^{18}F-FDG PET/CT Delayed Images After Diuretic for Restaging Invasive Bladder Cancer

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PET with ^{18}F-FDG has been considered of limited value for detection of bladder cancer because of the urinary excretion of the tracer. The purpose of this study was to investigate the role of PET/CT in the detection and restaging of bladder cancer using furosemide and oral hydration to remove the excreted ^{18}F-FDG from the bladder. **Methods:** Seventeen patients with bladder cancer (11 without cystectomy, 6 with total cystectomy and urinary diversion) underwent ^{18}F-FDG PET/CT from head to the upper thighs 60 min after the intravenous injection of 370 MBq of ^{18}F-FDG. Additional pelvic images were acquired 1 h after the intravenous injection of furosemide and oral hydration. PET/CT findings were confirmed by MRI, cystoscopy, or biopsy. **Results:** PET/CT was able to detect bladder lesions in 6 of 11 patients who had not undergone cystectomy. These images changed the PET/CT final reading in 7 patients: Recurrent bladder lesions were detected in 6 patients, pelvic lymph node metastases in 2 patients, and prostate metastasis in 1. This technique overcame the difficulties posed by the urinary excretion of ^{18}F-FDG. Hypermetabolic lesions could be easily detected by PET and precisely localized in the bladder wall, pelvic lymph nodes, or prostate by CT. Seven of 17 patients (41%) were upstaged only after delayed pelvic images. **Conclusion:** Detection of locally recurrent or residual bladder tumors can be dramatically improved using ^{18}F-FDG PET/CT with delayed images after a diuretic and oral hydration.

Key Words: bladder cancer; ^{18}F-FDG; PET/CT; furosemide; oral hydration

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Bladder cancer represents 7% of all malignancies in men and 2% of all malignancies in women (*1*). More than 90% of bladder cancers are transitional cell carcinomas (*2*). Bladder cancer is usually multifocal and has a high local recurrence rate. Low-grade tumors are usually superficial and confined to the epithelial or transitional cell layer of the bladder and have low potential for metastatic spread. High-grade tumors are those that invade the deeper layers of the bladder wall and have a much greater potential for metastatic spread (*3*). Recurrences of superficial bladder cancer remain confined to the bladder wall in 70%–80% of patients, but 20%–30% of recurrent tumors may subsequently become muscle-invasive and lead to metastatic disease (*3,4*). At least 50% of the high-grade tumors may have occult metastatic disease at initial diagnosis and gross metastases within 2 y of diagnosis despite prompt aggressive regional intervention (*3*). Common sites of metastases include the pelvic and retroperitoneal lymph nodes, lungs, liver, and bones (*5*).

Noninvasive imaging plays an important role in all stages of bladder cancer. Patients with muscle-invasive bladder cancers usually undergo a chest radiograph and a CT scan of the abdomen and pelvis. However, CT and MRI are not reliable in evaluating the extent of local or regional disease (*3,6*). Both generally tend to overestimate the degree of extension through the bladder wall but underestimate the presence of pelvic lymph node metastases. Previous biopsy, inflammation, radiotherapy, systemic chemotherapy, and intravesical agents such as bacille Calmette–Guérin can cause circumferential bladder wall thickening mimicking bladder cancer (*7*).

^{18}F-FDG uptake by bladder cancer was first demonstrated by Harney et al. in rats, with an estimated uptake ratio of tumor to normal bladder of 13:1 (*8*). A small number of studies have been done with ^{18}F-FDG PET in bladder cancer (*9–11*) and, to the best of our knowledge, none have been undertaken so far with PET/CT. Several investigators have considered ^{18}F-FDG PET of no utility in the detection of localized bladder cancers and perivesical lymph nodes (*12–15*). The limitation of ^{18}F-FDG PET has been attributed to the urinary excretion of ^{18}F-FDG. The pooled activity in the urinary bladder makes the evaluation of bladder wall lesions difficult or even impossible.

