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UROONCOLOGY

Original Article

The influence of post-diuretic late phase imaging in visual and quantitative evaluation of urothelial tumors by F-18 fluorodeoxyglucose positron emission tomography/computed tomography

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ABSTRACT

Objective: Although F-18 fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) is a valuable imaging method in most of the malignant tumors, it is considered to have limited diagnostic ability in urothelial tumors due to high physiologic urine activity. The aim of the present study was to evaluate the effect of post-diuretic late phase imaging to the visual and quantitative evaluation of urothelial tumors in the staging and restaging of the patients.

Material and methods: Two patients with ureter and 40 patients with bladder tumors (6 females and 36 males, mean age: 67.12±8.79 years) who were referred for staging or restaging or treatment response evaluation to the F-18 FDG PET/CT were included in the study. Late phase (at the second hour after FDG injection) images including the renal pelvis and bladder region after the administration of approximately 40 mg furosemide were obtained after standard oncologic F-18 FDG PET/CT imaging. The images were evaluated by visual and quantitative interpretation, and index values were calculated. Paired samples T test was used to decide the significance of the difference between the early and late phase images. A p value <0.05 was considered significant.

Results: The activity accumulation in the primary or recurrent lesions in the bladder or ureter in the early and late phase images was statistically significantly different. Additionally, in 15/41 (37%) patients, the primary tumor in the bladder was only determined in late phase images, and additional lymph node metastases adjacent to the bladder or ureter were only observed in diuretic late phase images in some of the patients. The sensitivity, specificity, and diagnostic accuracy of the PET/CT with this methodology for N staging and M staging were 67%, 78%, and 82% versus 80%, 91%, and 82%, respectively.

Conclusion: Late phase imaging after diuretic administration should be performed in case of non-visualization of primary tumor in the bladder region. The late phase post-diuretic imaging revealed significant improvement in the visual and quantitative diagnostic performance of the FDG PET/CT and has high diagnostic accuracy for the staging of urothelial tumors.

Keywords: Bladder; fluorodeoxyglucose; late; post-diuretic; ureter.

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Introduction

High-grade bladder tumors are more prone to dissemination into the deep layers of the bladder, and these tumors with invasion tend to have occult metastasis at the time of diagnosis in nearly half of the patients.[1,2] The possible metastatic sites are regional and abdominal lymph nodes, lungs, liver, and bones.[3] Cross-sectional imaging modalities, such as computed tomography (CT) or magnetic resonance imaging (MRI), are insufficient in the evaluation of locoregional disease.[2] Transurethral resection (TUR) results are considered the gold standard for bladder tumors.[4] Additionally, F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT has limitations in the primary tumor evaluation of the bladder due to physiological elimination of the FDG. Previous studies consider PET/CT as useless in the primary tumor and local lymph node determination.[5] Previous intentions, such as early diuretic administration, bladder irrigation, and post-void imaging, did not gain sufficient success.[1] However, recent studies with late phase imaging with diuretic administration revealed successful

results in the T staging and regional lymph node evaluation of the bladder tumors.[1] The aim of the present study was to evaluate the effect of late phase diuretic imaging in the locoregional staging and restaging of urothelial tumors by visual and quantitative interpretation of the F-18 FDG PET/CT imaging.

Material and methods

Patients

A total of 42 (6 female and 36 male) patients with a diagnosis of urothelial tumors (bladder tumors in 40 patients and urethral tumors in two patients) were included in the study. The mean age of the patients was 67.12±8.79 years. Patients with a diagnosis of urothelial tumors who were referred from the oncology or urology clinics for staging or restaging purposes were subjected to the standard oncologic F-18 FDG PET/CT study. The images of the patients were evaluated retrospectively by an experienced nuclear medicine physician by visual and quantitative methods, and the early and diuretic late phase images were compared.

Imaging methods

The study was approved by the local ethics committee. Informed consents were obtained from the patients prior to the examination. Lactating and pregnant patients, children, and patients who have special contraindication for the F-18 FDG PET/CT examination were excluded from the study. The patients were prepared for examination with at least 6 h of fasting and decreasing physical effort at least 24 h before the study. A radiopharmaceutical injection was performed (mean 370 MBq (10 mCi), according to body weight) to each patient via venous line 60 min before the imaging while the blood glucose levels were documented to be <200 mg/dL for each patient. The imaging was performed by PET/CT scanner (GE, Discovery PET/CT 610, USA) with additional low-dose CT scan (130 kV, 50 mAs, a pitch of 1.5, a thickness of 5 mm, in 70 cm field of view) for attenuation correction without intravenous contrast administration with oral contrast administration from the skull base to the upper thigh with an acquisition time of 3 min per bed position. After routine imaging, additional images were obtained from the urethral and pelvic regions at the second hour with additional diuretic administration (40 mg lasix from venous line). All the patients were advised to consume at least 1.5 l of water prior to and during the imaging study.

