumbersome systems presented in studies, e.g. using dictated PET reports and then analysing imaging studies (e.g. CT) alongside to establish the accuracy of PET, are abandoned [7]. New radiotracers may change the ability of PET to diagnose lesions.

**STAGING**

The identification of lymph-node metastases is still problematic for conventional imaging with CT, as the limiting size is 4 mm and this results in a false-negative rate of 10%, especially in the presence of micrometastases. A higher false-positive rate of 3–43% is mainly due to reactive hyperplasia [22]. Against this, PET staging of RCC has had promising sensitivities of 64–100% with most at ≈100% for metastatic disease (Table 2). This may be explained by urinary excretion and renal accumulation being eliminated as factors from areas of interest. Clinically, for staging, the most important role of imaging is to detect occult lymph node visceral metastases, but bony disease is also important (Fig. 2). Traditionally the realm of nuclear medicine is in bone scintigraphy, but PET can

**FIG. 1.** Axial images of <sup>18</sup>F-FDG-PET/CT in a patient with left RCC (left, CT; centre, thermal PET; right, fused PET/CT). The tumour with increased uptake of <sup>18</sup>F-FDG is indicated (arrow) with uptake confined almost entirely to the periphery, highlighting the necrotic nature of this large tumour.



**TABLE 2** A summary of published reports of <sup>18</sup>F-FDG PET in RCC

Study	Year	Patients, n	Patients (n), sensitivity (% or n/N) and false-negatives (n)		
			Diagnosis	Staging	Re-staging
Kang <i>et al.</i> [7]	2004	66	17, 60, 6	54, 75, 32	–
Majhail <i>et al.</i> [8]	2003	24	–	24, 64, 9	–
Jadvar <i>et al.</i> [9]	2003	25	–	25, 71, 6	–
Chang <i>et al.</i> [10]	2003	15	–	–	15, 90, 1
Miyakita <i>et al.</i> [11]	2002	19	19, 32, 13	–	–
Brouwers <i>et al.</i> [12]	2002	20	–	–	20, 69, NA
Safaei <i>et al.</i> [13]	2002	36	–	–	36, 87, 4
Montravers <i>et al.</i> [14]	2000	20	13, 85, 1	–	7, 100, –
Ramdave <i>et al.</i> [6]	1998	22	17, 94, 1	8, 8/8, 0	–
Goldberg <i>et al.</i> [15]	1997	10	9, 9/10, 1	2, 2/2, 0	–
Hoh <i>et al.</i> [16]	1996	21	–	–	21, 100, 0
Bachor <i>et al.</i> [17]	1996	26	26, 77, 6	3, 3/3, 0	–
Bachor <i>et al.</i> [18]	1995	9	9, 8/9, 1	–	–
Kocher <i>et al.</i> [19]	1994	10	10, 4/10, 6	10, 10/10	–
Wahl <i>et al.</i> [20]	1991	4	4, 4/4, 4	4, 4/4, 4	–

be used to accurately define bony metastatic deposits, and may in the future replace traditional bone scintigraphy, although further studies are required [23].

**RE-STAGING**

PET has been shown to be accurate in detecting recurrent RCC, with sensitivities of 87–100% reported in studies of almost 100 patients (Fig. 3). Thus, <sup>18</sup>F-FDG-PET is highly sensitive and accurate for detecting local disease spread and metastatic disease in patients with RCC. Importantly, in one study it was highlighted that the PET study altered the management of 40% of the patients [6]. Ultimately, that is the real benefit to patients, especially in cases where other forms of anatomical imaging such as CT are inconclusive because they lack the ability to delineate the functional capacity of tissues in most instances.

**MOLECULAR IMAGING OF RCC WITH PET**

**RADIOLABELLED NITROIMIDAZOLES**

Hypoxia within tumours is an important factor because it confers resistance to radiation and chemotherapy. Tumours require oxygen and their major supply is via blood vessels derived from the host. At a critical size tumour oxygen consumption will outstrip supply, leading to tumour death [24]. However, even in the presence of a blood supply a tumour can remain hypoxic due to the distance from blood vessels and poor quality of blood vessels created [24].

