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[F-18]-Fluorodeoxyglucose PET and PET-CT in diagnostic imaging evaluation of locally recurrent and metastatic bladder transitional cell carcinoma

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Abstract

Background—Little data is available on the utility of positron emission tomography (PET) and positron emission tomography-computed tomography (PET-CT) with [F-18]-fluorodeoxyglucose (FDG) in patients with bladder cancer. We retrospectively assessed the diagnostic utility of dedicated PET and hybrid PET-CT scans with [F-18]-FDG in the imaging evaluation of recurrent and metastatic bladder transitional cell carcinoma.

Methods—The study group included 35 patients who were previously treated for the primary disease. We performed PET in 17 patients and 23 PET-CT scans in 18 patients. Diagnostic validation was by biopsy in 1 patient and clinical and radiological follow-up for up to 5 years in the remaining patients.

Results—PET and CT were true negative (TN) in 12 patients and true positive (TP) in 19 patients. In 4 patients in this group, both locally recurrent pelvic mass and distant metastases were demonstrated, while in 3 of these patients, unsuspected skeletal and/or nodal metastases were detected by PET-CT and these patients received additional courses of chemotherapy. PET was discordant with CT in 4 patients. PET was negative in 2 of these patients, while post-chemotherapy CT showed enlarged nodes that were determined to represent successfully treated disease. In another patient, a hypometabolic soft-tissue mass was considered to represent a scar, and a wait-and-watch strategy was pursued. In the remaining patient, PET showed random hypermetabolic osseous lesions that represented early marrow metastatic infiltration. The combined diagnostic information provided by PET-CT affected the clinical management in 17% of patients.

Conclusion—FDG PET and PET-CT scanning may improve the imaging evaluation of patients with recurrent and metastatic bladder cancer.

Keywords

FDG; PET; PET-CT; Bladder; Cancer

Introduction

Bladder carcinoma is the most frequent tumor of the urinary tract and accounts for 2% of all cancer deaths in the United States. It is most prevalent in the fifth to seventh decade of life and usually presents with dysuria and hematuria. Transitional cell carcinoma (TCC) is the most common tumor histology. Diagnosis is made by various diagnostic tests, including urine

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cytology and cystoscopy with biopsy. Conventional imaging evaluation includes ultrasonography (US), computed tomography (CT), and magnetic resonance imaging (MRI). Treatment depends on the disease stage, but may include endoscopic resection and fulguration, cystectomy with urinary diversion, and palliative radiation therapy. The standard chemotherapy for metastatic bladder cancer is a combination of four drugs – known as MVAC (methotrexate, vinblastine, adriamycin, and cisplatin). A chemotherapy regimen with a combination of gemcitabine and cisplatin demonstrates similar response rates to MVAC but is less toxic. Prognosis is highly dependent on the depth of tumor penetration into the bladder wall, with 5-year survival of 85% for superficial disease and 55% for invasive disease. Metastatic disease is associated with very poor prognosis.¹

Early animal model studies with implanted orthotopic or xenograft bladder tumors demonstrated high [F-18]-fluorodeoxyglucose (FDG) localization in the tumor, indicating that FDG positron emission tomography (PET) imaging of bladder cancer might be feasible.^{2,3} Preliminary assessment of FDG PET in patients with bladder cancer revealed that FDG PET could detect distant metastatic lesions and was useful in differentiating viable recurrent tumor from radiation-induced alterations.⁴ However, detection of the primary bladder tumor was difficult due to intense accumulation of excreted FDG in urine. Interventions such as bladder irrigation, forced diuresis with furosemide, or both, may contribute significantly to overcoming this handicap.⁵ Further studies provided additional evidence for the utility of FDG PET in the imaging evaluation of bladder cancer, including its utility in the staging of pelvic lymph nodes.⁶⁻⁸ Additional pitfalls, such as limited ability in detecting micrometastases, premalignant lesions, and small noninvasive tumors were also described.^{9,10} More recent studies have found that FDG PET is particularly useful in the preoperative staging of patients with invasive bladder cancer and no known metastatic disease based on conventional procedures.¹¹ In this group of patients, FDG PET provided important prognostic information, such that patients with PET-positive nodes had a statistically significant shorter median survival than those with PET-negative nodes (13.5 months vs 32.0 months, respectively).¹¹ In patients who had still not undergone chemotherapy, FDG PET showed a sensitivity of 77% and a specificity of 97% for detecting metastatic disease.¹² Our early observations corroborated these findings.¹³ Other than a single case report,¹⁴ the contribution of recent hybrid PET-computed tomography (CT) imaging systems has not been systematically reported in this clinical setting. Therefore, the purpose of our retrospective study was to evaluate the diagnostic utility of FDG PET and PET-CT in the imaging evaluation of patients with metastatic bladder transitional cell carcinoma.

