
Forced Diuresis Improves the Diagnostic Accuracy of ^{18}F -FDG PET in Abdominopelvic Malignancies

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Our aim was to evaluate the role of forced diuresis in improving the diagnostic accuracy of abdominopelvic ^{18}F -FDG PET.

Methods: Thirty-two patients were enrolled. Besides the presence of known intravesical tumors or undefined renal lesions on the initial PET scan, the inclusion criterion was the appearance of indeterminate or equivocal ^{18}F -FDG foci that extended along the course of the urinary tract and could not confidently be separated from urinary activity. For each patient, a second abdominopelvic PET study was performed after intravenous injection of 0.5 mg of furosemide per kilogram of body weight (maximum, 40 mg) coupled with parenteral infusion of physiologic saline. **Results:** Forced diuresis coupled with parenteral hydration eliminated any significant ^{18}F -FDG activity from the lower urinary tract in 31 (97%) of 32 patients after the bladder had been voided 3 successive times. Twelve intravesical lesions were visualized with outstanding clarity, whereas radiologic suspicion of locally recurrent bladder tumors was ruled out in 3 patients. Among 14 indeterminate or equivocal extravesical foci, 7 were deemed of no clinical value because they disappeared after furosemide challenge, whereas 7 persisting foci were proven to be true-positive PET findings. The performance of ^{18}F -FDG PET in characterizing 3 renal-space-occupying lesions could not be improved by our protocol. **Conclusion:** Furosemide challenge has the potential to noninvasively resolve the inherent ^{18}F -FDG contrast handicap in the lower urinary tract.

Key Words: ^{18}F -FDG PET/CT; forced diuresis; bladder cancer

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PET with the glucose analog ^{18}F -FDG has an increasing role in evaluating many malignant disorders that arise from or extend to the abdomen and pelvis (1). However, incidental and nonspecific ^{18}F -FDG accumulation in the gastrointestinal tract and urinary tracer activity may compromise the accuracy of abdominopelvic PET. With the recent introduction of integrated PET/CT systems, the concomitantly

acquired CT data have offered an anatomic reference frame for ^{18}F -FDG PET, and the PET/CT technique has improved the overall accuracy of data interpretation in the gastrointestinal tract (1,2). Physiologic ^{18}F -FDG activity in the urine can still be an interpretive challenge despite the remarkable improvement with PET/CT. High levels of ^{18}F -FDG activity in urine can mask lower levels of abnormal activity in neighboring structures such as the kidney and urinary bladder (3). Furthermore, potential stagnation of excreted ^{18}F -FDG in the ureters can occasionally be mistaken for active tumor foci (4). In an attempt to overcome these limitations, some authors have advocated retrograde irrigation of the urinary bladder using saline irrigant and a Foley catheter either before or during PET data acquisition (5,6). This technique, albeit proven to be of marginal benefit in evaluating tumors that originate from the urinary bladder, may also result in considerable morbidity to the patient, besides unnecessarily exposing the PET personnel to radiation (7). Forced diuresis coupled with parenteral hydration, in contrast, is a safe and well-tolerated method that enhances urinary flux and allows rapid evacuation of the urinary bladder (8,9).

On the basis of this background, we hypothesized that direct comparison of pre- and postdiuretic PET may allow the discrimination of physiologic from pathologic ^{18}F -FDG signals in selected patients with indeterminate or equivocal abdominopelvic findings. For that purpose, we prospectively studied a cohort of oncology patients who underwent ^{18}F -FDG PET for different diagnostic purposes, including primary staging and restaging of bladder cancer.

