^{18}F-FDG-PET/CT in Potentially Advanced Renal Cell Carcinoma: A Role in Treatment Decisions and Prognosis Estimation

JIRI FERDA[1], EVA FERDOVA[1], MILAN HORA[2], ONDREJ HES[3], JINDRICH FINEK[4], ONDREJ TOPOLCAN[5] and BORIS KREUZBERG[1]

[1]Clinic of Imaging Methods, [2]Urological Clinic, [3]Sikl's Institute of Pathological Anatomy, [4]Department of Oncology and Radiotherapy, [5]Department of Nuclear Medicine – Radioisotope Laboratory, Charles University Teaching Hospital Plzen, Plzen, Czech Republic

Abstract. *Aim: to assess the influence of positron emission tomography/computed tomography with ^{18}F-fluorodeoxyglucose (^{18}F-FDG-PET/CT) on the treatment decision in renal cell carcinoma and to assess the prognostic value of the ^{18}F-FDG accumulation assessments. Patients and Methods: Data from 60 patients were included. The cohort consisted of 43 males, 17 females, mean age 66.2 years (range=49-86 years). All patients underwent ^{18}F-FDG-PET/CT including two-phase CT-angiography of the kidneys. Locally advanced or generalized renal cell carcinoma was suspected in all patients. The level of the ^{18}F-FDG accumulation within the tumor was compared with the histological grading and the development of the disease was assessed 12 months after ^{18}F-FDG-PET/CT. Results: Overall mortality reached 46.7%, the highest ^{18}F-FDG accumulation showed tumor of grade 4 (mean SUV_{max}=10.7, range=5-23), the highest mortality was found for tumors exceeding SUV_{max} value of 10 (mortality 62.5%). New information was brought by ^{18}F-FDG-PET/CT in 85% of cases. Conclusion: ^{18}F-FDG-PET/CT has the potential to estimate the patient´s survival according to the ^{18}F-FDG accumulation measured in SUV_{max}. Depiction of occult metastatic disease has an emerging role in decision making regarding surgery.*

Renal carcinoma is a malignancy with increasing incidence in the Western population mainly due to incidental findings. Renal carcinoma is a tumor that has a relatively high rate of therapeutic success if treated sufficiently early at a time without metastatic dissemination (1). Surgical removal of the tumorous tissue, performed either in open surgery or with laparoscopy, represents the causal treatment. If the tumor is still of a small size, surgical resection is preferred instead of nephrectomy as such so-called nephron-sparing surgery preserves a healthy, functional kidney parenchyma. In pre-surgical imaging of smaller tumors it is sufficient to perform computed-tomography (CT) in the two phases including CT angiography or magnetic resonance imaging (MRI) including magnetic resonance angiography (MRA) (2, 3). However, for tumors of a larger size, or tumors in which infiltration of vascular structures and surrounding tissues is suspected, we are at the very limit of the technical feasibility of a surgical solution. In such cases, an exact assessment of the extent of distant or lymphatic metastases can be crucial for the decision regarding conservative or surgical treatment. If the tumor is invading into the vena cava, it affects both the resectability and the extent of tumor thrombosis in the retroperitoneal veins and in the lower vena cava.

The essential benefit of planning a surgical solution with two-phase CT angiography has already been proven by a number of articles in 16-row and higher systems (2, 3). The significance of positron emission tomography/computed tomography with ^{18}F-fluorodeoxyglucose (^{18}F-FDG-PET/CT) with an integrated visualization of CT angiography (CTA) has not yet been assessed. The significance of ^{18}F-FDG-PET/CT-alone has been assessed mainly from the perspective of disease prognosis. The view of ^{18}F-FDG-PET/CT as an unreliable method for renal carcinoma visualization has been countered by recent studies using hybrid systems (4, 5). Currently a multi-detector sub system CT (MDCT) is an obvious part of hybrid equipment for PET/CT. The aim of the present study was to assess the contribution of ^{18}F-FDG-PET/CT to decisions on therapy, as well as to the assessment of disease prognosis.

Correspondence to: Jiri Ferda, MD, Ph.D., Clinic of Imaging Methods, Charles University Teaching Hospital in Plzen, Alej Svobody 80, 304 60 Plzen, Czech Republic. Tel: +42 0377103436, Fax: +42 0377103438, e-mail: ferda@fnplzen.cz

Key Words: Renal cell carcinoma, ^{18}F-FDG-PET/CT, hybrid imaging, prognosis, SUV_{max}.