Because most recurrences of superficial bladder cancer remain confined to the bladder wall, washing out the excreted ^{18}F-FDG is key to overcoming the limitations of PET. Some investigators have attempted to achieve this and improve the sensitivity of PET by using furosemide injection before image acquisition, or retrograde bladder irrigation with a double-lumen Foley catheter, or postvoid images or other

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tracers; however, their results have been disappointing (*11, 16–19*).

The purpose of this study was to assess the usefulness of ^{18}F-FDG PET/CT with delayed images after diuretic and oral hydration in the detection of local and regional recurrences of bladder cancer.

MATERIALS AND METHODS

Patient Population

All patients with a known history of bladder cancer referred to our laboratory from June 2003 to December 2004 for whole-body ^{18}F-FDG PET/CT were retrospectively included for analysis. PET/CT scans were requested for restaging purposes, as the patients did not have symptoms of recurrence and no abnormalities were detected in previous radiologic studies. Seventeen patients (age range, 49–83 y; mean age, 68 y; 15 males, 2 females) underwent PET/CT with ^{18}F-FDG from head to the upper thighs.

All patients had been previously submitted to primary tumor resection by transurethral resection or cystectomy. Histopathology confirmed transitional cell carcinoma in all cases. The time interval between the primary tumor resection and the PET/CT scan was at least 3 mo to minimize inflammatory reaction caused by the surgical procedure.

Patients were divided into 2 groups: those without cystectomy (11 patients) and those with total cystectomy and urinary diversion (6 patients). All patients underwent routine restaging studies, such as serial cystoscopy or MRI after PET/CT.

PET/CT Protocol

Fourteen patients were submitted to a single PET/CT study and 3 patients were submitted to 3 consecutive studies. Therefore, 23 studies were available for interpretation.

Patients were instructed to fast for at least 4 h before the intravenous injection of 370 MBq (10 mCi) of ^{18}F-FDG. Blood glucose was measured before injection of the tracer to ensure glucose blood levels below 120 mg/dL. Before and after injection, patients were kept lying comfortably in a quiet, dimly lit room. No urinary bladder catheterization was performed, and no diuretics were administered at this time. Saline infusion (approximately 500 mL) was given before tracer injection.

Whole-body PET/CT images were acquired 1 h after radiotracer injection, using a Biograph PET/CT scanner with bismuth germanate detectors (Siemens Medical Solutions USA, Inc.).

CT images were acquired without breath-holding instructions. The PET emission scan was obtained immediately after acquisition of the CT scan, without changing the patient's position. Five to 8 bed positions were used, with an acquisition time of 5 min for each bed position, starting from the pelvis and ending at the base of the skull. An additional single bed position acquisition was always performed for the head. PET image datasets were reconstructed iteratively using the CT data for attenuation correction, and coregistered images were displayed on a workstation.

After obtaining the PET/CT acquisitions from head to the upper thighs, the patients were injected with 20 mg of furosemide intravenously. They also received oral hydration with 800–1,000 mL of water. Patients were instructed to void frequently. Additional pelvic images were acquired 1 h after the intravenous injection of furosemide. PET/CT images before and after furosemide were compared with each other and their findings correlated with MRI, cystoscopy, and biopsy.

All PET/CT images were interpreted by 2 experienced nuclear medicine physicians; a third nuclear medicine physician helped to interpret the study when a final consensus was needed.

RESULTS

As expected, all patients demonstrated high tracer activity in the urinary bladder after the standard PET/CT acquisition. Delayed pelvic images after furosemide and oral hydration showed marked reduction of urinary bladder activity: Urine with a low concentration of ^{18}F-FDG replaced urine with a high concentration of the tracer in the bladder as a result of the diuresis promoted by oral hydration and furosemide. Bladder activity was reduced to background levels in all bladder-preserved patients.

Among the 11 patients without cystectomy, PET/CT delayed images after furosemide and oral hydration detected bladder hypermetabolic lesions in 6 patients (54%) (Table 1). All bladder lesions were detected only after furosemide injection, oral hydration, and voiding. Patients 1, 7, and 17 underwent 3 studies each.