MATERIALS AND METHODS

From February 2004 to November 2005, a total of 32 patients (23 men and 9 women; mean age, 66 y; age range, 35–79 y) were enrolled in the study after having given written informed consent. Indications for ^{18}F -FDG PET were initial staging or restaging of bladder cancer ($n = 14$), gynecologic tumors ($n = 4$), gastrointestinal tumors ($n = 3$), lymphoma ($n = 2$), lung cancer ($n = 2$, of whom 1 had previously treated prostate cancer), head and neck cancer ($n = 1$), melanoma ($n = 1$), poorly differentiated prostate cancer ($n = 1$), and testicular cancer ($n = 1$). Additionally, 3 patients

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were examined to characterize a renal-space-occupying lesion ($n = 2$) or for initial staging of renal cell carcinoma ($n = 1$).

Inclusion and Exclusion Criteria

The primary inclusion criteria were the presence of known intravesical tumors or undefined renal lesions on the initial PET scan and the appearance of indeterminate or equivocal ^{18}F -FDG-accumulating lesions along or near the course of the urinary tract or in the renal parenchyma. Indeterminate or equivocal foci were defined as those that could not confidently be identified as of urinary or tumor origin on prediuretic PET or that had no frankly correlating morphologic finding on a recent cross-sectional imaging study. Patients with known cardiac decompensation or obstructive uropathy were excluded from the study.

PET and PET/CT Protocols

The patients were asked to fast for at least 6 h (mean \pm SD, 11 ± 4 h) before undergoing the ^{18}F -FDG PET examination. They received an intravenous injection of 5.25 MBq of ^{18}F -FDG per kilogram of body weight and rested for 45–70 min (mean, 57 ± 11 min) to allow uptake of ^{18}F -FDG by the organs and tumor. During the uptake phase, patients were asked to drink water (500–1,000 mL) and to void the bladder frequently to favor urinary excretion and minimize exposure to radiation. At 50–75 min after injection of the ^{18}F -FDG, a static whole-body emission PET or PET/CT scan from the pelvic floor to the head was initiated. The data for 24 patient studies were acquired using an Advance NXi PET scanner (GE Healthcare) as previously described (10). Starting in March 2005, all imaging and data acquisitions were performed with a combined PET/CT in-line device (Discovery LS; GE Healthcare). Eight patients were examined in this way. The acquisition parameters for CT are described in detail elsewhere (1). For postdiuretic PET, both the emission and the transmission times were kept the same as for the prediuretic studies. Similarly, the emission scan time for PET/CT was kept unchanged in the 2 acquisitions, whereas a low CT tube current (40 mA) was intentionally applied for attenuation correction in the postdiuretic PET/CT study to reduce the patient's radiation burden.

Forced-Diuresis Protocol

Immediately after the initial PET or PET/CT scan, each eligible patient received 0.5 mg of furosemide per kilogram of body weight (maximum, 40 mg) followed by infusion of 500 mL of physiologic saline through an intravenous line. During the saline infusion, which lasted 25–30 min, the patients were also encouraged to drink 2 cups (400 mL) of water. Arterial blood pressure was monitored every 10 min, and the last value was obtained just before the second acquisition began. For each postdiuretic PET or PET/CT study, 2 or 3 abdominopelvic cradle positions were acquired directly after the last voiding of the bladder. The length of the second acquisition depended on the patient's clinical history or the prediuretic PET findings.

Evaluation of PET Images

Pathologic ^{18}F -FDG accumulation was identified by tracer uptake exceeding that of the normal hepatic parenchyma. A consensus reading of all PET examinations was done by 2 board-certified nuclear medicine physicians who had full access to the patients' history, the results of other imaging studies, and the results of histopathologic staging (if available). All PET/CT examinations were interpreted by at least 1 board-certified nuclear medicine physician and 1 board-certified radiologist.