Patients and Methods

Within a period of five years a total of 60 examinations were performed using ^{18}F-FDG-PET/CT in patients with a tumor of the kidney that was suspected to be an advanced renal carcinoma. These patients were 43 men and 17 women with an average age of 66.2 years (between 49 and 86 years of age) and either a conservative approach to therapy or radical surgery were considered. A retrospective analysis of prospectively obtained data was performed, with regard to the option of therapeutic strategy and the further fate of the patients. The patients were monitored for at least 12 months from the decision as to the kind of therapy. Mortality was monitored over the whole group, in subgroups of surgically treated patients and patients treated conservatively. An analysis of the relationship of the maximum ^{18}F-FDG accumulation with mortality was performed, as well as the relationship between the level of ^{18}F-FDG accumulation and histological grading of tumors. Histological examinations were performed by a specialist in urogenital histopathological diagnostics. ^{18}F-FDG was administered via the ante-cubital vein to the patients after prior checking of glycaemia at an activity dose of 4 MBq/kg. During the 60 minutes accumulation of the radiopharmaceutical while resting in bed, there was oral preparation through drinking of a 1000 ml 2.5% aqueous solution. of mannitol The accumulation and per oral preparation were followed by data acquisition, first with MDCT and then PET. The examinations were performed on a PET/CT set with a sixteen-row MDCT system (Biograph 16, Siemens, Erlangen, Germany). The MDCT part of the examination was performed with 16×0.75 mm collimation, with a pitch factor of 1.5 and with exposure values of 120 kV and 240 effective mAs. One hundred milliliters of iodinated contrast agent was administered intravenously (iomeprol at 350 mgI/ml; Bracco, Milano, Italy) at a flow rate of 3 ml/s with washing of 50 ml of physiological solution through a double barrel power injector (Stellant; Medrad, Millwaukee, MI, USA). The examinations were performed both in arterial and venous phases. The arterial phase of the examination was performed 20 seconds after administration of the contrast agent, in the span from the skull base to the proximal third of the thighs. The venous phase continued in the caudal cranial direction after a 5 second pause, within a span from the proximal third of the thighs to the level of diaphragmatic dome. The data were reconstructed in a field of view of 700 mm, with a layer thickness of 5 mm for the attenuation correction of the PET image, and diagnostic CT images in a field of view of 450 mm, with a layer thickness of 5 mm and 1 mm with a reconstruction algorithm for soft tissues and with a layer thickness of 1 mm with the algorithm for high resolution CT. Reconstruction of thin layers with a reconstruction increment of 0.7 mm was performed for the assessment of MDCT sub-millimeter isotopic space resolution (a cubic voxel of 0.7 mm edge). The subsequent PET data acquisition was distributed over seven positions (beds), the acquisition for each of one position lasted 3 minutes. Spatial resolution of PET reached 5 mm. Both the images with attenuation correction and the uncorrected images were reconstructed online.

For the examination assessment itself, corrected and uncorrected PET images were used, together with CT examination in arterial and venous phases, HRCT of the lungs and PET/MDCT fusion. Metabolic activity in renal tumors was assessed through the highest measured standardized uptake value (SUV_{ma}) in the area of the tumor. According to the SUV_{max}, the grade of glycolytic tumor activity was allocated into four categories: low (SUV_{max}<3) (Figure 1), increased level of activity (SUV_{max} between 3 and 5) (Figure 2), high level of activity (SUV_{max} between 5 and 10) (Figure 3) and finally extreme level of glycolysis (SUV_{max} exceeded 10) (Figure 4). The presence of metabolically active metastases was assessed in the lymphatic nodes, liver, adrenal glands, skeleton and lungs.

Apart from the metabolic activity and general morphological changes, the vascular system was also evaluated with a focus on blood supply to the kidneys, as well as pathophysiological blood vessel changes connected with the tumor, by the use multiplanar reconstructions (MPR) and layer reconstructions with the aid of maximum intensity projection (MIP). The presence of arterio-venous malformation was evaluated, as well as the presence of tumor hypervascularization of a nodular or diffuse character and the presence of tumor invasion into the renal vein or vena cava.

Results

Histological diagnosis of renal carcinoma in the group was confirmed in a total of 47 patients (78.3%). Ten patients with a large tumor and advanced disease underwent no further biopsy, and their tumors were not classified histologically. Out of the total of 60 patients, the size of the tumor was assessed as T1 only in two (3.3%). Metastatic spread was present in 32 patients (53.3%). Total mortality in the group of 40 patients was 46.7% (28/60) during the course of the 12 months following the PET/CT (Table I and II).

On the basis of ^{18}F-FDG-PET/CT a total of 25 patients (41.6%) were designated for radical surgery. Out of these in the later course of the disease 4 patients died (16%) within one year after surgery, and these were all patients with a metastatic dissemination, demonstrated with ^{18}F-FDG-PET/CT and a high level of ^{18}F-FDG accumulation. Surgery was performed on a total of seven patients with metastatic spread, of whom only three patients survived more than 12 months, which means that mortality in the group of surgically treated generalized patients was 57%. Of the patients-treated conservatively, 19 (including nine treated with sunitinib) out of the 35 patients died (mortality in the subgroup was 54.3%).

There is an interesting result in the value analysis of accumulation of radiopharmaceutical through SUV_{max}. With the level of accumulation divided into four groups A (0 to 3 SUV_{max}), B (3 to 5 SUV_{max}), C (5 to 10 SUV_{max}) and D (more than 10 SUV_{max}), the mortality was as follows: 20.0% (2/10) in group A, 33.3% (4/12) in group B, 36.8% (7/19) in group C and 62.5% (10/16) in group D. It was, therefore, established that a value of SUV_{max} above 10 is a significant predictor of death.