Visual interpretation

Visual interpretation was performed from both early and combined early and late phase imaging. The results were recorded and compared with gold standard follow-up results.

Quantification

The standardized uptake values (SUV_{max}) were obtained from the regions of interests (ROIs) in the bladder wall, regional and distant lymph nodes, and distant metastatic sites (liver or bone) as an oval or round ROI by the automatic program of the workstation (Mac iOs/OsiriX MD).

Index values

The index values were generated from the early and late phase images to evaluate the lesions. The oval or round ROIs were used from the lesion and background (from the bladder or surrounding tissues for the patients without bladder) regions.

The statistical evaluation of the results was performed by paired samples T test. A p value <0.05 was considered significant. The sensitivity, specificity, and accuracy values of the PET/CT according to the receiver operating characteristic curves and cutoff values are generated, and SUV_{max} cutoff values were calculated.

Results

Bladder lesions

The mean diameter of the lesions in the bladder or operation region was 2.9±5.6 cm, and the number of the lesions in this region was determined as 1 to 3 or disseminated. One patient in this study group with a diagnosis of chronic kidney failure could not be evaluated sufficiently regarding primary tumor due to no visualization of any bladder activity. Of the 41 evaluated patients, 15 did not have any significant FDG uptake related to the primary or recurrent tumor in the early phase images due to high background activity. However, all of the 41 patients had one or more primary or recurrent tumor in the late phase post-diuretic images. Perineum invasion (prostate, penis, vaginal, and skin) was observed in nine patients in the study group (significant FDG uptake with or without discrete lesion in the late phase post-diuretic images) (Figure 1).

Metastatic lymph nodes

Twenty-two patients had pathological lymph nodes (>0.5 cm in diameter and/or high SUV_{max} levels >2.5), which were considered disseminated (extending outside the abdomen) in five patients. Some of the regional lymph nodes adjacent to the bladder activity or urethral activity cannot be considered in the early phase images, but the late phase images only (Figure 2) or the implant lesions as well (Figure 3). The lymph node status of the patients was considered according to histopathology, as well as follow-up results, as summarized in Table 1.

Distant metastases

Bone metastasis was recorded in seven patients (osteolytic hypometabolic metastasis or significant increased activity SUV_{max} >2.5) (Figure 4), liver metastasis in five patients (SUV_{max} higher than liver background with or without suspicious parenchyma lesion), lung metastasis in three patients (single or multiple

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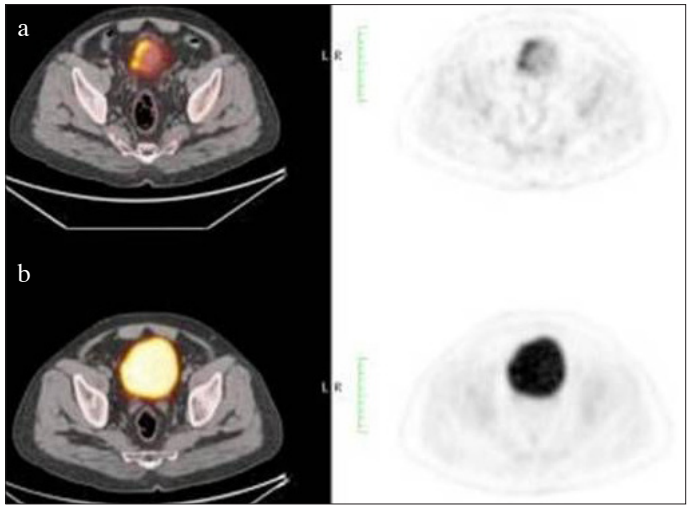

Figure 1. a, b. A 58-year-old male patient who has bladder lesions in the late phase images (upper line) although no discrete lesion in the early phase images (lower line)

round nodules >1 cm/mass with or without significant FDG uptake), implants in six patients (discrete lesions with significant FDG uptake >2.5 in pelvic or abdominal lesions), and adrenal metastasis in one patient.