RESULTS

Forced diuresis coupled with parenteral hydration eliminated any significant ^{18}F -FDG activity from the urinary bladder and both ureters in 31 (97%) of 32 patients. Voiding of the bladder 3 successive times was sufficient to reduce the urinary activity to a background level without the need for a catheter to evacuate or irrigate the bladder (Figs. 1–6). The mean postdiuretic maximum standardized uptake value (SUV) of the bladder was 2.2 ± 0.5 , whereas the mean prediuretic value was 18.9 ± 15 ($P < 0.0001$, paired t test). One patient with chronic renal insufficiency (pre-PET serum creatinine, 115 $\mu\text{mol/L}$; normal value, 44–106 $\mu\text{mol/L}$) revealed significant residual activity in his bladder (postdiuretic maximum SUV, 3.9) despite a protocol of complete diuresis coupled with hydration and 3 spontaneous voidings of the bladder. Furthermore, in 9 (60%) of 15 patients who had their kidneys within the field of view of the second acquisition, a background activity level of the renal parenchyma was not reached. The whole study group has tolerated the postdiuretic PET (14–21 min) or PET/CT (9–13 min) acquisition without an urgent need to void the bladder. In no patient did any untoward effect develop in the form of hypotension, allergic reaction, or fluid overload.

Patients with Intravesical Lesions

Nine primary and 2 locally recurrent bladder tumors were visualized with outstanding clarity on the postdiuretic PET or PET/CT images (Figs. 1 and 2). All 11 of these lesions were confirmed histopathologically (papillary [$n = 5$], transitional [$n = 4$], and sarcomatoid [$n = 2$] carcinoma).

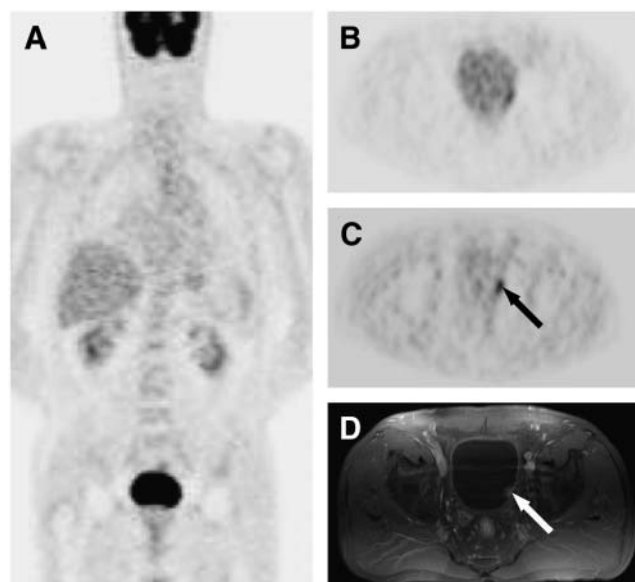


FIGURE 1. A 69-y-old man with papillary bladder cancer. (A) Coronal prediuretic ^{18}F -FDG PET image shows complete masking of primary tumor by urinary activity. (B) Transaxial postdiuretic ^{18}F -FDG PET image after 2 voidings of urinary bladder shows equivocal finding. (C and D) Transaxial postdiuretic ^{18}F -FDG PET after 3 voidings (C) and correlative MRI (D) reveal T1 tumor in left lateral wall of bladder (arrows).



FIGURE 2. Transaxial postdiuretic ^{18}F -FDG PET (A) and correlative transaxial CT (B) and PET/CT (C) images of 71-y-old man show ^{18}F -FDG-avid T2 sarcomatoid carcinoma of bladder after residual urinary activity has been discarded (arrows).

The postdiuretic maximum SUV of these lesions ranged from 3.2 to 25 (mean, 9.4). Furthermore, 1 poorly differentiated adenocarcinoma of the prostate that invaded the bladder base was clearly visualized after furosemide challenge (Fig. 3). Additionally, 3 patients with a radiologic suspicion of recurrent bladder cancer after chemotherapy ($n = 2$) or radiotherapy ($n = 1$) did not show any pathologic ^{18}F -FDG accumulation within their empty bladders (Fig. 4). True-negative ^{18}F -FDG PET results in these 3 patients were confirmed by clinical and radiologic follow-up (range, 7–20 mo; mean, 13 mo).

