Preliminary Study of Detecting Urothelial Malignancy with FDG PET in Taiwanese ESRD Patients

SHUNG-SHUNG SUN[1,2], CHAO-HSIANG CHANG[3], HUEISCH-JY DING[4], CHIA-HUNG KAO[1], HSI-CHIN WU[3,5] and TE-CHUN HSIEH[1]

Departments of [1]Nuclear Medicine and PET Center and [3]Urology, China Medical University Hospital, Taichung; [2]Department of Biomedical Imaging and Radiological Science and [5]School of Medicine, China Medical University, Taichung; [4]Department of Medical Imaging and Radiological Sciences, I-Shou University, Kaohsiung, Taiwan, R.O.C

Abstract. *The study aimed to evaluate the possibility of applying ^{18}F-fluorodeoxyglucose positron-emission tomography (FDG PET) for detecting primary urothelial malignancies in end-stage renal disease (ESRD) patients and the possible absence of interference by normal physiological excretory urinary radioactivity. Patients and Methods: Fifteen consecutive ESRD patients who had undergone preoperative FDG PET and computed tomography (CT) for their suspected urothelial malignancies from December 2002 to March 2004, were retrospectively enrolled for comparison with the postoperative histological findings. Results: The histological findings revealed 27 urothelial malignancies. The sensitivity and positive predictive value of FDG PET (CT in parentheses) were 67% (59%) and 90% (84%), respectively. A tendency was also observed towards a positive correlation between the sensitivity of FDG PET and the grade/stage of the urothelial malignancies. Conclusion: FDG PET may serve as a feasible supplementary method for the diagnosis of urothelial malignancies in ESRD patients and a possible indicator of prognosis.*

Patients with end-stage renal disease (ESRD) have been found to have an increased risk of cancer (1). Transitional cell carcinoma (TCC) is the most common carcinoma in Taiwanese patients (2-4) with a very high standardized incidence ratio as compared with the general population and usually synchronous multiple foci (5). The common diagnostic imaging procedures include cystoscopy, renal ultrasonography and retrograde pyelography. In addition, computed tomography (CT) is used for detailed evaluation of the entire urinary system as well as detection of lymph node and distant metastases (6, 7). However, certain ureteral lesions may sometimes be difficult to distinguish from inflammation, benign stricture and malignancy. Moreover, the use of contrast media is also equivocal for uremic patients (8-10). Traditionally, ^{18}F-fluorodeoxyglucose positron-emission tomography (FDG PET) had not been appropriate for the detection of malignancies in the urinary system because of high physiological urinary radioactivity. Diuresis (11, 12) has been known to effectively decrease the background radioactivity in the urinary tract and hence facilitate the identification of hypermetabolic lesions on FDG PET. Therefore, FDG PET may be potentially useful for detecting primary urothelial malignancies in patients who are oliguric or auric by avoiding the interference of the usual physiological urinary radioactivity. The following retrospective analysis attempted to evaluate the validity of this hypothesis and furthermore, the efficacy of FDG PET for detecting primary urothelial malignancies in ESRD patients.

Correspondence to: Te-Chun Hsieh, Department of Nuclear Medicine and PET Center, China Medical University Hospital, No. 2, Yuh-Der Road, Taichung 404, Taiwan, R.O.C. Tel: +886 422052121 Ext 7411, Fax: +886 422336174, e-mail: rancholosamigos@yahoo.com.tw

Key Words: ^{18}F-fluorodeoxyglucose positron-emission tomography, end-stage renal disease, transitional cell carcinoma, computed tomography.

Patients and Methods

Patients. In our hospital from December 2002 to March 2004, 15 consecutive ESRD patients (11 females and 4 males; age: 59.93±10.53 years old) had undergone preoperative FDG PET and abdominal/pelvic CT for suspected urothelial malignancies (clinical manifestations of painless gross hematuria or atypical cells in routine urinalysis). All of them subsequently obtained histological proof through ureteroscopic biopsy or ureteronephrectomy specimens. Fourteen out of these 15 patients underwent CT first followed by FDG PET. The other one underwent FDG PET first. The range of intervals between the two studies was less than 2 months (1 to 47 days; average: 9.4±10.8 days; median: 7 days).