The contribution of ^{18}F-FDG-PET/CT itself in the group of monitored patients can also be summarized with new information that was obtained during the examination. New information was obtained in 51 patients (85.0%). The most significant piece of information was the demonstration of tumor spread outside the area where routine pre-operative CT is performed – this concerned metastases in 26 patients

Table I. *Patients sample description, treatment and 12 months mortality.*

	No.	%
Patients	60	100.0
Histology proven	47	78.3
Surgery	25	41.7
Conservative treatment	35	58.3
Deaths overal	23	38.3
Deaths in surgically-treated	4	6.7
Deaths in conservative-treated	19	31.7

Table II. *^{18}F-FDG SUV$_{max}$ and twelve months mortality.*

	0 to 3	3 to 5	5 to 10	>10
No.	10	12	19	16
Died, n	2	4	7	10
Mortality, %	20.0	33.3	36.8	62.5

(43.3%). On the other hand, the exclusion of dissemination in locally large tumors in 18 patients (30.0%) led to radical surgery in these patients. In two cases, a double tumor was discovered (one lung carcinoma, one colorectal carcinoma and one gastric carcinoma). In both patients the second malignancy was resected in time and none of them died within the monitoring period of 12 months after the removal of renal carcinoma.

In seven cases tumorous invasion into the inferior vena cava was demonstrated with PET/CT, in two cases even above the level of the diaphragm. In all cases the tumor tissue invading into the inferior vena cava was depicted as hypermetabolic tissue, in three cases even where the renal tumor itself had only an accumulation comparable with the rest of the parenchyma.

Discussion

The prognosis for patients with renal carcinoma where metastases are already present at the time of diagnosis is unfavorable. The median survival time given is between 10 and 21 months (1). Since in newly-diagnosed renal carcinomas up to one third of patients have distant metastases, the distinction between patients with the and without metastases makes a significant contribution to reaching a prognosis. Although dissemination of renal carcinoma has been known to occur even at an interval of several years after the radical surgical removal of the primary tumor, the claim that distant metastases occur in one to two fifths of patients after surgery might be distorted by the fact that metastases are not diagnosed in an early stage of the disease (1, 2). The evaluation in our group of patients shows that in more than half of the patients suspected as having T3 size tumor, metastases were present, and moreover, that in one-third of patients they were located outside the region from the level of diaphragm to the inguinal area. This fact shows that in studies evaluating *de novo* tumor dissemination after surgery, some of the metastases have been already present at the time of diagnosis but were not detected (6).

Glycolytic activity of renal carcinoma tumor tissue itself may be variable. Older studies pointed out that ^{18}F-FDG-PET is not a suitable method for detecting renal carcinoma. The reasons given were superposition of radioactive urine in the renal pelvis and also the variable level of energy metabolism in the tumor tissue (4). Current opinion on the role of ^{18}F-FDG-PET/CT in patients with renal carcinoma suggests the reliability of the method in the assessment of metastases in the retroperitoneal nodes and adrenal glands (7), or during detection of local recurrence (8). The latest studies also comment on assessment of the prognostic potential of ^{18}F-FDG-PET/CT (9), as well as on the possibility of using PET/CT in assessing the effect of biological therapy (10-13). Our own results indicate that a hybrid image with fully-fledged CT examination considerably improves the possibility of detecting tumors in the kidneys. ^{18}F-FDG-PET/CT then makes it possible to fully-use all the advantages of a phased post-contrast image with the assistance of MDCT, including excellent imaging of the vascular system (3).

Present-day studies dealing with the imaging of renal carcinoma through PET/CT often mention the use of alternative radiopharmaceuticals, such as ^{11}C-acetate (14, 15), ^{18}F-fluoro-ethylcholine (16), as ^{18}F-fluoro-thymidine (17). The use of these pharmaceuticals is explained by prognostic reasons for the prescription of molecular-targeted therapy, such as tyrosine kinase inhibitors – sunitinib and sorafenib or mammalian target of rapamycine inhibitors. It, therefore, represents a type of usage that is targeted at predicting the effect and the assessment of an early response to the therapy. Apart from the proliferative activity, the level of which can be monitored with DNA synthesis markers (^{18}F-fluoro-thymidine), or building of phospholipid dual membranes (^{18}F-fluoro-ethylcholine), tissue hypoxia is also assessed before and after treatment with ^{18}F-fluoro-misonidasol (11, 18). The behavior of ^{18}F-FDG in these indications has not yet been sufficiently and unambiguously explained, but the level of energy metabolism can also reflect the response to the molecular-targeted therapy (10). ^{18}F-FDG-PET/CT, on the other hand, as our report shows, may already contribute to the assessment of tumor grading before histological diagnosis is established. Our findings, showing that tumors of grade IV have the highest level of accumulation, can be used in the assessment of the disease, since these are the most aggressive