No techniques to evaluate intratumoral hypoxia have entered widespread use, and hypoxia cannot be predicted by tumour size, grade or histology. The critical tumour oxygen partial pressure is proposed to be 8–10 mmHg [25]. Below this level there is ATP depletion,

intracellular acidosis and decreased energy supply. Normal tissues typically have median oxygen concentrations of 40–60 mmHg, whilst half of solid tumours studied have median values of <10 mmHg. Inter-tumour variability in the oxygenation pattern is more pronounced than the intra-tumour heterogeneity [26].

Recently, radiolabelled nitroimidazoles (e.g.  $^{18}\text{F}$ -fluoromisonidazole,  $^{18}\text{F}$ -FMISO) have emerged as noninvasive techniques for assessing tumour hypoxia. Nitroimidazoles (e.g. metronidazole) are effective against organisms thriving in hypoxic environments; they are metabolized by intracellular nitroreductases, and at low oxygen levels serve as competing electron acceptors. They are reduced and form covalent bonds with macromolecules, thus becoming biochemically trapped within these hypoxic yet metabolically active cells [27]. Such drugs bind to cells at a rate that is maximal under conditions of severe hypoxia and is inhibited at increasing oxygen concentrations. Variation in radiotracer uptake between individuals is to be expected in tissues. In particular, the sensitivity of nitroimidazole (e.g.  $^{18}\text{F}$ -FMISO) imaging for detecting hypoxic tissue will be determined by several factors, including delivery, retention and metabolism of the nitroreductase [28].

Because RCC is resistant to radiation and chemotherapy, it behaves like a tumour that contains hypoxic cell populations. This has been confirmed in a recent study at our institution, with hypoxia of  $\approx 10$  mmHg in RCC measured by polarographic oxygen sensors [29]. In an attempt to gauge the level of hypoxia noninvasively and explore  $^{18}\text{F}$ -FMISO PET as a potential tool for investigating RCC, 11 patients with confirmed RCC were assessed [29]. However, only seven of 11 tumours had mildly increased  $^{18}\text{F}$ -FMISO uptake (Fig. 4). The identification of hypoxia in RCC and its impact on tumour biology and prognosis is an area of ongoing research.

#### RADIOISOTOPES BASED ON ACETATE

Acetate is converted to acetyl-coenzyme A in the mitochondria, followed by rapid clearance as carbon dioxide through the citric acid cycle.  $^{11}\text{C}$ -Acetate can be used to detect areas of high metabolism and blood flow, such as are found in normal renal parenchyma. Increased uptake in renal malignancies with no significant excretion into the urinary tract

was reported, but further studies are needed to delineate its role in RCC [30].