Table I. *Characteristics of ESRD patients, histological results, FDG PET findings and CT findings.*

Patient no.	Gender	Age (years)	Histology	Grade tumor	Longest stage results length (mm)	Tumor PET	FDG urinary	Excretory FDG radioactivity	CT
1	F	45	Bladder TCC	2/3	3	T1	N	Absent	N
			Left UPJ TCC	2/3	26	T1	P		P
2	F	71	Right lower third ureteral TCC	2/3	1 (biopsy)	NA†	P	Absent	N
			Left lower third ureter inflammation				P		N
3	F	70	Right renal pelvic TCC	2/3	10	T2a	P	Absent	P
			Right upper/middle third ureteral TCC	2/3	15	T2a	N		N
4	F	45	Right middle third ureteral TCC	1/3	28	Ta	P	Absent	P
			Bladder dome TCC	1/3	5	Ta	N		N
5	M	65	Right renal pelvic TCC	2/3	30	Ta	P	Intense	P
			Right lower third ureteral TCC	1/3	2	Ta	N		N
			Bladder TCC	2/3	7	Ta	N		N
6	F	62	Right renal pelvic TCC	3/3	8	T1	P	Intense	P
			Left renal pelvic TCC	3/3	5	T1	P		P
			Bladder TCC	2/3	9	T1	N		N
									P (Left proximal ureter)
									P (Left lumbar para-aortic lymph node)
7	F	37	Left renal pelvic TCC	2/3	50	T3b	P	Intense¶	P
			Left upper/middle third ureteral TCC	2/3	1 (biopsy)	Ta	P		P
			Left perirenal lymph node metastasis				N		N
						P (bladder)‡			
8	M	60	Left renal pelvic TCC	2/3	30	T3a	P	Intense	P
9	M	59	Bladder TCC	3/3	55	T2b	P	Absent	P
			Right renal pelvic TCC	2/3	12	Ta	P		N
			Left renal pelvic TCC	2/3	9	Ta	P		P
									P (Left upper third ureter)
10	F	59	Left renal pelvic TCC	3/3	20	T1	P	Moderate	P
			Left upper third ureteral TCC	2/3	1.5	Ta	N		N
11	F	68	Right renal pelvic TCC	3/3	110	T3a	P	Mild	P
12	F	68	Left upper third ureteral TCC	2/3	20	T2a	P	Intense	P
13	M	68	Left UPJ TCC	2/3	1 (biopsy)	Ta	P	Absent	P
14	F	53	Right renal pelvic TCC	3/3	1 (biopsy)	T1	P	Moderate	P
15	F	69	Left ureteral TCC	2/3	8	Ta	N	Absent	N

†Not available because of too little stroma to evaluate the invasiveness; ‡persistent focalized intense radioactivity; ¶presence of urine FDG radioactivity in the graft kidney and urinary bladder; TCC: transitional cell carcinoma; UPJ: ureteropelvic junction; M: male; F: female; P: positive; N: negative.

Patients were retrospectively enrolled for further evaluation with the postoperative histological findings (Table I).

FDG PET. All the patients fasted for at least 4 hours before the examination. Whole-body PET images were acquired on a GE Advance NXi scanner (General Electric Medical Systems, Milwaukee, WI, USA) with an axial field of view of 15 cm (35 slices per field of view with a slice thickness of 4.30 mm) 40 minutes to 1 hour after the intravenous injection of 370 MBq (10 mCi) of ^{18}F FDG. Emission PET images of the neck, chest, and abdomen were acquired in the 2-dimensional mode, 3 minutes per bed position, followed by 1-minute transmission scans at selected sites. The images were reconstructed using vendor-provided software and formatted into transaxial, coronal, and sagittal image sets. Delayed images were acquired 10 minutes after intravenous administration of 40 mg furosemide and patient's voiding, if there was still noticeable urine radioactivity on the initial whole-body images.

Interpretation. The results of CT were retrospectively reviewed and classified as positive or negative findings for malignancy according to the reports of radiologists. The principle radiological features of urothelial carcinomas were an identifiable soft tissue mass and contiguity of the lesion with the urothelium, various degrees of enhancement by contrast media and the presence or not of proximal obstruction and enhancement by contrast media. Suspected peri-renal or regional lymph node metastases were also notified as positive findings. All the FDG PET images were reviewed separately by at least two experienced nuclear medicine physicians who were unaware of the results of CT. Positive findings on FDG PET were defined as any focalized radioactivity in the urinary system that was higher than the background radioactivity if there was complete absence of physiological excretory urinary radioactivity, or any focalized radioactivity equal to or higher than the hepatic