Patients and methods

Our study included 35 patients (25 male, 10 female; age range, 39–86 years) with a history of bladder transitional cell carcinoma (initial stages B2 and C) who were referred to our PET Imaging Center for evaluation during a 6-year period from 2000 to 2006. Prior treatments included cystectomy with urinary diversion in all patients, followed by chemotherapy in 13 patients, combined chemoradiation therapy in 11 patients, and no additional treatment in the remaining 11 patients. None of the patients had diabetes mellitus. We performed dedicated PET (Siemens 953/A; Knoxville, TN, USA) in 17 patients and 23 hybrid PET-CT scans (Siemens Biograph) in 18 patients. For dedicated PET scans, attenuation correction was performed from transmission images acquired with a rotating pin source containing Ge-68. For hybrid PET-CT scans, all patients received oral contrast material followed by acquisition of a nonenhanced CT transmission scan (120 kVp, 220 mAs at 15 mm/rot; each data set consisted of 47 contiguous, 3.375-mm-thick, tomographic sections, for a total field of view of 16.2 cm) for attenuation correction. The patient was instructed to breathe normally during the PET-CT scan. As per our routine clinical imaging protocol, a breath-hold chest CT was also obtained during the same imaging session. PET emission images were obtained 60 min after intravenous administration of 15 mCi (555 MBq) FDG (4 min per bed position) in the caudo-cranial

direction from upper thighs to skull base. Images were reconstructed using an iterative procedure with an ordered subset expectation maximization (OSEM) algorithm with a PET image spatial resolution of about 7 mm. All patients had plasma glucose levels of less than 120 mg/dl and had fasted for at least 6 h prior to FDG administration. For PET-CT, hardware-fused images were presented on a dedicated color monitor. Focal accumulation of FDG above nonworking muscle background was considered as a positive finding. The maximum standardized uptake values (SUVmax) were also recorded for selected lesions, using a system software image tool utility. The combined metabolic information content of PET and structural information content of CT were used for image interpretation. Discordant metabolic-structural findings were further analyzed. Available correlative imaging studies at the time of PET-CT interpretation included contrast-enhanced CT studies of the chest, abdomen, and pelvis in 13 patients and bone scintigraphy in 4 patients. All these studies were obtained within 3 months of the PET scans. Diagnostic validation was by biopsy in 1 patient and by radiological follow-up for up to 5 years after the PET or PET-CT study in the remaining patients.

Results

PET and CT were true negative in 12 patients who remained free of evident disease based on available clinical and radiological follow-up for up to 2 years. Both PET and CT were true positive in 19 patients. In 4 patients in this group, both locally recurrent hypermetabolic pelvic mass and distant metastases were demonstrated (Figs. 1 and 2). These patients underwent an additional course of combined chemoradiation therapy. In 3 of these patients, unsuspected skeletal, pulmonary, and/or abdominal lymph nodal metastases were detected by PET-CT and they received additional courses of chemotherapy based on the PET detection of extensive metastatic disease (Fig. 3). In another 3 patients in the concordant positive group, PET-CT demonstrated hypermetabolic enlarged lymph nodes in the mediastinum, as well as multiple pulmonary nodules compatible with metastases, although PET revealed additional hypermetabolic disease in subcentimeter left bronchial nodes in 1 of these patients. Osseous metastasis was present in the left humerus of 1 patient who presented with left arm pain and subsequently underwent external radiation therapy to the left arm. In another patient, PET-CT demonstrated hypermetabolic pelvic nodal and peritoneal nodular metastatic disease.

PET was discordant with CT in 4 patients. In 2 of these patients, PET scans were negative while post-chemotherapy CT study showed larger than 1-cm lymph nodes in the abdomen and pelvis. However, because the nodes were smaller than those on the pre-chemotherapy CT and there were no significant changes over the 1 year of follow-up, the negative PET findings were considered to be indicative of a successful treatment response. In another patient, CT demonstrated a soft-tissue density in the irradiated surgical bed which was not hypermetabolic on PET. Although histological confirmation was unavailable, the PET finding was considered to represent scar tissue, and prompted a wait-and-watch strategy. In the remaining patient, PET showed hypermetabolic osseous lesions that did not demonstrate corresponding abnormalities on concurrent CT. The random distribution of the osseous lesions was considered to represent early marrow metastatic infiltration similar to what has been observed with other conditions such as multiple myeloma.¹⁵ The complementary information provided by the combined PET-CT affected the clinical management in 6 patients (17% of total), by prompting additional therapy in 5 patients and a wait-and-watch strategy in 1 patient. The clinical management of the remaining 29 patients could be decided based on either the CT or the PET information alone, without new additional benefit from the combined diagnostic information other than the advantage of precisely localizing the hypermetabolic disease.

Discussion

The overall prognosis for recurrent and metastatic bladder TCC is poor. However, additional salvage and/or palliative therapy is prompted when disease is discovered. Accurate restaging is therefore important before additional costly and toxic therapies are considered. Imaging plays a pivotal role in the staging and restaging of disease. Despite the promise of FDG PET in the imaging evaluation of a variety of cancers, detection of a primary bladder tumor and staging of adjacent lymph nodes may be difficult in view of the intense accumulation of excreted FDG in urine. Interventions such as retrograde bladder irrigation and forced diuresis with furosemide have been shown to be useful in overcoming this problem in most patients.⁵ However, such additional and somewhat cumbersome procedures are often not performed in most imaging clinics, because elimination of intravesical urine activity does not guarantee detection of the primary tumor.⁴

There has been little data available on the utility of FDG PET or PET-CT in assessing for recurrence and metastatic disease in patients who have previously undergone treatment for their primary tumor. The intense diverted intraluminal urine activity can hinder the detection of an adjacent small local recurrence or metastatic lesions, but anecdotally, this seems to be less problematic in comparison to the detection of the primary disease.^{4,13} In our study, the urinary diversion did not pose a diagnostic problem; this was particularly the case with the PET-CT studies where precise structural correlates of metabolic findings were inherently available.