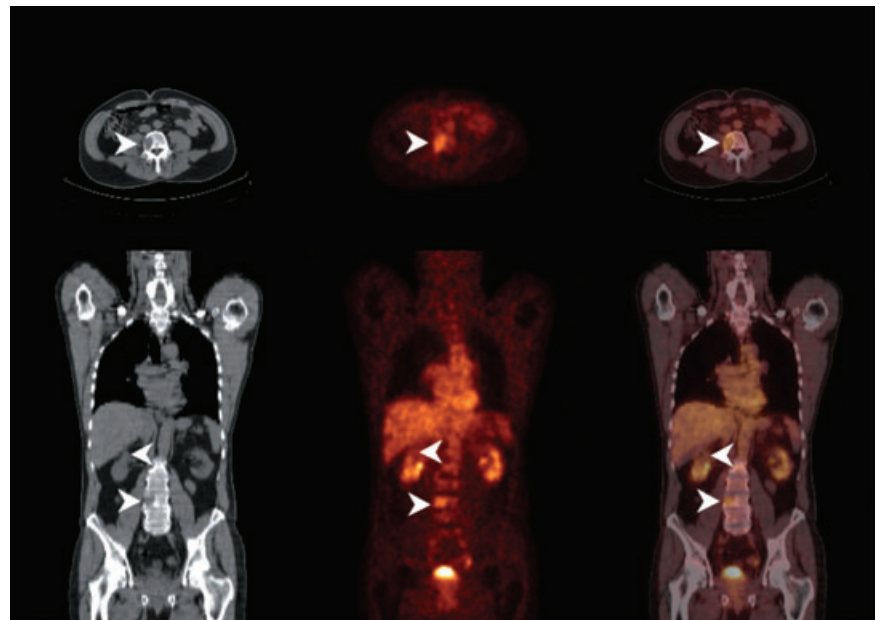


FIG. 2.  $^{18}\text{F}$ -FDG-PET/CT (left, CT; centre, thermal PET; right, fused PET/CT) of a patient with metastatic RCC. The metastatic deposit in L4 is easily delineated on the axial images above and the coronal images below (arrows). Additional arrows on the coronal images indicate the 3-cm right upper pole renal tumour, highlighting the lower uptake of  $^{18}\text{F}$ -FDG in the primary tumour than in metastatic disease in RCC.

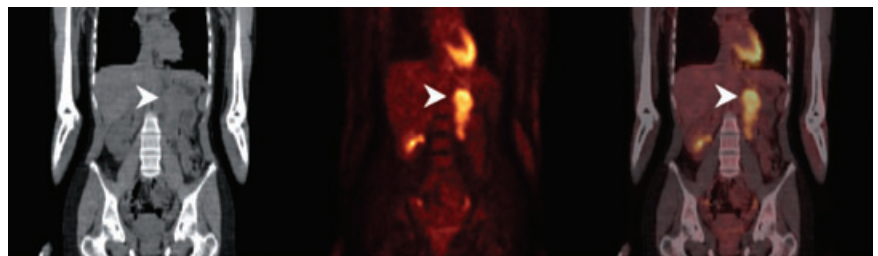
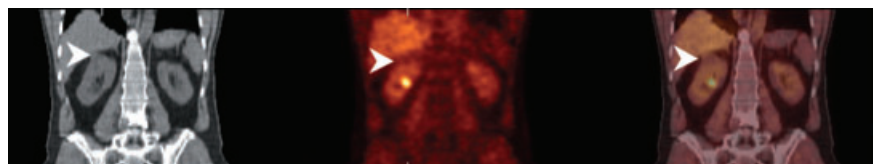


FIG. 3.  $^{18}\text{F}$ -FDG-PET/CT of a patient 1 year after left radical nephrectomy for RCC, after a mass was detected in the renal bed on CT (left, CT; centre, thermal PET; right, fused PET/CT). To help delineate if it was fibrosis or tumour, PET/CT was used for re-staging and showed dramatically greater uptake of  $^{18}\text{F}$ -FDG in the mass (arrow), indicating recurrence.



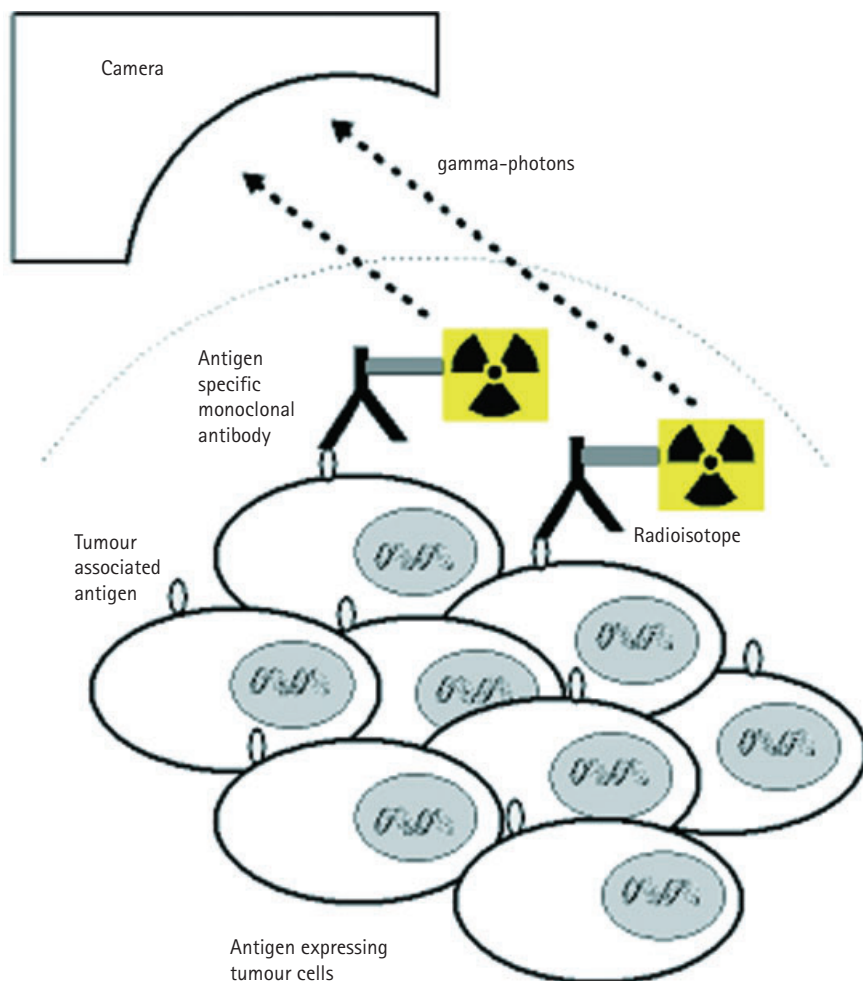
was reported, but further studies are needed to delineate its role in RCC [30].