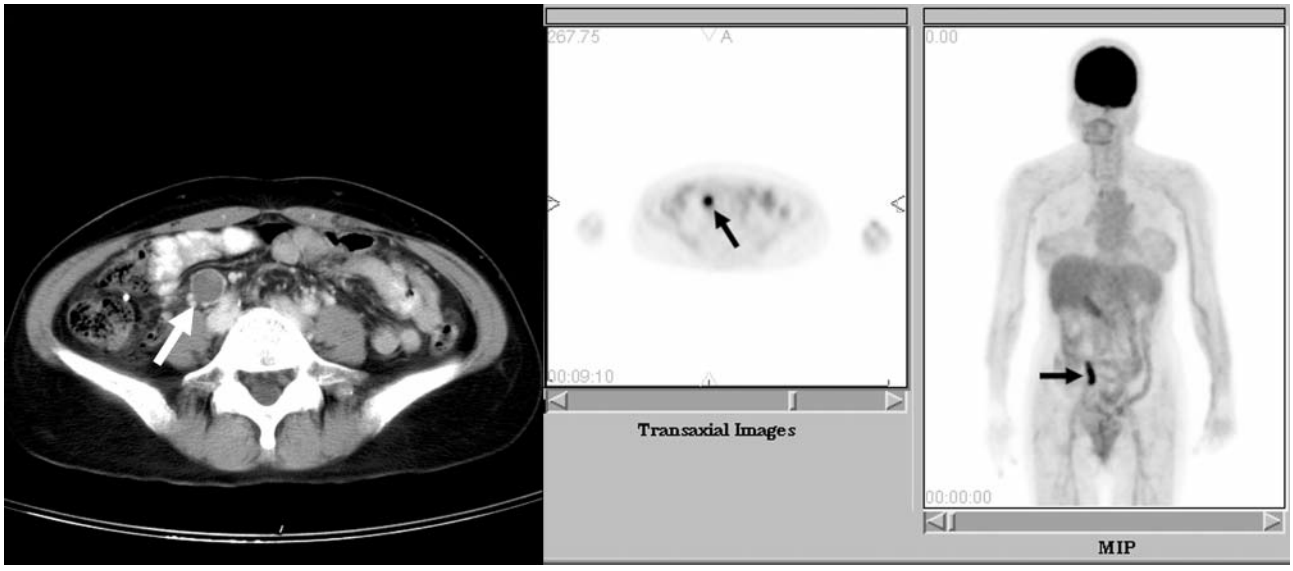

Figure 1. *Right middle third ureteral TCC of patient no. 4 arrowed in the transaxial slice of CT, transaxial slice of FDG PET and the maximum intensity projection (MIP) image of FDG PET. Notice in the MIP image that there is no excretory urinary FDG radioactivity in the urinary system.*

Table II. *Relation of tumor stages and FDG PET findings.*

	Tumor stage of urothelial carcinoma†			
	Ta	T1	T2	T3
FDG PET				
Positive	6	5	3	3
Negative	5	2	1	0
Total	11	7	4	3

†No T4 tumor in this study.

Table III. *Relation of histological malignant grade to FDG PET findings.*

	Malignant grade of urothelial carcinoma†		
	1	2	3
FDG PET			
Positive	1	11	6
Negative‡	2	6	0

†Not including the one metastasizing to the perirenal lymph node; ‡Four false-negatives in urinary bladders, and another 4 in kidneys and ureters.

radioactivity if there was still some physiological excretory urinary radioactivity persistent after diuresis (Figure 1). The final interpretation was achieved by consensus if the initial interpretations differed. The results of CT and FDG PET were further compared with the histological findings to verify their efficacy (Table I).

Results

The histological findings revealed 27 malignant urothelial malignancies (26 in the urinary tract and 1 in the perirenal lymph node). Among the 20 positive findings in the urinary system by FDG PET, 18 malignancies were identified (sensitivity: 67%; positive predictive value: 90%). The 2 false-positive findings were inflammation in the ureter and persistent retained urinary bladder focal radioactivity in a patient who had excretory urinary FDG radioactivity from the graft kidney. Among the 19 positive findings in the abdominal/pelvic region in CT, 16 were true malignancies and 3 were false-positive findings. The sensitivity and positive predictive value of CT were 59% and 84%, respectively. FDG PET and CT failed to detect 9 and 11 lesions, respectively. There was no distant metastasis identified in these patients.

