Original Article

Detecting primary bladder cancer using delayed ^{18}F-2-fluoro-2-deoxy-D-glucose-positron emission tomography/computed tomography imaging after forced diuresis

Laura S Mertens, Annemarie Fioole-Bruining[1], Erik Vegt[2], Wouter V Vogel[2], Bas WG van Rhijn, Simon Horenblas

Departments of Urology, [1]Radiology, and [2]Nuclear Medicine, The Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands

ABSTRACT

Objective: The aim of this study was to evaluate the use of delayed pelvic ^{18}F-2-fluoro-2-deoxy-D-glucose-positron emission tomography combined with the computed tomography (FDG-PET/CT) imaging, according to a standardized protocol including, pre-hydration and forced diuresis, for the detection of primary bladder cancer. **Materials and Methods:** We evaluated 38 consecutive patients with primary cT1-4 bladder cancer. They underwent standard FDG-PET/CT followed by delayed pelvic imaging after administration of 20 mg furosemide intravenously and extra oral water intake of 0.5 L. Two observers, blinded for patient data, scored both image sets for tumor visibility using a 3-point ordinal scale: (1) negative; (2) indeterminate; (3) positive. FDG-PET/CT findings were compared with histopathology and/or follow-up imaging. **Results:** The procedure was completed successfully in 37/38 patients and the reference standard revealed a bladder tumor in 26/37 patients. Delayed PET/CT images showed reduction of urinary bladder activity to (near) background levels in 17 of 37 cases (45.9%). Standard PET/CT detected hyper-metabolic bladder lesions in 15/37 patients (40.5%) of which 8 were indeterminate. Delayed FDG-PET/CT showed hyper-metabolic bladder lesions in 30/37 (81.1%) patients, of which 5 were indeterminate. When indeterminate lesions were considered positive, the sensitivity of standard and delayed PET/CT was 46% versus 88%, respectively. The specificity was 72% versus 36%. When indeterminate lesions were considered negative, the sensitivity of standard and delayed PET/CT was 23% and 85%. The specificity was 93% versus 73%. **Conclusions:** Our data suggest that delayed pelvic FDG-PET/CT imaging after forced detects more primary bladder tumors than standard FDG-PET/CT protocols. However, indeterminate bladder lesions on delayed PET/CT remain a problem and should be interpreted cautiously in order to avoid false positive results.

Keywords: Diagnostic imaging, fluorodeoxyglucose F18, positron emission tomography and computed tomography, urinary bladder neoplasms

INTRODUCTION

High-uptake of ^{18}F-2-fluoro-2-deoxy-D-glucose (FDG) in urothelial cancer of the bladder was already reported in 1991.[1] Nowadays, FDG-positron emission tomography combined with computed tomography (FDG-PET/CT) is an established standard for pre-operative staging and detecting metastatic lesions of bladder cancer.[2-4] The visualization of primary bladder tumors with FDG-PET/CT, however, has remained problematic. FDG is excreted into the urine, causing high-FDG activity in the bladder. Standard FDG-PET/CT protocols are therefore, not useful for imaging or response evaluation of bladder tumors.

Elimination of accumulated FDG from the urinary system is essential to overcome this limitation of FDG-PET/CT. Several strategies have been proposed to overcome this limitation.[5-10] The most promising strategy seems to be delayed pelvic FDG-PET/CT imaging after adequate hydration and voiding. A limited number of small studies have assessed the role of delayed PET/CT in the detection of bladder cancer.

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Address for correspondence:
Prof. Dr. S Horenblas, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands. E-mail: s.horenblas@nki.nl

However, studies lacked standardization of the technique and the majority of patients had recurrent bladder cancer after previous cystectomy.

The purpose of this study was to evaluate the use of delayed pelvic FDG-PET/CT imaging, according to a standardized protocol including pre-hydration and forced diuresis, for the detection of primary bladder cancer.