Patients with Extravesical Lesions

In 7 patients examined by ^{18}F -FDG PET, 6 indeterminate hot spots that mimicked retroperitoneal lymph node metastases ($n = 4$), a previously enucleated kidney metastasis ($n = 1$), or local recurrence of prostate cancer ($n = 1$) were deemed of urinary origin because they disappeared after forced diuresis, whereas 1 indeterminate hot spot corresponded to a histologically proven advanced rectosigmoid adenoma that stacked to the posterior bladder wall on the prediuretic PET images. In another patient, with previously treated rectosigmoid adenocarcinoma, an indeterminate focal hot spot was seen along the course of the sigmoid colon just beyond the bladder roof. Despite the availability of PET/CT in that patient, it was quite challenging to refer this hot spot to either the sigmoid colon or the distal part of the left ureter, where a reimplantation had recently been performed (Fig. 5). After application of forced diuresis, the suspicion of recurrence was confidently ruled out by disappearance of the indeterminate hot spot.

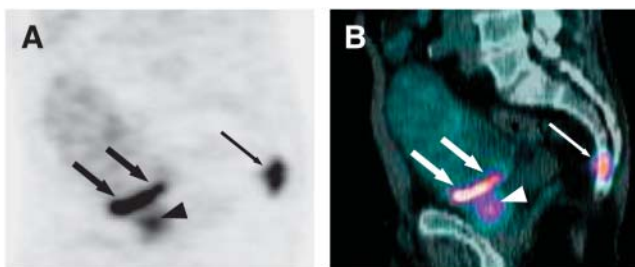


FIGURE 3. Sagittal ^{18}F -FDG PET (A) and correlative PET/CT (B) images of 73-y-old man after furosemide challenge show poorly differentiated adenocarcinoma of prostate (arrowheads) that invades bladder base (large arrows) and metastasizes to sacrum (small arrows).

Six equivocal ^{18}F -FDG PET findings, in 6 patients, were unmasked on the postdiuretic scan. The final diagnoses in these patients were recurrent uterine cervical cancer ($n = 2$), recurrent endometrial carcinoma ($n = 2$), and retroperitoneal lymph node involvement by lymphoma ($n = 1$) or by recurrent colorectal carcinoma ($n = 1$). These 6 lesions were verified by histologic examination ($n = 4$) or by clinical and radiologic follow-up ($n = 2$). Interestingly, 2 (50%) of the 4 cases of recurrent cervical or endometrial carcinoma were small lesions (~ 1 cm) confined to the vaginal stump. These 2 lesions were liable to be easily missed on the initial prediuretic PET scan because they were superimposed by the adjacent urinary activity (Figs. 6A and 6B). However, because the clinical probability of local tumor recurrence was elevated for both of them (1 patient presented with vaginal spotting and the other with a per vaginum cytologic analysis in favor of adenocarcinoma), furosemide challenge was undertaken to unmask any potential disease recurrence. The diagnostic value of ^{18}F -FDG PET in characterizing renal-space-occupying lesions could not be improved by our protocol. In fact, one clear cell carcinoma was indistinguishable from the renal parenchyma on both the prediuretic and the postdiuretic examinations, and another appeared as a photopenic area as well as a renal cyst (Bosniak category II).

DISCUSSION

The high accuracy of ^{18}F -FDG PET in detecting many malignant and inflammatory disorders of the abdomen and pelvis may be reduced by physiologic ^{18}F -FDG excretion along the urinary system. Continuous efforts have been devoted to overcoming this limitation inherent in ^{18}F -FDG PET. For instance, Kosuda et al. (5) evaluated 12 patients with suspected recurrent or residual bladder cancer. In 9 of them, retrograde irrigation of the urinary bladder was applied. Although a remarkable reduction of urinary activity was observed, a background level was never reached in any patient, ending in 4 false-negative intravesical lesions that were masked by residual urinary activity. Likewise, in another prospective study, Koyama et al. (6) observed that at least 8 (20%) of 41 studied patients failed to eliminate all ^{18}F -FDG activity from the urinary tract despite continuous bladder irrigation using prewarmed physiologic saline solution. These initial trials imply that an ideal approach to