FDG urine radioactivity was absent in 7 patients (8 proven malignancies among 9 positive PET findings) and present in the other 8 patients (10 proven malignancies among 11 positive PET findings; 7 PET findings among 5 patients had intense urine radioactivity). It was noted that a tendency for the sensitivity of FDG PET to detect urothelial malignancies was positively correlated with the histological malignant grade and tumor stage (Tables II and III).

Discussion

Unlike the effectiveness of FDG PET in detecting distant and recurrent urothelial malignancies, results for the evaluation of locoregional disease are poor (13). Some procedures have been proposed to improve the efficacy of FDG PET. Kosuda *et al*. (14) used retrograde saline irrigation of the urinary bladder to remove ^{18}F-FDG radioactivity. Leisure *et al*. (15) and Vesselle *et al*. (16) utilized diuretics, intravenous saline infusion and bladder catheters to eliminate artifacts from the urinary system. However, the need for transuretheral catheterization was invasive and uncomfortable and the effectiveness was still variable. Kamel *et al*. (17) used furosemide forced diuresis and parenteral hydration and significantly improved the sensitivity of FDG PET for detecting ureteral and bladder malignancies. However, limited improvement was observed when the lesions were in the renal regions.

Several new PET tracers were developed (9, 18) to address the great obstacle of physiological urinary FDG radioactivity in the detection of malignancies in the urinary system and limited current available solutions. ^{11}C-Methionine PET was reported to be superior to ^{18}F-FDG PET (9). ^{11}C-Choline was also tried due to its low level of urinary excretion. Picchio *et al*. (19) and Gofrit *et al*. (20) found better results with ^{11}C-choline PET and PET/CT than CT alone in the detection of nodal metastases. However, the relatively short physical half-life and inconvenience/limited availability of ^{11}C still make ^{11}C-methionine and ^{11}C-choline less clinically practical.

In contrast, owing to the characteristic oliguria or auria of patients with ESRD, we assumed that FDG PET of urothelial malignancies would possibly not be interfered with by the usual abundant physiological excretory urinary radioactivity of FDG. Our findings revealed little difference of sensitivity between FDG PET and CT. Nevertheless, excretory urinary FDG radioactivity was not universally absent even though these patients had ESRD. However, a true lesion could be intuitively interpreted if any focalized FDG radioactivity in the urinary system higher than the background radioactivity in the routine whole-body images of those patients who did not have excretory urinary radioactivity was found (only one false-positive finding that was in reality inflammation but appeared as a true-positive lesion on FDG PET occurred). CT was somewhat more complicated because of its various manifestations in urothelial malignancies.

In addition, a tendency towards a positive correlation between the sensitivity of detecting urothelial malignancies by FDG PET and the histological malignant grade or tumor stage was found. This finding may reflect the fact that the single most prognostic factor of urothelial malignancies is the tumor stage and that is also positively correlated with the histological malignant grade. Therefore, FDG PET might potentially be able to play a role in prognosis in addition to its ability to detect urothelial malignancies.

There were 9 false-negative FDG PET findings, including 3 lesions smaller than 5 mm maximum length which were beyond the image resolution of PET, 2 lesions in the urinary bladder with the presence of excretory urinary radioactivity and a small perirenal lymph node metastasis obscured by the radioactivity of an adjacent huge renal pelvic tumor (50 mm maximum length). Another lesion in the urinary bladder without excretory urinary radioactivity which measured 5 mm maximum length, might still have been influenced partially by the volume effect. The reason for the other two false-negative findings was unknown. There were two false-positive findings, one was an inflammatory lesion and the other was focal persistent radioactivity in the urinary bladder where there was excretory urinary FDG radioactivity from the graft kidney. It seemed that although diuretics were applied, there was still limited improvement in the interpretation of the urinary bladder finding if excretory urinary radioactivity was still present.

Overall, the present study, albeit a small series, showed a possible feasible supplementary method using FDG PET to evaluate urothelial malignancies of ESRD patients who have significantly higher risk than the general population and whose urothelial malignancies are usually synchronous and multifocal when they manifest suspicious symptoms (5). The possibility for FDG PET to play a potential prognostic role was also revealed. However, FDG PET should still serve as a supplement to the current standard invasive studies because a negative FDG PET scan cannot obviate the need for invasive studies for histological proof, especially when the lesions may be too small to be detected by FDG PET. On the other hand, any focalized FDG radioactivity in the urinary system without excretory urinary radioactivity in a uremic patient should prompt further investigation of the highly possible urothelial malignacy.