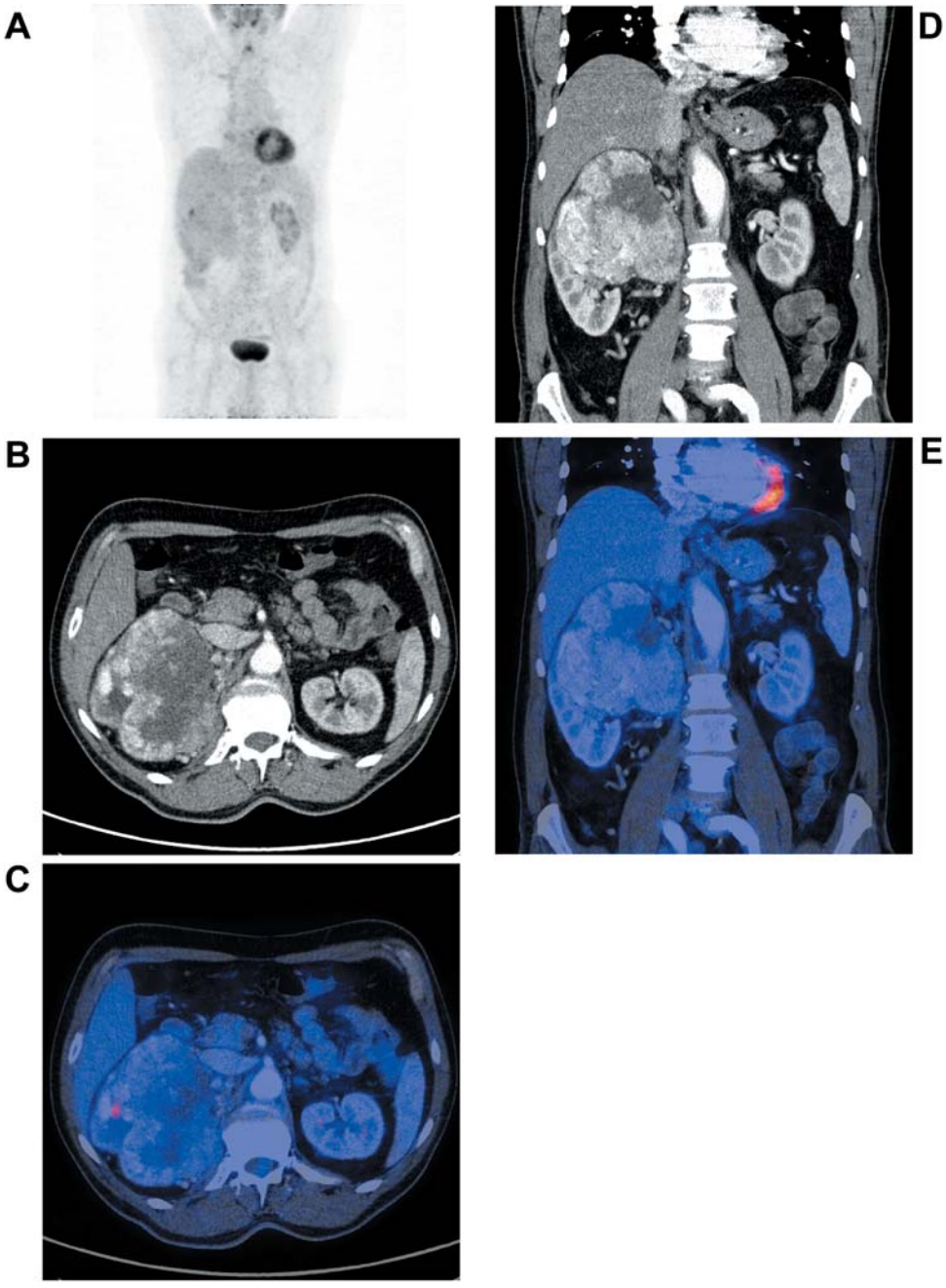

Figure 1. *patient surviving more than 24 months after nephrectomy, conventional renal cell carcinoma well differentiated with low level accumulation of FDG. A – whole body MIP PET; B, D – CT images, C, E – PET/CT fusions – levels of displayed* SUV_{max} *0-10.*

tumors with an early and late massive formation of metastases (9). In this group, sarcomatoid carcinoma, a highly non-differentiated type of tumor, represents a considerable proportion of the diagnoses. However, since it is impossible for some tumors to specify their type histologically because of the lack of surgery in some patients and biopsy in other patients, owing to the advanced stage of the disease, there is a possibility of using the level of glycolytic activity of the tumor tissue as a prognostic factor for further development of the disease (9). Our results, comparing mortality depending on the level of accumulation, showed that the highest mortality occurs in patients with ^{18}F-FDG accumulation exceeding a SUV_{max} of 10. This finding is in agreement with the conclusions of Namura et al´s study (9). They showed a