MATERIALS AND METHODS

Patients

All patients with primary bladder cancer referred to our hospital from June 2011 to January 2012 for whole-body FDG-PET/CT were retrospectively included. All had previously undergone transurethral resection (TUR) of the tumor for confirmation of the diagnosis. The patients were referred to the bladder cancer out-patient clinic of our hospital for staging and definitive treatment (radical cystectomy, brachytherapy, neoadjuvant chemotherapy, irradiation or a combination of therapies). Baseline characteristics of the patients are summarized in Table 1.

PET/CT protocol

Patients first underwent a standard FDG-PET/CT scan, including oral pre-hydration and fasting for at least 6 h before the FDG-PET/CT. Blood glucose was measured to ensure glucose blood levels below 10 mmol/L. Subsequently, 190-240 MBq FDG was intravenously administered. One hour after the FDG injection, FDG-PET/CT imaging was performed from the head to the upper thigh. Additional delayed pelvic PET/CT imaging was performed according to the following protocol: Directly after the standard PET/CT scan (approximately 90 min after injection of FDG), the patients were injected with 20 mg of furosemide intravenously. They were also instructed to drink an additional 500 mL of water and to void frequently. Delayed pelvic images were acquired 2.5-3.0 h after the injection of FDG. All PET acquisitions were performed using a Gemini TF-II PET/CT scanner (Philips, Amsterdam, the Netherlands), and were combined with low dose CT for anatomical correlation and attenuation correction. The PET acquisitions were performed with the patient in supine position with the arms above the head. The delayed phase PET/CT acquisitions covered a range of 2 bed positions centered at the location of the bladder.

Table 1: Baseline patient characteristics

Patients	*n*=38
Age, years	
Mean	63
Range	42-83
Gender	
Male	31
Female	6
Histological type	
Urothelial carcinoma	34
Squamous cell carcinoma	2
Small cell carcinoma	2
CT-stage	
A	2
1	9
2	13
3	7
4	6
cis	1
Grade	
3	34

CT: Computed tomography

PET/CT interpretation

Both image sets were reviewed by two observers blinded for patient data. They evaluated the presence of primary bladder cancer using a 3-point ordinal scale: (1) negative; (2) indeterminate; (3) positive. A positive lesion was defined as a FDG-avid focus in the bladder, in a non-physiological distribution. An indeterminate lesion was defined as a FDG-avid focus in the bladder, in which it could not be distinguished whether it was physiological or non-physiological. A negative lesion was defined as no suspect FDG-avid focus in the bladder. Discrepancies between observers were resolved by consensus. Lesions classified as (2) or (3) were quantitatively evaluated by determination of maximum standardized uptake values (SUV_{max}), and the quantifiability with a $SUV_{50\%}$ isocontour of these lesions.

Reference standard

Both the standard and the delayed PET/CT findings were compared with histopathological studies and/or follow up imaging. If histopathology based on radical cystectomy was obtained after FDG-PET/CT in patients who had not received neoadjuvant chemotherapy ($n = 14$), this was used as the reference standard. In all other patients ($n = 24$), follow up imaging (cystoscopy and contrast-enhanced [CE] CT and/or magnetic resonance imaging [MRI]) was used. The minimum follow up period was 6 months. Indeterminate and inaccurate findings on delayed pelvic FDG-PET/CT images were retrospectively reviewed in order to find a specific cause.

Statistics

We dichotomized the scored discrete categories 1-3 (cut-off between category 1: Not visible = no tumor; vs. 2-3: Visible = tumor) for comparison with the reference standard. We calculated sensitivity and specificity with corresponding 95% confidence intervals (CI-95%) for both acquisitions. We repeated the analysis after redefining indeterminate lesions as being no tumor. Sensitivity and specificity were compared using Fisher's exact test. A 1-sided $P < 0.05$ was considered statistically significant. Paired proportions of correct findings were compared using the McNemar test. A two-sided $P < 0.05$ was considered a significant difference between the two proportions. Statistical analysis was performed by using SPSS software version 17.0 (SPSS Inc., Chicago, Illinois).