Quantification

Early and late phase SUV_{max} levels of the primary/recurrent tumor in considerable 41 lesions (15.6±36.5 and 23.7±42.85, respectively; p=0.00) and lesion/non-lesion ratio (index value) of the considerable 22 lesions (8.7±1.8 and 10.7, respectively; p=0.002) were statistically significantly different (Figure 5).

Lymph node metastases also had significantly different early and late phase SUV_{max} levels in the determined 22 lesions (6.7±4.6 and 9.0±5.3, respectively; p=0.01) (Figure 5). The metastatic lesions that were considered in both early and late phases in the field of view had significantly different SUV_{max} levels (n=19, 10.4±5.2 and 13.9±7.1, respectively; p=0.001) according to dual phase images (Table 1).

Surgery and pathology results

Cystectomy (n=12), TUR (n=20), nephroureterectomy combined with TUR (n=3), and nephrectomy (n=1) operations were performed mean 5±6.1 months before the PET/CT imaging.

Follow-up

Three patients died during the follow-up. Nine patients were out of oncology follow-up and were thus excluded. The final diagnosis based on pathology, follow-up PET/CT, and other imaging modalities was decided by the oncologist and is listed in all patients in the table with initial FDG PET/CT results (Table 1). The sensitivity, specificity, and diagnostic accuracy of the PET/

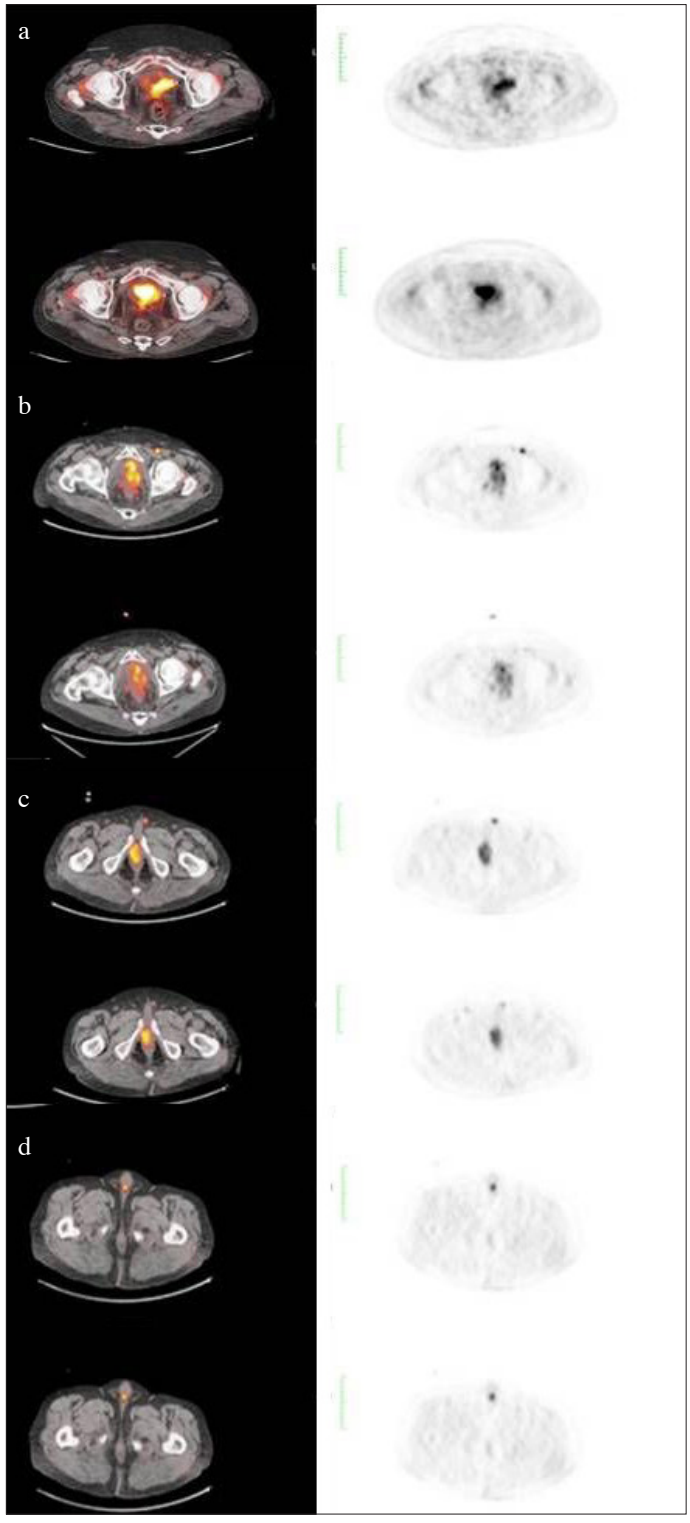

Figure 2. a-d. A 74-year-old male patient with gross tumor in the bladder (a) and inguinal lymph node metastasis (b) observed in the late phase images (upper line) but not in the early phase images (lower line) also perine (c) and penile (d) metastases more prominent in late phase images (upper line) compared with early phase images (lower line)