#### RADIOISOTOPES BASED ON CHOLINE

Choline is a precursor for phospholipid synthesis and has been investigated as a

tracer in several tumours [4]. Choline is necessary for phospholipid synthesis in cell membranes, cholinergic neurotransmission, methyl metabolism, transmembrane signalling, as well as lipid cholesterol transport and metabolism [4]. Phosphorylcholine has been found at

FIG. 5. Diagram of radioimmunotherapy.



high levels in most cancers and at low or undetectable levels in normal tissues, using MRI studies [31]. In tumour cells, choline metabolism is directed toward cell membrane synthesis, and the *de novo* synthesis of choline is negligible in tumour cells [4].

Radioisotopes used for labelling choline are carbon ( $^{11}\text{C}$ -choline) or fluorine ( $^{18}\text{F}$ -fluoroethylcholine and  $^{18}\text{F}$ -fluoromethylcholine). One disadvantage of fluorine-based radioisotopes is their prompt urinary excretion, requiring bladder irrigation or early scanning. Alternatively,  $^{11}\text{C}$ -choline has less urinary excretion, resulting in a better target to background ratio. It has been used for detecting a variety of tumours, with prostate cancer also visualized [32]. Studies of RCC are lacking and normal uptake in renal tissue will need to be

overcome, but would be aided by reduced renal excretion.

#### OTHER RADIOTRACERS

Tumour tissues that have high proliferation rates require high rates of DNA synthesis, and tracers such as those based on the nucleic acid thymidine have been developed. The advantages of a proliferative marker over  $^{18}\text{F}$ -FDG is that a proliferation marker (e.g.  $^{18}\text{F}$ -fluorothymidine) may give better specificity in assessing tumours or better accuracy in evaluating early response, because proliferation is more sensitive than glucose use [33].

A radiotracer that reflects DNA synthesis is radiolabelled thymidine (TdR), and has been used to track cell proliferation both *in vitro* and *in vivo*. Rapid metabolism by thymidine

phosphorylase makes TdR a cumbersome molecule to analyse, as large numbers of molecules resulting from breakdown require analysis, but current PET software can be used for this task [34]. No trials using radiolabelled fluorothymidine for RCC have been conducted in humans, so we are currently investigating patients at our institution, using this tracer.

Radiotracers based on methionine provide a similar measure of proliferation to those based on glucose, but instead reflect amino-acid metabolism; no studies with RCC have been published.