RESULTS

The procedure was completed successfully in 37/38 patients. In one patient the procedure failed: At standard imaging the bladder did not contain urine. This patient had a large cT4 bladder

tumor which almost covered the entire bladder and obstructed the ureteral ostia causing severe bilateral hydroureteronephrosis. A percutaneous nephrostomy and a transurethral catheter were placed. We excluded this patient from our accuracy analysis. Delayed images after furosemide and oral hydration showed reduction of urinary bladder activity to (near) background levels in 17 of 37 remaining cases (46%). At delayed imaging there was a significantly lower mean bladder SUV_{max} (7.5 ± 4.8 vs. 17.3 ± 11.0, $P < 0.001$) and mean bladder SUV_{mean} (5.9 ± 4.8 vs. 15.2 ± 4.0, $P = 0.001$) than at standard imaging. Standard FDG-PET/CT detected hypermetabolic bladder lesions in 15 patients (40.5%). Delayed FDG-PET/CT detected hypermetabolic bladder lesions in 30 patients (81.1%).

Accuracy for the presence of tumor

The reference standard revealed a bladder tumor in 26/37 cases. The remaining 11 patients were considered to be pathologically or clinically free of primary bladder tumor (total removal of tumor by TUR). First, we calculated the diagnostic values with indeterminate lesions considered positive. Table 2 displays estimates of sensitivity, specificity and predictive values of standard and delayed FDG-PET/CT. Delayed imaging reduced the number of false negative results (14 vs. 3), but yielded 4 additional false positive findings (3 vs. 7). The difference in proportion of correct diagnoses tended towards significance ($P = 0.059$). Figure 1 shows a good reduction of FDG-activity in the bladder at delayed images, and a true positive result. We repeated the analysis after redefining indeterminate lesions as being no tumor [Table 3]. In this setting, delayed imaging reduced the number of false negative results much more (20 vs. 4), but yielded 2 additional false positive findings (1 vs. 3). The proportion of correct diagnosis was significantly higher with delayed imaging than that with standard imaging ($P = 0.001$). The proportion of correct diagnosis was higher with indeterminate lesions considered negative, but this difference did not reach statistical significance ($P = 0.240$).

Quantification of metabolism

At standard imaging, 4/15 tumor borders (26.7%) could be quantitatively evaluated and delineated with $SUV_{50\%}$ isocontour. At delayed imaging 20/30 tumor borders (66.7%) could be delineated with $SUV_{50\%}$ isocontour.

Indeterminate and inaccurate findings

Eight of 15 visible lesions (53.3%) at standard imaging were indeterminate. After furosemide and oral hydration, five of

Table 2: Sensitivity and specificity of standard and delayed FDG-PET/CT for detecting residual bladder cancer after transurethral resection (dichotomized scored discrete categories; category transurethral resection 1 [no tumor: FDG-PET/CT negative] versus category 2-3 [uncertain tumor or definite tumor: FDG-PET/CT positive]), compared to reference standard. There was a statistically significant difference in sensitivity between standard and delayed imaging (*P*<0.001)

	Standard estimated value (95% CI)	Delayed estimated value (95% CI)
Sensitivity	0.46 (0.27-0.66)	0.88 (0.69-0.97)
Specificity	0.72 (0.39-0.93)	0.36 (0.12-0.68)
PPV	0.80 (0.51-0.95)	0.77 (0.57-0.89)
NPV	0.36 (0.18-0.59)	0.57 (0.20-0.88)

PPV: Positive predictive value, NPV: Negative predictive value, CI: Confidence interval, FDG-PET/CT: F-2-fluoro-2-deoxy-D-glucose-positron emission tomography combined with the computed tomography