Among these 6 patients with PET/CT-positive findings in the bladder, CT detected wall thickening in 4 of them. CT images were carefully interpreted, with special attention to causes of false-positive PET, such as bladder diverticulum and urinary leak. No other patients had bladder wall thickening on the CT images. In 3 patients, PET/CT hypermetabolic lesions in the bladder wall were the only abnormality detected (Fig. 1).

Bladder lesions were not known before PET/CT, and all lesions were confirmed by MRI, cystoscopy, or biopsy. Of the 6 patients with positive bladder findings, 2 were confirmed by MRI and further cystoscopic biopsy, and 4 by cystoscopic biopsy alone. The maximum standardized uptake values (SUVmax) ranged from 5.0 to 10.1 for all hypermetabolic bladder lesions. Histopathologic grades were not available for all biopsy samples. Only 1 of the 6 patients with PET/CT-positive finding was submitted to radical cystectomy after the PET/CT scan. The pathologic study of this patient's bladder was concordant with the previous cystoscopic biopsy, revealing transitional cell carcinoma. The remaining 5 patients were treated with bladder-preserving strategies.

None of the 5 patients with negative bladder PET/CT had positive findings in other diagnostic imaging studies. This subgroup of patients and the patients with bladder diversions followed routine restaging protocols such as serial cystoscopies and MRI. Because PET/CT, MRI, and cystoscopy studies were negative, malignancy was completely ruled out and therefore bladder wall biopsies were not performed.

As expected, PET/CT false-positive results due to inflammatory reaction after cystoscopic biopsy or transurethral resection were not observed in the bladder wall. The 3-mo time interval between the primary tumor resection and the PET/CT scan was enough to heal any possible inflammatory reaction.

TABLE 1
PET/CT Findings Before and After Diuretic and Hydration

		PET/CT before diuretic			PET/CT after diuretic		
Patient no.	Cys	Bladder wall	Pelvic lymph nodes	Distant metastases	Bladder wall	Pelvic lymph nodes	Distant metastases
1	No	−	−	−	**+**	−	**Prostate**
2	No	−	−	−	**+**	−	−
3	No	−	−	−	**+**	−	−
4	No	−	+	−	**+**	+	−
5	No	−	−	−	**+**	−	−
6	No	−	−	−	**+**	**+**	−
7	No	−	+	−	−	+	−
8	No	−	−	−	−	−	−
9	No	−	+	Liver	−	+	Liver
10	No	−	+	Bone	−	+	Bone
11	No	−	−	−	−	−	−
12	Yes	N/A	+	−	N/A	+	−
13	Yes	N/A	−	−	N/A	−	−
14	Yes	N/A	−	Liver	N/A	−	Liver
15	Yes	N/A	−	−	N/A	**+**	−
16	Yes	N/A	−	Mediastinum	N/A	−	Mediastinum
17	Yes	N/A	+	Mediastinum, liver, lung	N/A	+	Mediastinum, liver, lung

Cys = cystectomy; N/A = nonapplicable; − = negative; + = positive.
Changed results are in boldface type.

Pelvic lymph node metastases were detected in 6 patients before furosemide injection (Fig. 2). In 2 patients (patients 6 and 15), pelvic lymph nodes near the bladder were detected only on the delayed pelvic images after diuretic and oral hydration.

Distant metastases were detected by early images in 5 patients. However, 1 prostate lesion was detected only after the delayed pelvic images (patient 1) (Fig. 3). Liver, bones, lungs, and mediastinum were the other sites involved.