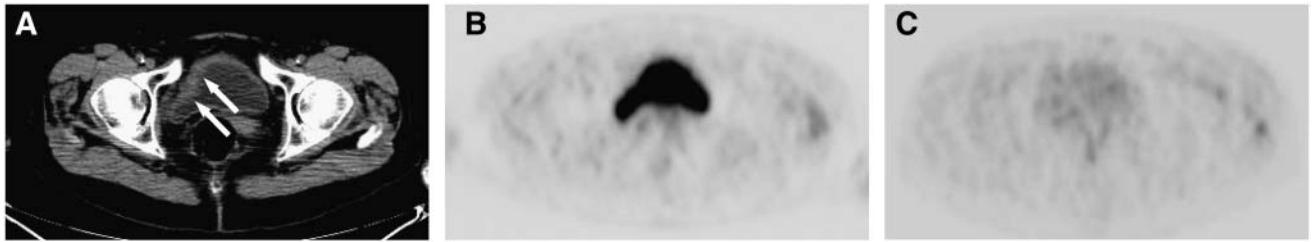


FIGURE 4. (A) Transaxial CT image of 68-y-old woman with bladder lymphoma shows residual wall thickening after chemotherapy (arrows). (B and C) Transaxial ^{18}F -FDG PET images of bladder before (B) and after (C) furosemide challenge show significant residual urinary activity and complete, postdiuretic, washout with no evidence of active tumor manifestation. True-negative postdiuretic PET finding was confirmed by clinical and radiologic follow-up.

overcoming the aforementioned limitations must consider eliminating residual ^{18}F -FDG activity from the entire urinary tract rather than from only its distal partition, at least to avoid potential spillover from any proximal activity.

In the present study, we observed that a furosemide dose of 0.5 mg/kg (maximum, 40 mg) followed by parenteral infusion of 500 mL of physiologic saline over 25–30 min successfully eliminated any significant ^{18}F -FDG activity from the bladder and both ureters (Figs. 1–6). Except for 1 patient with chronic renal insufficiency, a background activity level could be obtained in the lower urinary tract of 31 (97%) of 32 patients after they had voided their urinary bladder 3 successive times. Our results agree with those obtained from a recent study in which the application of diuretics significantly reduced residual ^{18}F -FDG activity in the bladder (11). However, in 9 (60%) of 15 patients whose kidneys were within the field of view of postdiuretic PET, renal activity did not reach a background level, potentially because of physiologic uptake of ^{18}F -FDG by the renal tubular epithelium (12,13). Given the known modest avidity of some renal cell carcinomas to ^{18}F -FDG (14,15), our protocol is not likely to further improve the performance of PET in characterizing renal-space-occupying lesions.

Since the introduction of PET, urinary ^{18}F -FDG excretion has not only veiled the visualization of primary bladder cancer but also aborted the opportunities of ^{18}F -FDG PET in the staging of this increasingly diagnosed tumor type (16). In the present series, we clearly visualized 9 primary and 2 recurrent bladder tumors after discarding the residual

^{18}F -FDG urinary activity (Figs. 1 and 2). The high postdiuretic ^{18}F -FDG uptake of these lesions (mean maximum SUV, 9.4; range, 3.2–25) portends an augmented rate of glycolysis. Furthermore, local treatment failure could confidently be ruled out in 3 patients who presented with equivocal posttherapy radiologic findings in the bladder wall (Fig. 4). Given the currently insufficient, albeit encouraging, data in the literature (17–19), our promising results are calling for larger prospective studies to further explore the real role of ^{18}F -FDG PET in the management of patients with bladder cancer.