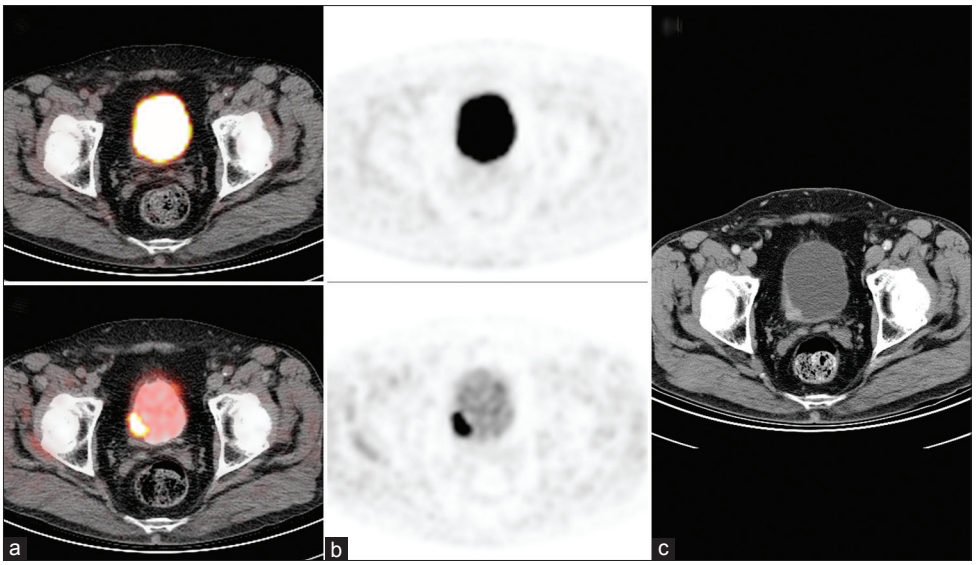

Figure 1: An 83-year-old male with a solitary cT2N0M0 G3 UCC of the bl adder. ^{18}F-2-fluoro-2-deoxy-D-glucose-positron emission tomography combined with computed tomography (FDG-PET/CT) and FDG-PET (from left to right) images before furosemide, (a) show high FDG activity in the bladder standardized uptake values (SUV_{max} = 22.2). Delayed pelvic images after intravenous furosemide and oral hydration, (b) show good tracer washout in the bladder (SUV_{max} = 5.0). It is clearly possible to identify uptake in the right bladder wall, which can be delineated with 50% isocontour (SUV_{max} = 16.1). CE-CT (c) showed focal wall thickening, corresponding to the intense uptake area on FDG-PET/CT. The tumor was also visualized by routine cystoscopy. The patient was treated with brachytherapy preceded by external radiotherapy because of a solitary cT2N0M0 G3 UCC of the bladder

these indeterminate lesions were clearly visible as bladder tumors, of which four were confirmed by the reference standard and one turned out to be false positive. The three other indeterminate lesions remained indeterminate. Additionally, two other indeterminate lesions became visible at delayed images in patients in whom no bladder tumor was visible at standard images. According to the reference standard, four of the five indeterminate lesions at delayed imaging were negative, one was positive.

The proportion of inaccurate findings at delayed imaging was 10/37. Delayed pelvic FDG-PET/CT yielded seven false positive and three false negative results. False positive results were seen for several reasons or a combination of reasons. In 4/7 false positive results, FDG-PET/CT was performed < 6 weeks after TUR. Histopathology (cystoprostatectomy, TUR or biopsy) showed inflammatory changes in these patients, a well-known cause of increased FDG-uptake [Figure 2]. In three patients, a layer of FDG active urine was present in (a) a TUR