Delayed pelvic images after diuretic and oral hydration changed the PET/CT final reading in 7 patients: Recurrent bladder lesions were detected in 6 patients, pelvic lymph node metastases in 2 patients, and prostate metastasis in 1 patient. Therefore, 7 of 17 patients (41%) were upstaged

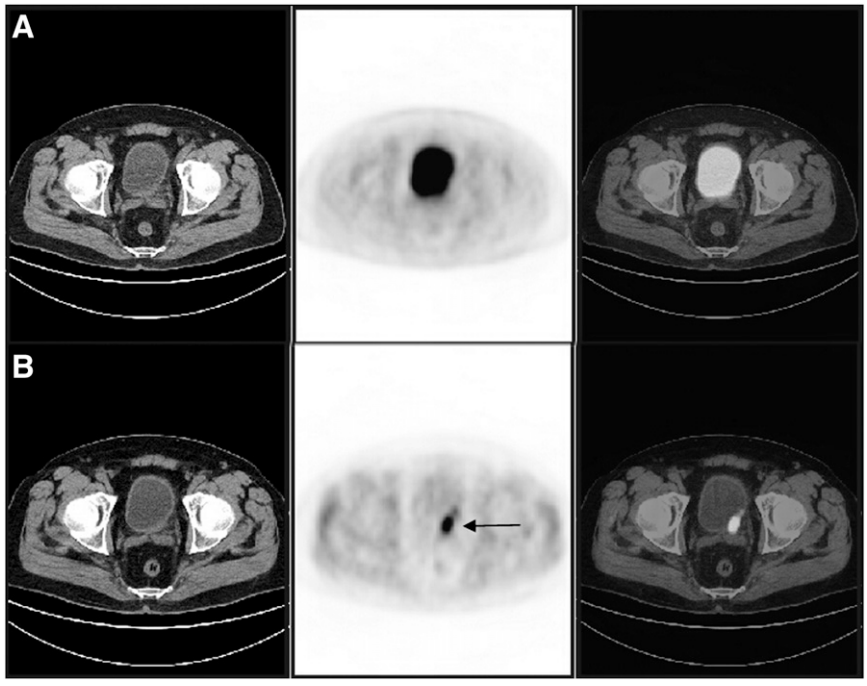

FIGURE 1. A 70-y-old male patient. (A) CT, PET, and PET/CT pelvic images (from left to right) show high concentration of ^{18}F-FDG in urinary bladder. (B) Delayed pelvic images after intravenous furosemide and oral hydration show excellent tracer washout. A marked hypermetabolic lesion (maximum standardized uptake value [SUVmax] = 9.0) is easily seen in posterior wall of bladder (arrow). Note mild bladder wall thickening in CT images.