#### RADIOIMMUNOSCINTIGRAPHY (IMMUNO-PET) AND RCC

Radioimmunoscintigraphy using positron emitters (immuno-PET) for tumour visualization has developed because antibodies can now be linked with positron emitters. Monoclonal antibodies (mAbs) have been labelled with  $^{111}\text{In}$  or  $^{99\text{m}}\text{Tc}$  as radioisotopic imaging agents in prostate, colorectal and ovarian carcinoma [35]. Immuno-PET involves radiolabelled mAb bound to an antigen on tumour cells, and the radionuclide then emits radiation ( $\gamma$ -photons) that is detected by a camera mounted within a PET scanner (Fig. 5). The half-life of common PET tracers ( $^{11}\text{C}$ ,  $^{18}\text{F}$ ) is too short for use with antibodies *in vivo*. Positron emitters ( $^{89}\text{Zr}$ ,  $^{124}\text{I}$  and  $^{86}\text{Y}$ ) with longer half-lives are better suited to the slow pharmacokinetics of radiolabelled mAbs (Table 1). The optimum uptake of such antibody conjugates in tumours is normally several days for intact immunoglobulins [36].

One mAb of interest in RCC is G250 [37]; this antigen (or carbonic anhydrase IX, known as CA IX) is a membrane-associated carbonic anhydrase thought to play a role in regulating cell proliferation in response to hypoxic conditions, and may be involved in oncogenesis and tumour progression. G250 refers to a mAb that was raised by immunisation of mice with human RCC homogenates [38]. Previous immunobiochemical studies revealed that G250 is highly expressed in RCC, with selective uptake of mAb G250 in antigen-positive cells over antigen-negative cells (Fig. 6) [38]. G250 has been labelled with  $^{89}\text{Zr}$  and  $^{124}\text{I}$  for immuno-PET, with promising results [36].

Previous studies using a murine and chimeric G250 mAb showed high uptake in RCC, but minimal uptake in most normal tissues. There have been trials aimed at G250 mAb therapy in patients with metastatic RCC, through immune effector function and radioimmunotherapy (discussed below). Newer agents such as  $^{99m}\text{Tc}$ -G250, as well as targeting of other tumour antigens, is progressing, with immuno-PET likely to have a greater role in the monitoring of radioimmunotherapy for dosage and response to treatment [39].

### RADIOIMMUNOTHERAPY

Radioimmunotherapy is an extension of immuno-PET. Broadly, it involves delivering radiation to the target cells by linking the radionuclide (e.g.  $^{131}\text{I}$ ) to a mAb that targets a specific antigen expressed by tumour cells. However, it is different to immuno-PET, as a different radiation ( $\beta$ -particles) is responsible for destroying cellular DNA, rather than providing the images obtained in PET, by detecting  $\gamma$ -photons. Thus, it is possible to have radioisotopes that only emit  $\beta$ -particles, such as  $^{90}\text{Y}$ , that are not suitable for imaging with PET. However, a radioisotope such as  $^{131}\text{I}$  emits both  $\gamma$ -photons and  $\beta$ -particles, making it suitable for imaging and treatment [36].

Therapeutic studies have focused on the use of radiolabelled mAbs with radionuclides including  $^{131}\text{I}$ ,  $^{111}\text{In}$  or  $^{99m}\text{Tc}$  [35]. Early therapeutic studies were in patients with lymphoma expressing multiple tumour antigens, and more specialized agents such as those targeting with anti-CD80 mAb (galiximab) are now available [40].

Targeting of RCC by G250 has been amongst the highest reported in solid tumours and radioimmunotherapy has seemed promising with this agent. A study of 15 patients with metastatic RCC was undertaken with radiolabelled  $^{131}\text{I}$ -G250 [41]. Although only modest, the results were promising in predicting who might respond to treatment with fractionated radiolabelled G250, but this study was also done before the use of PET/CT, and thus the localization of tumour deposits was not ideal.

### SUMMARY

The status of PET is developing (Table 3); certainly,  $^{18}\text{F}$ -FDG-PET has a role in staging

FIG. 6. An example of radioimmunosintigraphy (A) using the radiolabelled monoclonal antibody G250 in a patient with metastatic RCC. The arrows highlight uptake of the radioisotope in the extensive locally advanced disease, as seen on CT (B).