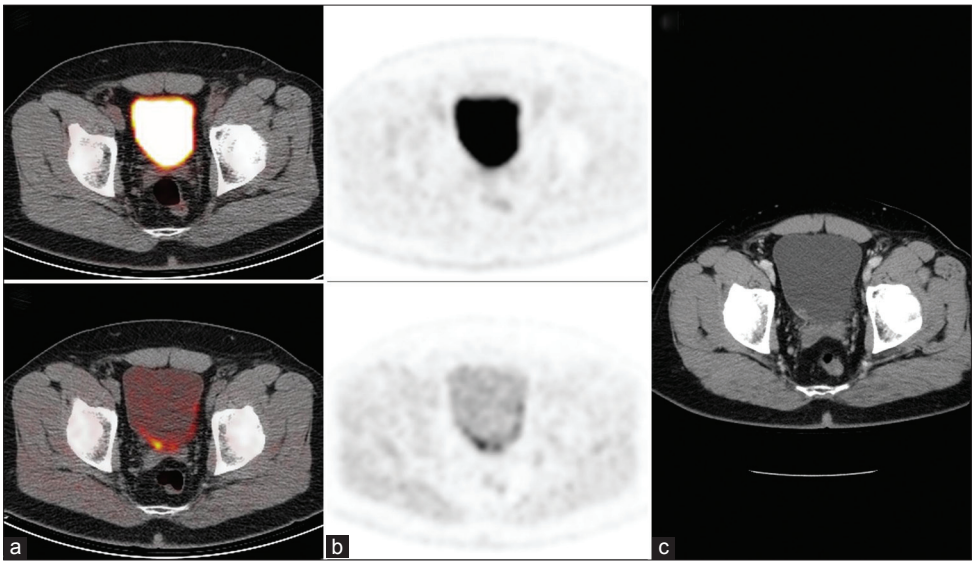

Figure 2: A 59-year-old male with a muscle invasive squamous cell carcinoma in the left dorsal bladder wall, who had a transurethral resection (TUR) and a second TUR. The last TUR was performed 4 weeks prior to ^{18}F-2-fluoro-2-deoxy-D-glucose-positron emission tomography combined with computed tomography (FDG-PET/CT) imaging. Standard FDG-PET/CT and FDG-PET (from left to right) images, (a) show high FDG activity in the bladder (SUV_{max} = 18.7). At delayed pelvic images, (b) FDG-activity in the bladder is reduced to near background levels (SUV_{max} = 3.2). Suspect FDG accumulation in the dorsocaudal wall of the bladder can be identified (SUV_{max} = 8.0). CE-CT, (c) showed focal wall thickening, corresponding to the intense uptake area on FDG-PET/CT. At cystoscopy a widespread area of necrosis was seen, but no active tumor. A cystoprostatectomy was performed. Histopathology of the specimen revealed no residual tumor. Extensive inflammatory changes were found in the area with FDG accumulation. The false-positive area of metabolic activity may be due to inflammation after recent TUR