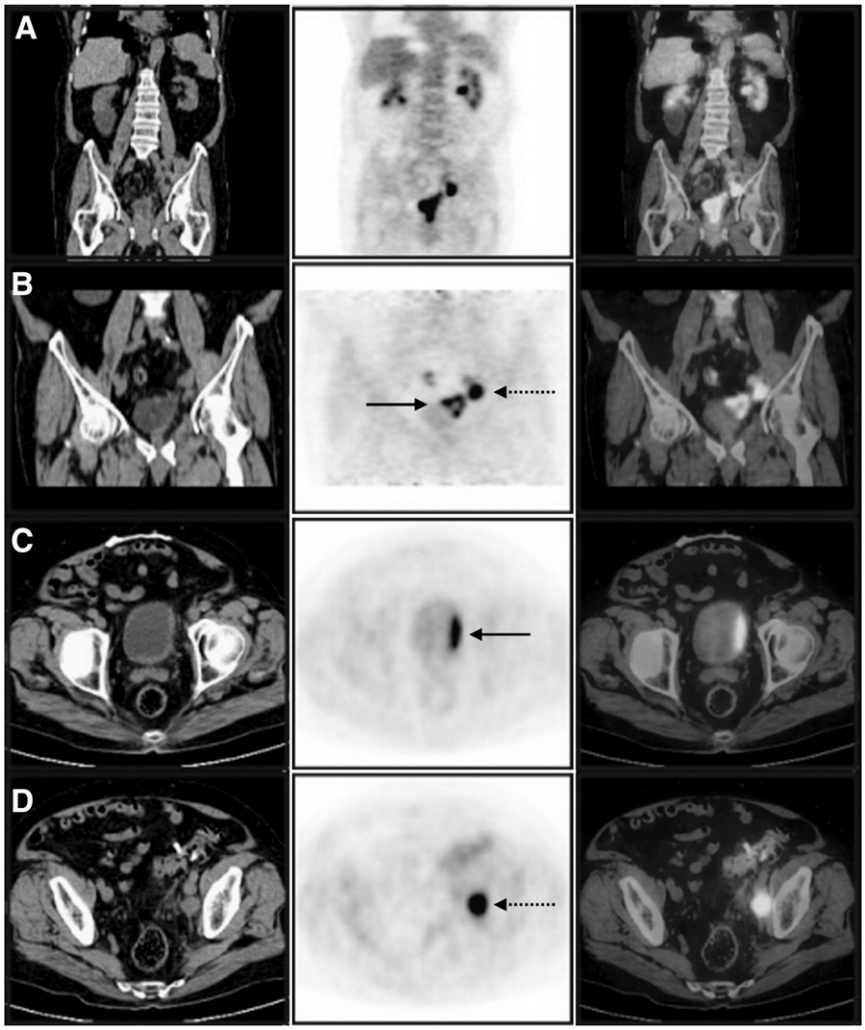

FIGURE 2. An 81-y-old male patient. CT, PET, and PET/CT images (from left to right) before furosemide (A) show a pelvic lymph node on left side (SUVmax = 17.0). Delayed pelvic images after intravenous furosemide and oral hydration show excellent tracer washout (B–D). It is possible to identify diffuse uptake in bladder wall (SUVmax = 10.0) (arrow) adjacent to pelvic lymph node (dotted arrow). Note that there is no bladder wall thickening in the CT images.

after the delayed pelvic images. Such a performance could not be achieved in patients with cystectomy because the urinary diversions showed larger residual volumes and, therefore, higher residual activities (Fig. 4).

DISCUSSION

Circulating ^{18}F-FDG undergoes glomerular filtration, is not reabsorbed as glucose, and is largely excreted in the urine (*20*). This poses a problem to identify kidney, ureter, bladder, and prostate tumors (*14,21–23*). Another limitation is the faint ^{18}F-FDG uptake by some malignant neoplasms—such as renal, prostate, and hepatocellular carcinomas—which has been attributed to high glucose-6-phosphatase activity, the enzyme that converts ^{18}F-FDG-6-phosphate back into ^{18}F-FDG with its excretion from the tumor cells (*24*). For these reasons, ^{18}F-FDG PET has been considered of no use to detect bladder cancer and perivesical lymph nodes (*12–15*).

Early investigations of imaging pelvic neoplasms with dedicated PET (non-PET/CT) were disappointing and were hindered by technical limitations. Older image reconstruction algorithms (filtered backprojection) created streak artifacts around the bladder, making pelvic evaluation difficult. Iterative reconstruction algorithms provide better image quality (*21*). Etchebehere et al. compared iterative and filtered backprojection algorithms in patients with prostate cancer and found that iterative reconstruction provided better images and detected 8.7% more lesions (*25*). In the present study, all images were iteratively reconstructed and no streak artifacts were observed in the early or delayed images.

Since the pioneering study of Harney et al. (*8*), a small number of studies have investigated the value of PET with ^{18}F-FDG in bladder cancer. Kosuda et al. used retrograde saline irrigation of the urinary bladder to remove ^{18}F-FDG radioactivity, but they were unable to reduce tracer activity to background levels and reported a 40% false-negative rate for detection of recurrent or residual tumor in the bladder (*11*). In fact, continuous bladder irrigation and immediate postvoid images are not effective in reducing intravesical activity because the kidneys keep filling the bladder with urine with high concentration of ^{18}F-FDG.