Table 1. Staging of the patients according to the PET/CT results and oncological follow-up

	T1		T2		T3		T4	
1	T1N0M0	T1/2N0M0	T2N2M0	T1/2N2M0	T3N0M0	T3/4N0M0	T4N0M0	T3/4N0M0
2	T1N0M0	T1/2N0M0	T2N0M0	T1/2N0M0	T3N1M0	T3/4N1M0	T4N2M0	T3/4N0M0
3	T1N0M0	T1/2N0M0	T2N1M1	T1/2N1M1	T3N3M1	T3/4N2M0	T4N2M0	T3/4N0M0
4	T1N1M0	T1/2N1M0	T2N0M0	T1/2N0M0	T3N2M1	T3/4N0M1		
5	T1N2M0	T1/2N2M0	T2N3M1	T1/2N2M1	T3N0M1	T3/4N0M1		
6			T2N2M1	T1/2N2M1				
7			T2N2M1	T1/2N2M1				
8			T2N2M1	T1/2N0M0				
9			T2N3M0	T1/2N0M0				
10			T2N0M0	T1/2N0M0				
11			T2N3M1	T1/2N3M1				
12			T2N0M0	T1/2N0M1				
13			T2N0M1	T1/2N0M0				
14			T2N2M0	T1/2N2M0				
15			T2N0M1	T1/2N0M1				
16			T2N0M0	T1/2N0M0				
17			T2N0M0	T1/2N1M0				
18			T2N0M0	T1/2N0M0				
19			T2N0M1	T1/2N2M1				
20			T2N0M1	T1/2N0M1				

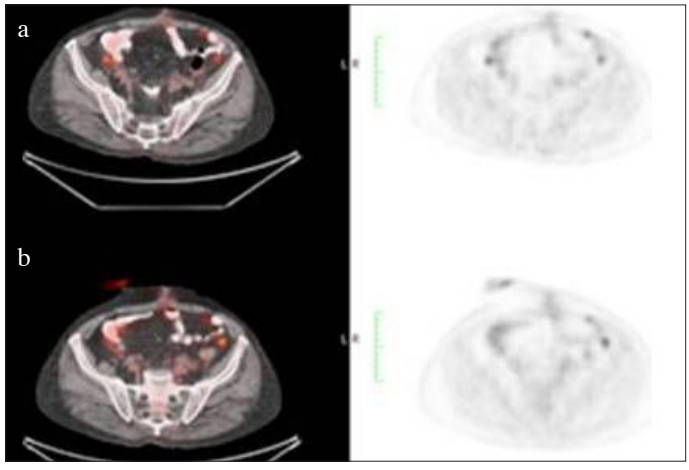

Figure 3. a, b. A 75-year-old male patient with multiple mesenteric implants in the late phase images (upper line) with only suspicious findings in the early phase images (lower line)

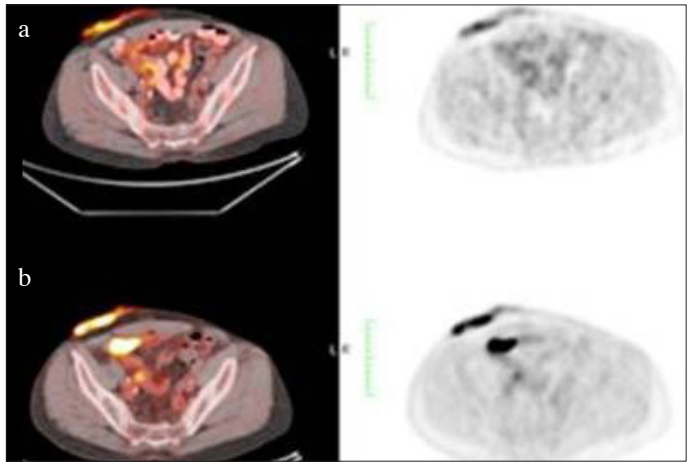

Figure 4. a, b. A 67-year-old male patient with metastatic iliac crest lesion with activity accumulation in the late phase images (upper line) without activity accumulation in the early phase images (lower line)