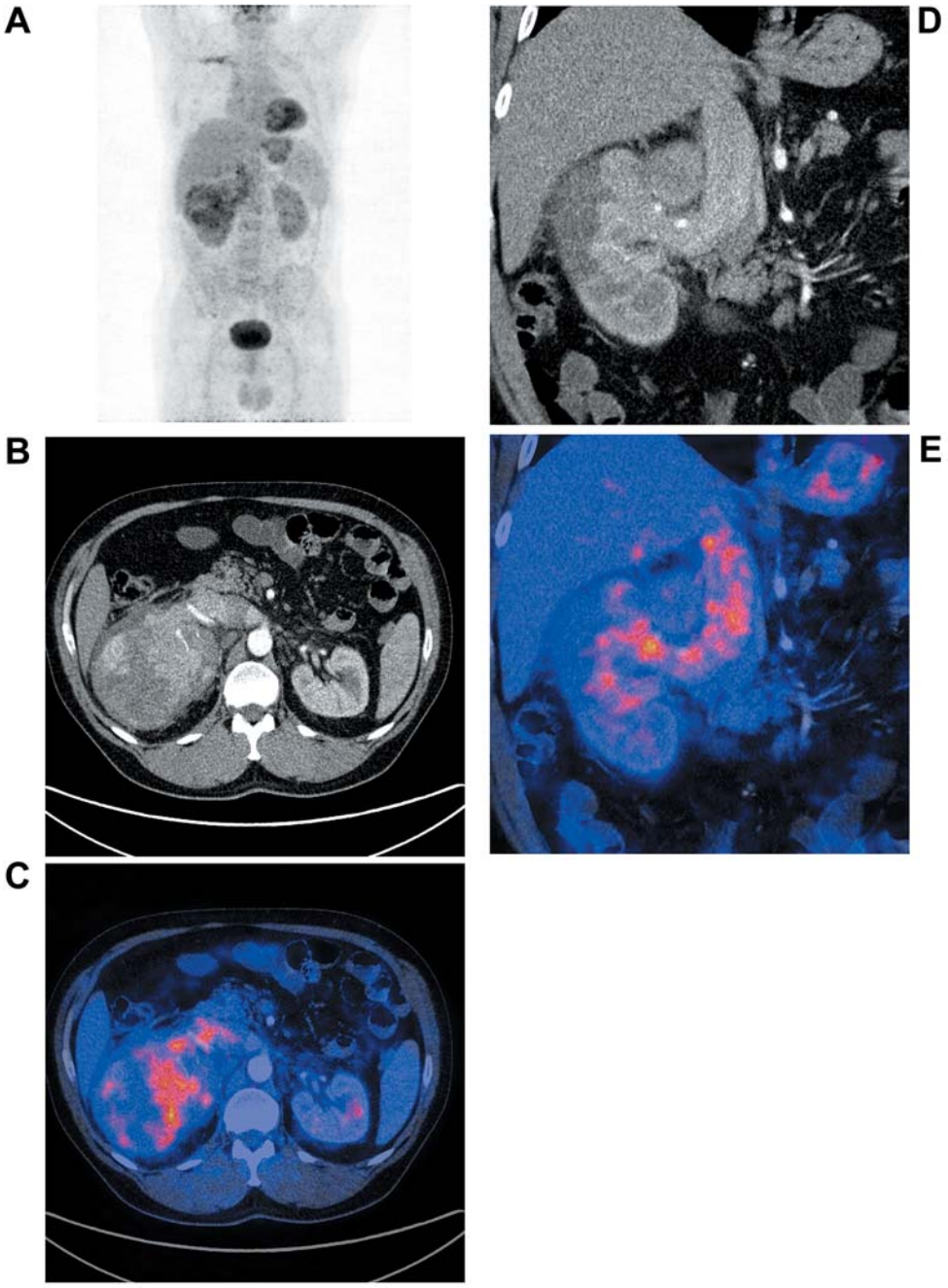

Figure 2. *patient surviving more than 48 months after nephrectomy and removal of the tumorous thrombus from the inferior vena cava, conventional renal cell carcinoma well differentiated with relative low level accumulation of FDG. A – whole body MIP PET; B, D – CT images, C, E – PET/CT fusions – levels of displayed* SUV_{max} *0-10.*

considerably worse prognosis in patients with tumors where ^{18}F-FDG accumulation exceeded values of 8.2. In comparison with this quoted article, however, we evaluated a different population in our group, namely those patients who were suspected of having a locally advanced tumor, and for whom surgery was considered.

There is a very significant surgical problem which limits the possibility of nephrectomy or resection. This is the presence of tumor thrombosis in the renal vein or in the inferior vena cava. Both in CT and in MRI we often encounter the problem of obtaining a correct image of the extent of the tumor thrombosis and the clotted blood in