Leisure et al. (*26*) and Vesselle and Miraldi (*27*) were successful in eliminating image artifacts originating from

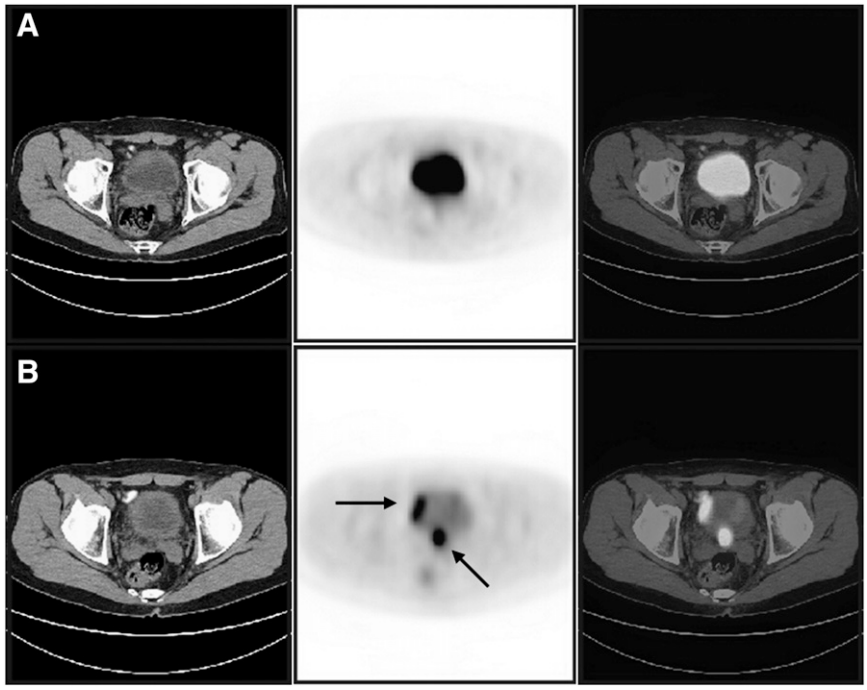

FIGURE 3. A 53-y-old male patient. CT, PET, and PET/CT images (from left to right) before furosemide (A) are normal. Delayed pelvic PET/CT images (B) after intravenous furosemide and oral hydration show hypermetabolic lesions in bladder wall and in prostate gland (arrows) that could not be identified before diuretic injection.

the kidneys, ureters, and bladder using diuretic, intravenous saline infusion, and a bladder catheter. Their studies were not focused on bladder cancer, in which radiotracer excretion is a major limitation. In addition, their technique has other problems: It is invasive; retrograde filling of the bladder causes discomfort to the patient and it is not always effective; bladder irrigation increases radiation to the staff and may cause infection; and catheterization and drainage reduce urinary bladder activity but still leave small amounts of concentrated urine that may resemble hypermetabolic lesions, causing even greater difficulty in interpretation (*21*).

In the present study, catheters and postvoid images were not used because these techniques make the CT evaluation of the bladder walls more difficult. A full bladder is required