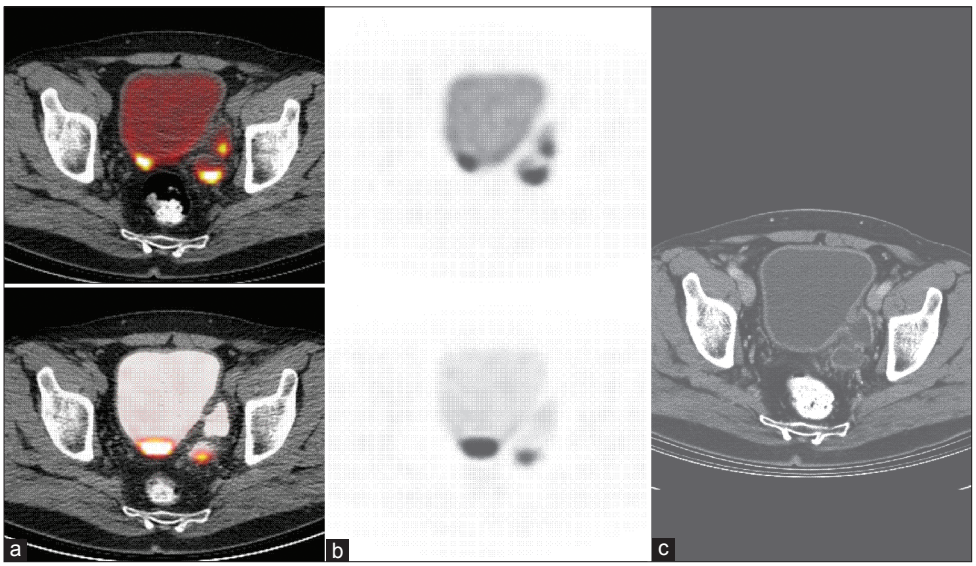

Figure 3: A 64-year-old male who underwent TUR of a papillary T1 tumor in a bladder diverticulum near the ureteral left orifice. Standard FDG-PET/CT and FDG-PET (from left to right) images, (a) show high FDG activity in the bladder (SUV_{max} = 21.8). Delayed pelvic images, (b) show a reduction of FDG-activity (SUV_{max} = 9.7), though not to background levels. Indeterminate FDG accumulation in the dorsal bladder wall and in the diverticula can be identified (SUV_{max} = 86.5). The differential diagnosis includes a (residual) bladder tumor, or a layer of FDG active urine. Contrast enhanced-CT, (c) and follow-up revealed no signs of tumor and/or recurrence. The false-positive area of metabolic activity might be due to insufficient elimination of FDG active urine, mimicking a tumor

Table 3: Estimates of sensitivity, specificity, and predictive values of standard and delayed FDG-PET/CT for residual bladder cancer after transurethral resection detecting bladder tumors (dichotomized scored discrete categories; category 1-2 (no tumor or uncertain tumor: FDG-PET/CT negative) versus category 3 (definite tumor: FDG-PET/CT positive), compared to reference standard. There was again a statistically significant difference in the sensitivity of standard and delayed imaging (*P*<0.001)

	Standard estimated value (95% CI)	Delayed estimated value (95% CI)
Sensitivity	0.23 (0.10-0.44)	0.85 (0.64-0.95)
Specificity	0.91 (0.57-0.99)	0.73 (0.39-0.93)
PPV	0.86 (0.42-0.99)	0.88 (0.68-0.97)
NPV	0.33 (0.18-0.53)	0.67 (0.35-0.89)

PPV: Positive predictive value, NPV: Negative predictive value, CI: Confidence interval, FDG-PET/CT: F-2-fluoro-2-deoxy-D-glucose-positron emission tomography combined with the computed tomography

lesion, (b) a diverticulum of the bladder wall or (c) in the dorsal surface [Figure 3]. In these cases, FDG-active urine was not sufficiently eliminated, mimicking a tumor. Six of the seven false positive results occurred in patients with non-muscle invasive bladder cancer. False negative results were mainly caused by insufficient reduction of FDG-activity in the bladder. When redefining indeterminate lesions as being no tumor, the proportion of inaccurate findings was 7/37.

DISCUSSION

The present study evaluates the use of delayed pelvic FDG-PET/CT imaging, according to a standardized protocol including pre-hydration and forced diuresis, for the detection of primary bladder cancer. Bladder tumors are usually not visible using standard PET/CT due to FDG active urine in the bladder at the time of scanning. Several strategies have been proposed to improve PET/CT imaging of bladder tumors. First, catheter-assisted FDG-PET/CT imaging has been investigated as a possible solution,[11,12] but this is an invasive procedure which does not yield optimal results. Moreover, it increases the exposure of workers to ionizing radiation. Protocols applying diuretics proved to reduce bladder urinary FDG-activity and increase bladder size,[13-15] but could not decrease FDG-activity to background levels. Subsequently, delayed imaging protocols after furosemide administration were proposed as a less invasive alternative for catheter-assisted FDG-PET/CT by Anjos *et al.* who showed 100% sensitivity and specificity for the detection of recurrent bladder tumors.[5] These results were confirmed by two other retrospective studies.[6,10] Delayed pelvic FDG-PET/CT imaging is therefore considered a promising technique in detecting recurrent bladder tumors.