For the second patient group, which was reexamined because of indeterminate or equivocal extravesical lesions, 7 suggestive foci were deemed of no clinical significance because they were washed away from the second acquisition by virtue of forced diuresis. This effect can certainly alleviate the need for a further diagnostic work-up to prove or disprove such types of ^{18}F -FDG PET or PET/CT findings (Fig. 5). Among the remaining 7 foci, which persisted, 2 corresponded to recurrent cervical or endometrial carcinoma in the vaginal stump that had been superimposed on prediuretic PET by urinary activity. These 2 lesions might have been missed if forced diuresis had not been applied (Fig. 6).

Aside from the fact that PET/CT can overcome most of these extravesical pitfalls, especially those that may be confused with adrenal metastasis or retroperitoneal lymph node metastases (4,20), our protocol remains mandatory for patients with bladder cancer and patients with gynecologic



FIGURE 5. (A–C) Coronal and sagittal ^{18}F -FDG PET (A and B) and sagittal PET/CT (C) images of 67-y-old man previously treated for rectosigmoid cancer show focal hot spot along sigmoid colon that mimics local recurrence (arrows). (D) Postdiuretic coronal PET image shows disappearance of this factitious hot spot, suggesting urinary origin. (E) Correlative intravenous urography reveals medially displaced left ureterovesical junction after recent reimplantation surgery of left ureter (arrowheads).

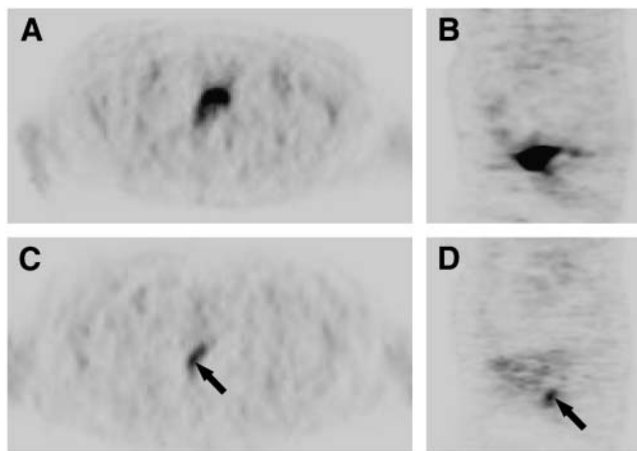


FIGURE 6. (A and B) Transaxial (A) and sagittal (B) prediuretic ^{18}F -FDG PET images of 67-y-old woman previously treated for uterine adenocarcinoma show no convincing evidence of local disease recurrence. (C and D) Transaxial (C) and sagittal (D) postdiuretic ^{18}F -FDG PET images display sharply delineated focal hot spot (arrows) that corresponds to disease recurrence in vaginal stump, as confirmed by histologic analysis.

tumors who present with negative CT or MRI findings despite a high clinical or laboratory suspicion of local recurrence (Fig. 6). Furthermore, given the promising role of ^{18}F -choline in the detection of recurrent prostate cancer, furosemide challenge may become an integral step in identifying local tumor recurrence that can be masked by excreted ^{18}F -choline in the urinary bladder (21).

A limitation of the present protocol may be the additional time needed for the second postdiuretic acquisition. However, with the recent trend to shorten the emission scan, and with the replacement of rotating ^{68}Ge sources in conventional PET scanners by high-speed CT in hybrid systems, the overall scan time can be significantly reduced (~50%) (22) without a significant increment in the patient's radiation burden, provided that low-dose CT is applied for attenuation correction in the second acquisition.

CONCLUSION

Forced diuresis coupled with parenteral hydration is a suitable tool for defining many confounding ^{18}F -FDG-avid lesions that stem from the lower urinary tract or its neighborhood. Except for patients with inadequate renal function, 3 successive voidings of the urinary bladder are sufficient to bring urinary activity to a background level. This practical approach, because it can noninvasively resolve the inherent ^{18}F -FDG contrast handicap in the bladder and both ureters, may have a major positive impact on the overall diagnostic accuracy of abdominopelvic PET and PET/CT.

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