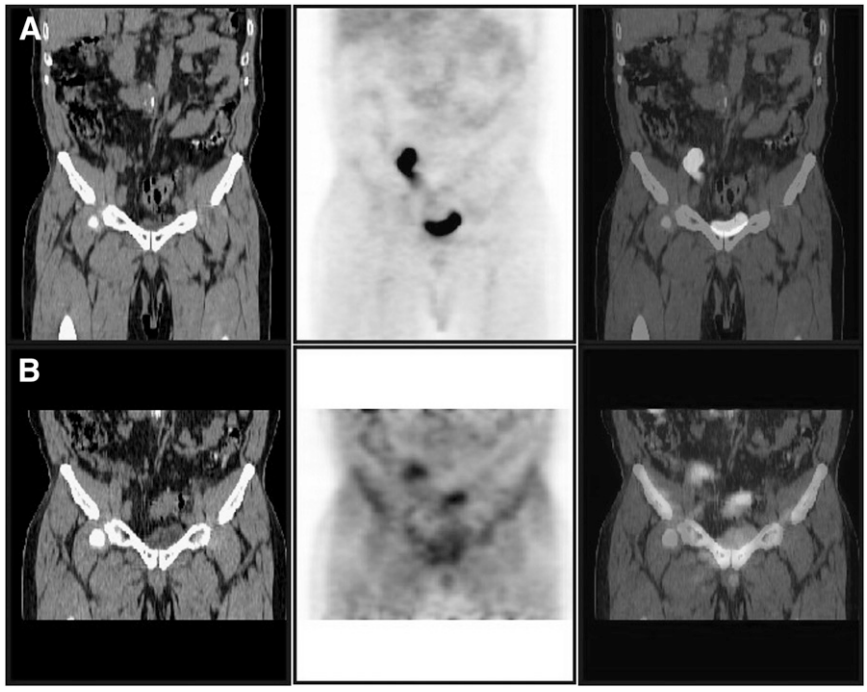

FIGURE 4. A 67-y-old male patient with bladder cancer after cystectomy and urinary diversion. (A) CT, PET, and PET/CT pelvic images (from left to right) show high concentration of ^{18}F-FDG in neobladder. (B) Delayed pelvic images after intravenous furosemide and oral hydration show mild tracer washout.

to avoid artifactual thickening of the walls, and bladder catheterization and continuous irrigation are too invasive for routine use.

Most investigators have obtained poor results when injecting a diuretic shortly before image acquisition. The increased diuresis at this time cannot dilute the urine because there is still a high concentration of ^{18}F-FDG in the blood. The optimal time to inject furosemide is key to obtaining a satisfactory urinary dilution.

In the present study, furosemide was injected at least 2 h after radiotracer injection, providing excellent urinary radiotracer washout. Bladder activity was reduced to background levels in all bladder-preserved patients. This result could not be obtained in patients with cystectomy because urinary diversions showed higher residual activities. Increased volumetric capacity of bladder diversions led to a slow washout of pooled urinary ^{18}F-FDG and, therefore, larger residual urinary volumes. Perhaps a higher dose of furosemide and even more delayed images and larger hydration volumes could overcome this limitation. However, this is not a critical limitation in the evaluation of these patients because recurrence is extremely rare in the bladder diversion walls (*28,29*).

Kamel et al. have recently shown the potential of PET images to detect abdominopelvic malignancies (including 12 bladder lesions) after furosemide and parenteral saline infusion (*30*). However, to our knowledge, the present study is the first to evaluate the usefulness of delayed pelvic images after diuretic administration and oral hydration with ^{18}F-FDG PET/CT in bladder cancer patients. PET images alone were not compared with PET/CT or CT alone. CT images could detect bladder wall thickening and ruled out known pitfalls such as bladder wall diverticulum and urinary leaks. Focally increased ^{18}F-FDG uptake in the pelvis revealed by delayed PET images alone after furosemide could be in the bladder wall or in lymph nodes close to the bladder as well. PET/CT images were of great importance to precisely locate pelvic hypermetabolic lesions.

As a metabolic and anatomic diagnostic tool, PET/CT with ^{18}F-FDG has the ability to overcome the limitations of stand-alone PET and conventional imaging modalities leading to changes in patient management (*10*). Our results show that delayed ^{18}F-FDG PET/CT images after diuretic and oral hydration can detect hypermetabolic lesions in the bladder walls with high-quality images.

Besides the improvement in the detection of bladder wall cancer, delayed pelvic images after furosemide and oral hydration also helped to detect 2 lymph nodes close to the bladder and 1 prostate invasion. These lesions would otherwise be missed. However, the small number of patients with such lesions does not allow more advanced conclusions.

Because of the small number of patients included in this study, further work with this technique is necessary to assess the role of PET/CT in the follow-up of bladder cancer patients and to determine whether there is a relationship between histology grading and SUV. Additional investigations are necessary to evaluate the influence of inflammatory reactions after cystoscopic procedures as possible causes of false-positive results and to determine whether intravesical chemotherapy agents can cause false-negative results.

CONCLUSION

These preliminary results in a small number of patients demonstrated that PET/CT images after furosemide and oral hydration were able to overcome the difficulties posed by the urinary excretion of ^{18}F-FDG. Detection of locally recurrent or residual bladder tumors can be dramatically improved. Up to 54% of patients without cystectomy had more accurate local staging. Potential applications of this technique include patients with other pelvic malignancies such as uterine, ovarian, and colorectal cancers.

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