Accordingly, the present study demonstrates that delayed pelvic FDG-PET/CT imaging also has significantly better sensitivity and success of quantification than standard FDG-PET/CT imaging for the detection of primary bladder tumors. However, despite adhering to a standardized protocol, delayed pelvic imaging did not reduce bladder FDG activity to (near) background levels in more than half of the patients. Not all indeterminate lesions could be clarified with the help of delayed imaging: Indeterminate lesions remained present, albeit considerably fewer than reported at standard FDG-PET/CT images, but also additional false-positive lesions were diagnosed on delayed PET/CT.

As illustrated in our series, multiple factors may cause inaccurate results. Homogeneous FDG-active urine in the bladder can hamper tumor recognition, resulting in false negatives. On the other hand, retention of concentrated urine in a diverticulum can cause false positive results. Incorrect or indeterminate results were also obtained for non-muscle invasive tumors after recent TUR. TUR can eradicate tumors completely, particularly non-muscle invasive tumors,[16] whereas inflammatory tissue reactions with enhanced metabolism can cause increased regional FDG-uptake, leading to avidly FDG-active false positive lesions. Since four of the five indeterminate visible lesions were inaccurate, the best accuracy was obtained when we considered indeterminate lesions as being no tumor.

Next to the difference in primary tumor and recurrent disease, other differences between the current study and the existing body of literature need to be discussed. Anjos *et al.* managed to avoid false positive results due to inflammatory reaction after biopsy or TUR by introducing a 3-month time interval between the resection and the FDG-PET/CT scan. When using FDG-PET/CT as a staging modality in potentially curable pre-treatment patients, a 3-month delay is not acceptable. Yang *et al.,* on the other hand, did not use a standardized protocol: Delayed PET/CT imaging was performed 1-3 h after the administration of FDG. If the delayed pelvic images still showed high concentration of FDG, more additional images were performed. These methodological differences may explain why other studies showed more favorable results.

Limitations of the present study are mainly those inherent to its retrospective design. Another potential drawback is the lack of histopathological studies in a subset of patients. Follow-up imaging with CE-CT, MRI, and cystoscopy are not perfect in identifying bladder tumors, particularly following previous biopsy, TUR or intravesical chemotherapy. However, we considered a combination of these imaging modalities and clinical findings during at least 6 months follow-up, as the most appropriate "second-best" reference standard in the absence of histopathology.

The authors acknowledge that interpretation according to a 3-point scale including an "indeterminate" option is subjective and may lead to interobserver variability. In clinical practice, however, it is not always possible to make a clear distinction between positive and a negative lesions, since a SUV cut off value is not applicable in this context. Another strength of this study is the fact that the image sets are evaluated by two observers, blinded for patient data.

A strength of the present study was the standardized protocol used to perform delayed PET/CT imaging. Moreover, this study closely resembled to clinical practice. The setting of the current

study was a bladder cancer outpatient clinic of a tertiary cancer hospital. Patients with proven bladder cancer were referred for further treatment. PET/CT images were obtained for staging bladder cancer–currently the only situation for which there is convincing evidence that PET/CT is of additional value.[2-4] When a PET/CT has to be performed, delayed pelvic imaging can be used as an attempt for baseline imaging of the situation. Whether delayed pelvic PET/CT is really of additional clinical value has yet to be substantiated by larger prospective cohorts.

In conclusion, these data suggest that delayed pelvic FDG-PET/CT imaging after forced detects more primary bladder tumors than standard FDG-PET/CT protocols. However, indeterminate bladder lesions on delayed PET/CT remain a problem and should be interpreted cautiously in order to avoid false positive results.

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