References

1 Maisonneuve P, Agodoa L, Gellert R *et al*: Cancer in patients on dialysis for end-stage renal disease: an international collaborative study. Lancet *354*: 93-99, 1999.

2 Ou JH, Pan CC, Lin JS *et al*: Transitional cell carcinoma in dialysis patients. Eur Urol *37*: 90-94, 2000.

3 Wang HB, Hsieh HH, Chen YT *et al*: The outcome of post-transplant transitional cell carcinoma in 10 renal transplant recipients. Clin Transplant *16*: 410-413, 2002.

4 Wu MJ, Lian JD, Yang CR *et al*: High cumulative incidence of urinary tract transitional cell carcinoma after kidney transplantation in Taiwan. Am J Kidney Dis *43*: 1091-1097, 2004.

5 Chang CH, Yang CM and Yang AH: Renal diagnosis of chronic hemodialysis patients with urinary tract transitional cell carcinoma in Taiwan. Cancer *109*: 1487-1492, 2007.

6 Kawamoto S, Horton KM and Fishman EK: Opacification of the collecting system and ureters on excretory-phase CT using oral water as contrast medium. Am J Roentgenol *186*: 136-140, 2006.

7 Zhang J, Gerst S, Lefkowitz RA *et al*: Imaging of bladder cancer. Radiol Clin North Am *45*: 183-205, 2007.
8 Powles T, Murray I, Brock C *et al*: Molecular positron-emission tomography and PET/CT imaging in urological malignancies. Eur Urol *51*: 1511-1520, 2007.
9 Jana S and Blaufox MD: Nuclear medicine studies of the prostate, testes, and bladder. Semin Nucl Med *36*: 51-72, 2006.
10 Bouchelouche K and Oehr P: Positron-emission tomography and positron-emission tomography/computerized tomography of urological malignancies: an update review. J Urol *179*: 34-45, 2008.
11 Anjos DA, Etchebehere EC, Ramos CD *et al*: ^{18}F-FDG PET/CT delayed images after diuretic for restaging invasive bladder cancer. J Nucl Med *48*: 764-770, 2007.
12 López-Gandul S, Pérez-Moure G, García-Garzón JR *et al*: Intravenous furosemide injection during ^{18}F-FDG PET acquisition. J Nucl Med Technol *34*: 228-231, 2006.
13 Ramdave S, Thomas GW, Berlangieri SU *et al*: Clinical role of F-18 fluorodeoxyglucose positron-emission tomography for detection and management of renal cell carcinoma. J Urol *166*: 825-830, 2001.
14 Kosuda S, Kison PV, Greenough R *et al*: Preliminary assessment of fluorine-18 fluorodeoxyglucose positron-emission tomography in patients with bladder cancer. Eur J Nucl Med *24*: 615-620, 1997.
15 Leisure GP, Vesselle HJ, Faulhaber PF *et al*: Technical improvements in fluorine-18-FDG PET imaging of the abdomen and pelvis. J Nucl Med Technol *25*: 115-119, 1997.
16 Vesselle HJ and Miraldi FD: FDG PET of the retroperitoneum: normal anatomy, variants, pathologic conditions, and strategies to avoid diagnostic pitfalls. Radiographics *18*: 805-823, 1998.
17 Kamel EM, Jichlinski P, Prior JO *et al*: Forced diuresis improves the diagnostic accuracy of ^{18}F-FDG PET in abdominopelvic malignancies. J Nucl Med *47*: 1803-1807, 2006.
18 Bouchelouche K and Oehr P: Recent developments in urologic oncology: positron-emission tomography molecular imaging. Curr Opin Oncol *20*: 321-326, 2008.
19 Picchio M, Treiber U, Beer AJ *et al*: Value of ^{11}C-choline PET and contrast-enhanced CT for staging of bladder cancer: correlation with histopathologic findings. J Nucl Med *47*: 938-944, 2006.
20 Gofrit ON, Mishani E, Orevi M *et al*: Contribution of ^{11}C-choline positron-emission tomography/computerized tomography to preoperative staging of advanced transitional cell carcinoma. J Urol *176*: 940-944, 2006.

Received January 23, 2009
Revised June 11, 2009
Accepted June 22, 2009