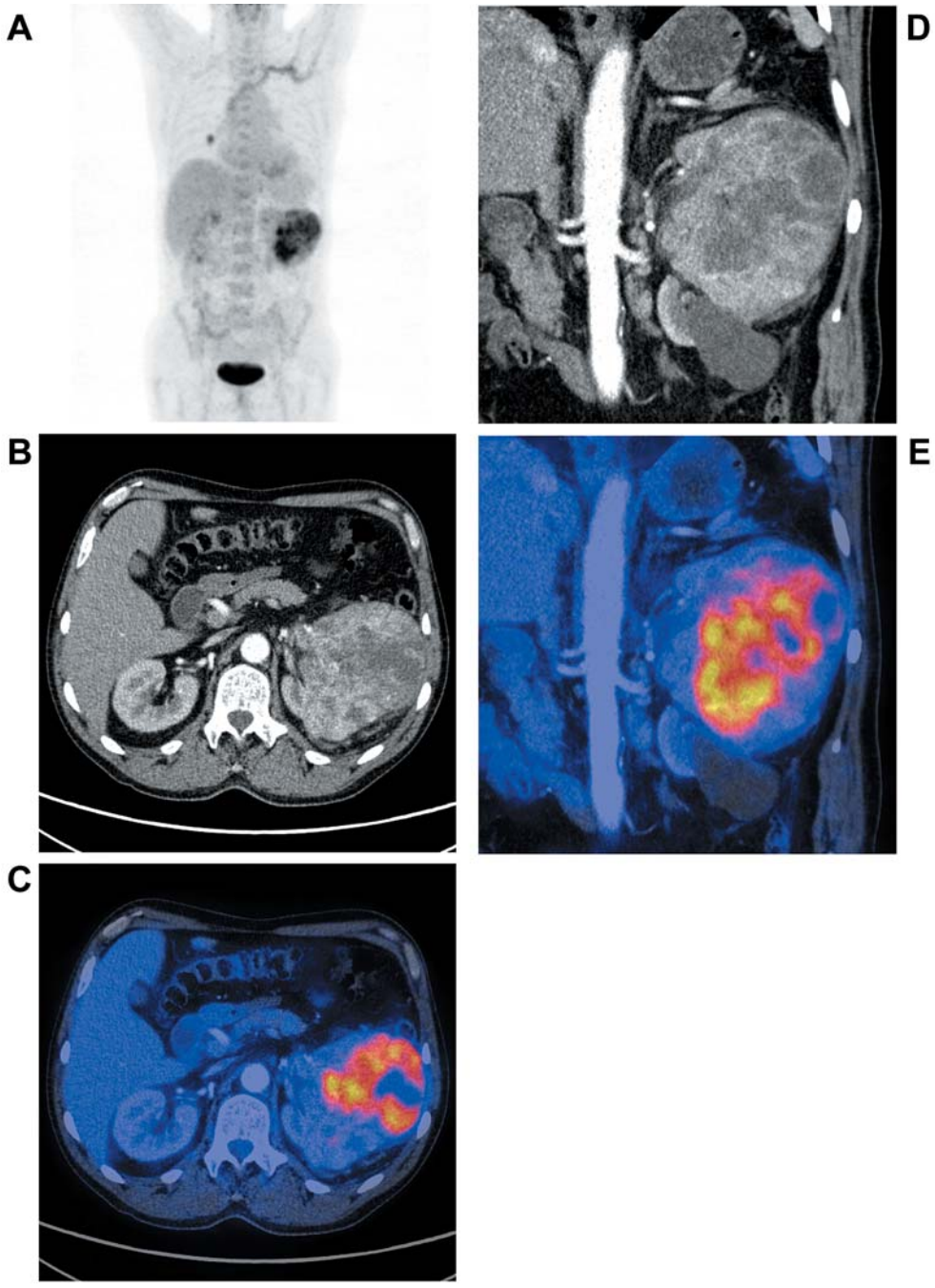

Figure 3. *patient surviving more than 24 months after nephrectomy, after 12 months progresiion of hematogenous metastases, currently surviving under sunitinib therapy, conventional renal cell carcinoma poorly differentiated with increased level accumulation of FDG not exceeding SUV_{max} 10. A – whole body MIP PET; B, D – CT images, C, E – PET/CT fusions – levels of displayed SUV_{max} 0-10.*

addition, since individual parts of the thrombosis have a different saturation or signal in different phases of adding the contrast agent (19). Hypermetabolism of the tumorous thrombus was documented in our group even in such cases where the tumor did not itself show a prominent increase in the level of glycolysis. High ^{18}F-FDG accumulation may, therefore, represent an extremely essential factor, which facilitates a correct image of the extent of tumor invasion into the inferior vena cava. This can have a considerable effect on the planning of combined urological and vascular surgery.