CT with this methodology for N staging and M staging were 67%, 78%, and 82% versus 80%, 91%, and 82%, respectively. The cutoff values for early SUV_{max} and late SUV_{max} for the lymph nodes were 7.8 and 13.08, respectively, with a sensitivity of 40% and 44%, specificity of 100% and 100%, and p value of 0.45 and 0.74, respectively, as shown in Figure 5. The SUV_{max} cutoff values for distant metastasis in the early and late phases were 12.1 and 10.4, respectively, corresponding to a sensitivity

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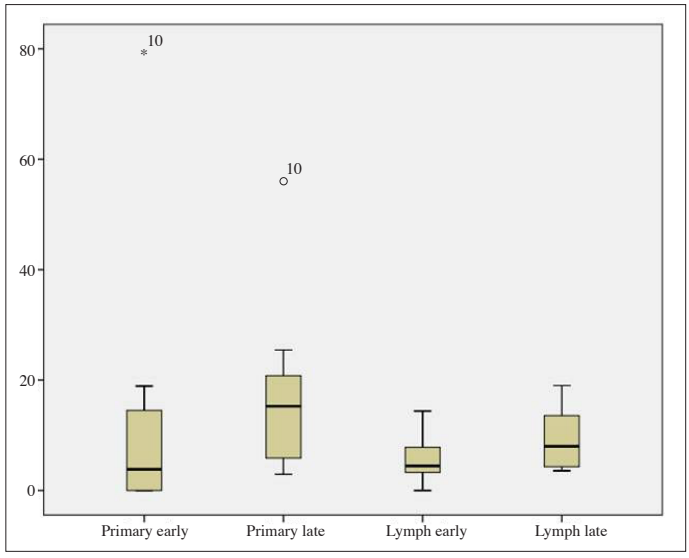

Figure 5. Graphic demonstration of the SUV_{max} levels of bladder lesions and lymph nodes in the early and late phase images with ROC curves

of 55% and 88.9% and specificity of 87.5% and 80%, respectively, as presented in Figure 5.

Discussion

The major limitation of the F-18 FDG PET/CT is the high physiologic excretion of the radiopharmaceutical from the urinary system. There are several different previous interventions to overcome this limitation. To the best of our knowledge, the late phase imaging with diuretic application is the most efficient methodology in the literature. In this retrospective study, we analyzed the effect of this modality in a heterogeneous group of patients who were referred for FDG PET/CT imaging for staging or restaging purposes. The methodology provided sufficient information regarding the local bladder/urethral disease and local lymph node evaluation as previously expected. Additionally, this application provided unexpected information including the field of view in the late phase, such as additional metastatic lymph node or distant metastasis, such as bone metastasis. The evaluation of the bladder region was not sufficient in both patients with TUR or cystectomy anamnesis in the early phase, but late phase imaging showed additional lesions and/or primary tumor not visible in the early phase in significant ratio of the patients included in the analysis (36.5%). Another significant subgroup in this study group was patients with local invasion (perineum, penis, and prostate), which demonstrated that this methodology might show local invasion more accurately.

Additionally, there are new technical advances in the investigation phase in bladder tumors, such as PET/MRI. In a prospective study with simultaneous PET and MRI in patients with bladder carcinoma, PET changed suspicion in pelvic lymph nodes in 52% of the patients with highly correct results (95%).[6] The same researchers observed that equivocal findings in the MRI might be clearly identified by PET. A study comparing PET/CT with PET/MRI has concluded that PET/MRI might change patients' management.[7]

Alongi et al.[8] have investigated recurrent bladder tumors by FDG PET/CT, which provided change in the patients' management in 40% of the patients and prognostic information regarding the progression-free and overall survival. In this study, early phase imaging was not considered sufficient in the evaluation of residual tumor in the cystectomy region due to a significant urine uptake around the field.

Among patients with muscle invasive bladder carcinoma, 30% has high risk of mortality due to distant metastasis.[9] In patients with lymph node metastasis, there might be additional distant metastasis.[10] Several previous studies have concluded that PET/CT may be problematic in the T staging of high-grade bladder tumors but has high diagnostic accuracy in determining distant metastatic disease.[11,12] Öztürk and Karapolat[11] have shown that the disease-free survival of the patients with PET negative and positive is completely different (50 vs. 16 months). Metastatic spread was also sufficiently evaluated in this study group, and there were additional metastatic sites only observed in the late phase images of several patients. This issue may be evaluated by prospective future studies in larger patient groups.