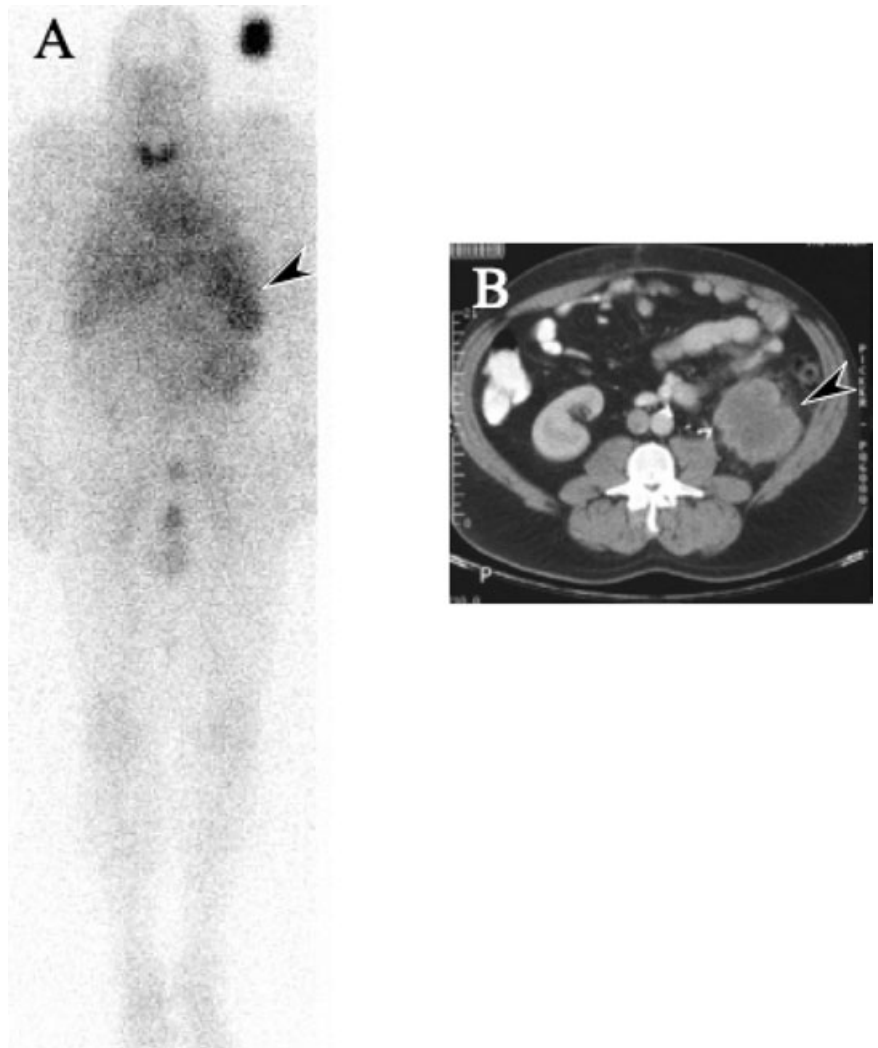


TABLE 3 Summary of current PET applications in RCC

PET method	Stage of disease	Current status
$^{18}\text{F}$ -FDG	Diagnosis	Not useful
	Staging and re-staging	Extremely useful for visceral, lymph node and bony disease
Other radiotracers	Diagnosis, staging and re-staging	Experimental only. More clinical data needed.
e.g. $^{18}\text{F}$ -FMISO, $^{11}\text{C}$ -choline		
Radioimmunosintigraphy (Immuno-PET)	Diagnosis, staging and re-staging	Promising but further human studies needed
Radioimmunotherapy	Treatment	Promising but clinical phase III trials needed

and re-staging disease, whilst other radiotracers need further clinical data. The use of PET/CT may alter the ability to detect pelvic and other small metastatic deposits, improving the sensitivity of staging and re-staging. Immuno-PET is advancing rapidly and an array of mAbs against various tumour antigens will lead to further imaging capabilities. It will also have an increasing role in the monitoring of radioimmunotherapy for dosage and response to treatment. Finally, radioimmunotherapy is being studied, and once toxicity and doses are adjusted correctly, this may be the key to treating RCC in the future.

#### CONFLICT OF INTEREST

None declared.

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**Abbreviations:** PET, positron emission tomography; <sup>18</sup>F-FDG, Fluorine-18-deoxyglucose; <sup>18</sup>F-FMISO, <sup>18</sup>F-fluoromisonidazole; TdR, radiolabelled thymidine; mAb, monoclonal antibody.