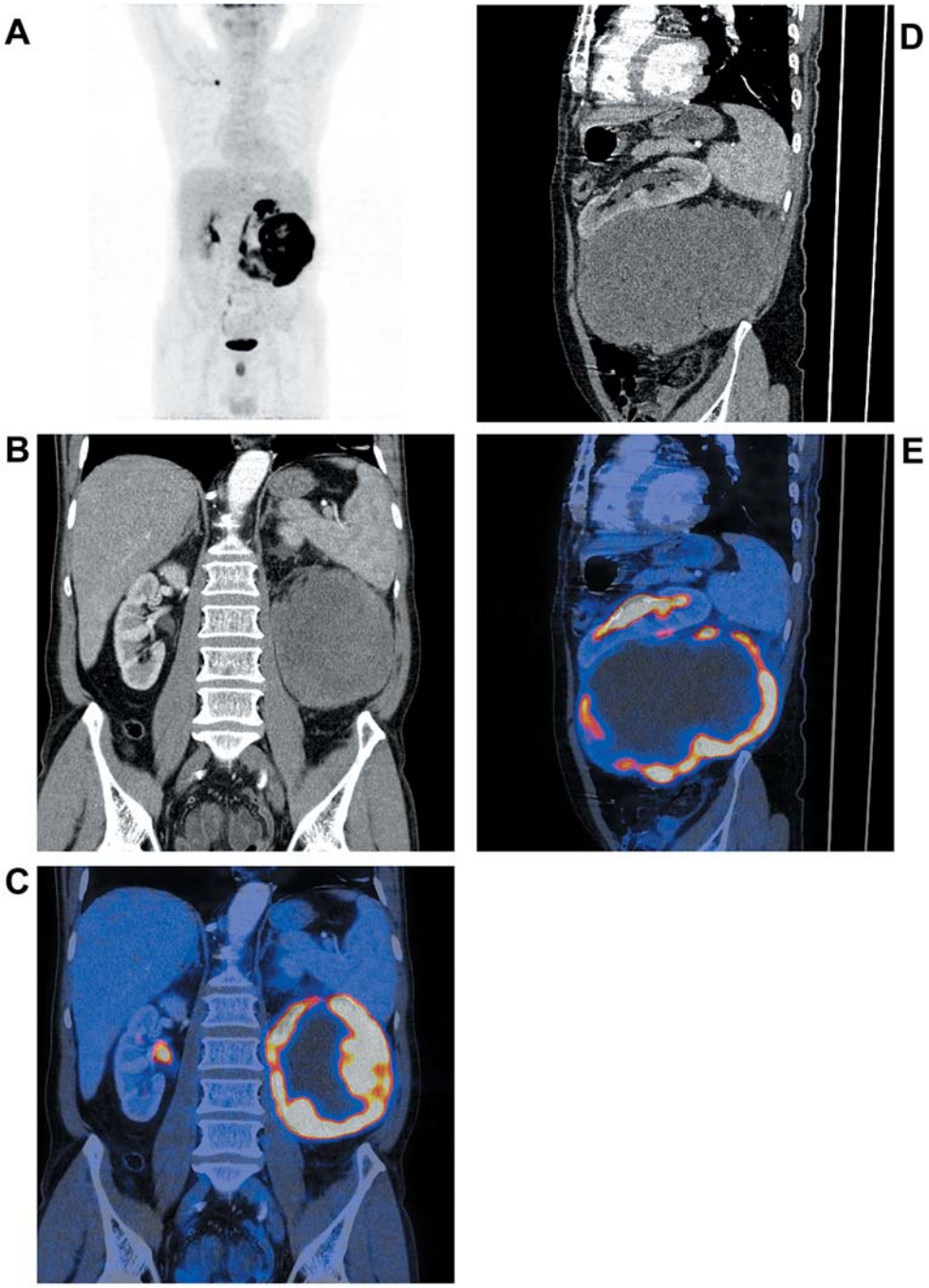

Figure 4. *patient dying after one month after nephrectomy due to the massive intraabdominal spread of tumor, conventional renal cell carcinoma with sarcomatoid transformation, extreme level accumulation of FDG exceeding SUV_{max} 20. A – whole body MIP PET; B, D – CT images, C, E – PET/CT fusions – levels of displayed SUV_{max} 0-10.*

The blood supply to the kidney itself, in much the same way as supplying the tumor, may be measured with the same precision as was shown in 16-detector MDCT (3), since PE/TCT with an integrated 16-detector subsystem can be used for sub-millimeter isotopic resolution. Apart from the assessment in layer images with MIP, the data can also be used for the production of three-dimensional angiograms.

Conclusion

According to our findings ^{18}F-FDG-PET/CT in renal carcinoma, where local or generally advanced disease is suspected, is an examination that assists decision-making about the strategy for therapy. It facilitates both giving a prognosis of the disease and determining a more accurate exclusion of neoplastic dissemination. Apart from other matters, it facilitates the prediction of the degree of tumorous differentiation with the help of the level of glycolytic activity, and also allows for prognosis of the disease on the basis of simple assessment of the level of accumulation in the tumorous tissue. A necessary condition for gaining the advantages of this examination is to perform ^{18}F-FDG-PET/CT with integrated and fully-diagnostic two-phase CT-angiography.

Acknowledgements

This research was supported by the Charles University Research Fund (project number P36) and by the project of Czech Ministry of Health: Conceptual Development of the Research Institution (00669806 - FN Plzen).

References

1 Motzer RJ, Bander NH and Nanus DM: Renal cell carcinoma N Engl J Med *335*: 865-875, 1996.

2 Mueller-Lisse UG, Mueller-Lisse UL, Meindl T , Coppenrath E, Degenhart C, Graser A, Scherr M and Reiser MF: Staging of renal cell carcinoma. Eur Radiol *17(9)*: 2268-2277, 2007.

3 Ferda J, Hora M, Hes O, Ferdová E and Kreuzberg B: Assessment of the kidney tumor vascular supply by two-phase MDCT-angiography. Eur J Radiol *62(2)*: 295-301, 2007.