One important reason for the poor cystectomy outcomes has been found to be occult metastatic disease; however, previous observations have concluded that F-18 FDG PET/CT upstages only 20% of the series in this kind of groups.[13] However, Kollberg et al.[13] have discovered that the late phase imaging with intravenous diuretic administration may provide several additional findings and change in the patients' management in the 27% of their series before operation. Anjos et al.[1] have found a sensitivity of 54%, and Harkirat et al.[14] have reported a sensitivity of 86.7% and a specificity of 100% in the T staging of bladder tumors with diuretic late phase imaging. A recent study has compared the diagnostic efficiency of two different diuretic protocols, early (F30) and late post-diuretic (F90) studies, and showed superiority of F90 injection.[15]

The estimated mean local recurrence rate is 30% in bladder cancer after radical cystectomy according to the literature.[1] Bimanual examination, CT, and MRI as a routine diagnostic workup prior to the operation can provide 70% success rate,[16] and F-18 FDG PET/CT additionally causes change in the treatment plan in 68% of the patients compared with this routine workup.[17] Another study has shown that SUV_{max} might predict recurrence risk independently.[18]

One of the other diagnostic interventions for the elimination of urine accumulation in FDG PET/CT imaging in the bladder region was the early dynamic imaging, which provided information regarding the grade of the primary tumors pathology in a previous study.[19] Delayed pelvic PET/CT imaging with the administration of diuretics previously has shown high detection rate for lymph node, distant metastases, as well as the primary tumors in a previous study in a small series.[20] Additionally, there have been some attends toward a more comfortable low-dose diuretic protocol with additional oral fluid intake in a previous series, which provided similar results.[21] Coquan et al.[22] have investigated the effect of diuretic administration in the treatment response evaluation by FDG PET/CT and have concluded that PET/CT might determine the treatment response in bladder tumor, such as other malignancies. Additionally, diuretic FDG PET/CT protocol has been found to be effective in the staging of the locoregional disease previously in a series compared with contrast-enhanced CT with gold standard histopathology.[23] In the same study, the investigators have shown that PET/CT might show perivesical soft tissue invasion effectively.[23] Another group has evaluated the performance of the test in the restaging of the patients with diuretic delayed imaging and has shown that delayed images may provide additional important information, which is not evident in any imaging modalities about bladder wall lesions and local lymph nodes.[14] Although a previous study has shown that early diuretic administration is more comfortable for the patients, most of the other studies suggest delayed phase imaging due to higher lesion/non-lesion ratio.[24,25] In a previous study, the researchers have demonstrated nine primary and two recurrent lower abdominal lesions with this methodology successfully except one patient with chronic kidney failure in their series who did not show any benefit.[25] In a patient in this series with kidney failure, the late phase PET/CT imaging considered is not beneficial as well.

A recent case report presented a new methodology of acquisition of F-18 FDG PET/CT dedicated for bladder carcinoma; in that study, the bladder wall lesion was discriminated in the early phase of the imaging before the radioactive urine fills the bladder.[26] In another previous reports, the identification of 2291 lymph nodes of patients with bladder carcinoma found that SUV_{max} is a reliable parameter in the discrimination of pathological lymph nodes.[18]

Our study has limitations. The limitations of the present study were the retrospective and cross-sectional nature of the study and the lack of pathological results of all lesions of the patients. The patients involved in the present study were referred mostly in the postoperative period, which was also a limitation. However, in the present study, we could evaluate the effect of this methodology in the same patient at the same examination.

According to the results of the present study, diuretic late phase imaging in patients with urothelial cancer is significantly more informative regarding the localization, severity, and FDG uptake of the primary and recurrent tumors and additionally local lymph node and distant metastasis evaluation in the imaging field. Prospective studies about especially late phase imaging of distant metastatic lesions are warranted in large patient groups.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Mersin University (Date: 5/10/2017-Number:2017/286).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – Z.P:K.; Design - Z.P.K., İ.S.K.; Z.P.K - P.Ö.K, E.S.; Resources - E.S.-K.E., P.Ö.K., Z.P.K; Materials - E.S.-K.E., P.Ö.K., Z.P.K.; Data Collection and/or Processing - E.S.-K.E., P.Ö.K., Z.P.K.; Analysis and/or Interpretation - Z.P.K, P.Ö. K.; Literature Search - Z.P.K, P.Ö. K.;; Writing Manuscript - Z.P.K, P.Ö. K.;; Critical Review - Z.P.K, P.Ö. K.;.; Other - E.S., K.E., Z.P.K, P.Ö. K.

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