4 Aide N, Cappele O, Bottet P, Bensadoun H, Regeasse A, Comoz F, Sobrio F, Bouvard G and Agostini D: Efficiency of [(18)F]FDG PET in characterising renal cancer and detecting distant metastases: a comparison with CT. Eur J Nucl Med Mol. Imaging *30(9)*: 1236-1245, 2003.

5 Lawrentschuk N, Davis ID, Bolton DM and Scott AM. Functional imaging of renal cell carcinoma. Nat Rev Urol *7(5)*: 258-266, 2010.

6 Harrison MR and George DJ: Better late than early: FDG-PET imaging in metastatic renal cell carcinoma. Clin Cancer Res *17(18)*: 5841-5843, 2011.

7 Ide M, Suzuki Y, Kameyama G, Takahashi W, Koide S, Hinohara S, Kawada S: The detection of renal cell carcinoma with adrenal and para-aortic lymph node metastases by FDG-PET. Eur J Nucl Med Mol Imaging *32(10)*: 1246, 2005.

8 Nakatani K, Nakamoto Y, Saga T, Higashi T and Togashi K: The potential clinical value of FDG-PET for recurrent renal cell carcinoma. Eur J Radiol *79(1)*: 29-35, 2011.

9 Namura K, Minamimoto R, Yao M, Makiyama K, Murakami T, Sano F, Hayashi N, Tateishi U, Ishigaki H, Kishida T, Miura T, Kobayashi K, Noguchi S, Inoue T, Kubota Y and Nakaigawa N: Impact of maximum standardized uptake value (SUV_{max}) evaluated by 18-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (^{18}F-FDG-PET/CT) on survival for patients with advanced renal cell carcinoma: A preliminary report. BMC Cancer *10*: 667, 2010

10 Lyrdal D, Boijsen M, Suurküla M, Lundstam S and Stierner U: Evaluation of sorafenib treatment in metastatic renal cell carcinoma with 2-fluoro-2-deoxyglucose positron emission tomography and computed tomography. Nucl Med Commun *30(7)*: 519-524, 2009.

11 Hugonnet F, Fournier L, Medioni J, Smadja C, Hindié E, Huchet V, Itti E, Cuenod CA, Chatellier G, Oudard S and Faraggi M: Hypoxia in Renal Cancer Multicenter Group. Metastatic renal cell carcinoma: Relationship between initial metastasis hypoxia, change after one month's sunitinib, and therapeutic response: An ^{18}F-fluoromisonidazole PET/CT study. J Nucl Med *52(7)*: 1048-1055, 2011.

12 Khandani AH, Cowey CL, Moore DT, Gohil H and Rathmell WK. Primary renal cell carcinoma: relationship between ^{18}F-FDG uptake and response to neoadjuvant sorafenib. Nucl Med Commun *33(9)*: 967-973, 2012.

13 Ueno D, Yao M, Tateishi U, Minamimoto R, Makiyama K, Hayashi N, Sano F, Murakami T, Kishida T, Miura T, Kobayashi K, Noguchi S, Ikeda I, Ohgo Y, Inoue T, Kubota Y, Nakaigawa N: Early Assessment by FDG-PET/CT of Patients with Advanced Renal Cell Carcinoma Treated with Tyrosine Kinase Inhibitors is Predictive of Disease Course. BMC Cancer *12(1)*: 162, 2012.

14 Kotzerke J, Linné C Meinhardt M, Steinbach J, Wirth M, Baretton G, Abolmaali N and Beuthien-Baumann B: [1-(11)C]acetate uptake is not increased in renal cell carcinoma. Eur J Nucl Med Mol Imaging *34(6)*: 884-888, 2007.

15 Oyama N, Okazawa H, Kusukawa N, Kaneda T, Miwa Y, Akino H, Fujibayashi Y, Yonekura Y, Welch MJ and Yokoyama O: ^{11}C-Acetate PET imaging for renal cell carcinoma. Eur J Nucl Med Mol Imaging *36(3)*: 422-127, 2009.

16 Middendorp M, Maute L, Sauter B, Vogl TJ and Grünwald F: Initial experience with ^{18}F-fluoroethylcholine PET/CT in staging and monitoring therapy response of advanced renal cell carcinoma. Ann Nucl Med *24(6)*: 441-446, 2010.

17 Lawrentschuk N, Poon AM and Scott AM: Fluorine-18 fluorothymidine: A new positron emission radioisotope for renal tumors. Clin Nucl Med *31(12)*: 788-789, 2006.

18 Lawrentschuk N, Poon AM, Foo SS, Putra LG, Murone C, Davis ID, Bolton DM and Scott AM: Assessing regional hypoxia in human renal tumours using ^{18}F-fluoromisonidazole positron emission tomography. BJU Int *96(4)*: 540-546, 2005.

19 Lawrentschuk N, Gani J, Riordan R, Esler Sand Bolton DM: Multidetector computed tomography *vs*. magnetic resonance imaging for defining the upper limit of tumour thrombus in renal cell carcinoma: A study and review. BJU Int *96(3)*: 291-295, 2005.

Received April 3, 2013
Revised April 29, 2013
Accepted April 20, 2013