Bladder TCC is FDG-avid. We noted a maximum SUV range of 2.3 to 7.8, which is in general agreement with a prior report that reported SUV ranges of 2.2–6.2 for the primary tumor and 1.7 to 4.8 for lymph node metastases.⁴ In an earlier rat bladder tumor model, a high tumor-to-blood FDG uptake ratio of 22 was noted.³ Therefore, unless the tumor deposits are adjacent to very high urine activity or the lesions are small (below the spatial resolution of the PET camera system), one expects that TCC will be detected. Peritoneal carcinomatosis may also be difficult to detect due to small deposits, which may not lead to a structural abnormality (such as peritoneal nodular thickening) or may not accumulate sufficient FDG above the background normal variable bowel metabolic activity. However, in one patient in our study, precise localization of the abnormal metabolic activity to the peritoneum by PET-CT facilitated the high suspicion for peritoneal involvement, which prompted additional chemotherapy. In another patient, no hypermetabolic activity was attributed to a soft-tissue density in the treated pelvic bed. This was interpreted as no evidence of macroscopic recurrent malignancy, and prompted a wait-and-watch strategy. Kosuda et al.⁴ showed that FDG PET could detect 80% of tumor sites and could differentiate viable tumor from radiation-induced alterations.

The metastatic sites detected by PET in the present study included the mediastinum, lungs, and bone. Overall, in this select group of patients, combined PET and CT diagnostic information was valuable in detecting, localizing, and characterizing the extent of metastatic disease. Structural abnormalities on CT were present in all sites, except for several randomly distributed osseous lesions in one patient, which was interpreted as representing early marrow deposits of metastatic tumor. However, no biopsy or follow-up imaging data were available to confirm this impression.

As has been demonstrated with many other cancers, the incorporation of metabolic information in the diagnostic imaging assessment can affect clinical management significantly. In our study, the complementary information provided by the combined PET-CT affected the clinical management in 17% of patients, by prompting either additional therapy or a wait-and-watch strategy. Whether such a change in short-term clinical management resulted in a long-term benefit in a cost-effective manner could not be addressed by our study.

Our study was based on FDG, which is the most common tracer used and available in PET imaging, but a few researchers have investigated the use of other tracers. Letocha et al.¹⁶ investigated whether PET with L-methyl-11C-methionine as a tracer could be used for the evaluation of therapy response in 44 patients with varying stages of urinary bladder TCC treated with chemotherapy. In their study, the diagnostic accuracy of PET was poor and the technique could not monitor the therapeutic effect of chemotherapy. More favorable findings have been reported with C-11 choline, which is not excreted into urine, overcoming a significant limitation of FDG in this clinical setting.^{17,18} Bladder TCC accumulated choline with a maximum SUV of 4.7+/-3.6, but, similar to FDG, micrometastases and noninvasive tumor could not be detected.¹⁷ Nonspecific small bowel, rectum, and prostate gland uptake was also observed. In a more recent case series of four patients, choline PET was able to detect osseous metastases which were negative on bone scintigraphy, but in the remaining three patients, choline PET was false-positive by localizing inflammatory lesions, which is also a common pitfall with FDG.¹⁸ Whether tracers other than FDG can have a role in the imaging evaluation of patients with bladder TCC requires additional experience.

In summary, our findings add to the current limited literature in suggesting that FDG PET and particularly PET-CT scanning may contribute significantly to the imaging evaluation of patients with bladder cancer who have been previously treated for the primary disease. PET and CT provide important diagnostic information on the location, extent, and metabolic characteristics of recurrent and metastatic bladder TCC lesions. Our study is limited with regard to post-imaging retrospective evaluation bias and lack of histological confirmation for all lesions. It must, however, be noted that it is impractical and probably unethical to perform multiple biopsies in individual patients. In order to reduce the effect of this limitation, we employed the commonly used content diagnostic validity method through clinical and radiologic follow-up to establish a suitable standard of reference. Prospective studies will be needed to determine the exact diagnostic performance and impact of FDG PET-CT on short-term clinical management decision-making and long-term patient outcome.

Conclusion

Bladder TCC recurrence and metastases are FDG-avid. Our findings add to the current limited body of literature that suggests that FDG PET and PET-CT scanning may improve the imaging evaluation of patients with known or suspected recurrent and metastatic disease. Further prospective studies in larger cohorts of patients will clarify the exact role of PET and PET-CT in clinical decision-making and long-term outcome in this clinical setting.

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Fig. 1.
a–d. Recurrent bladder cancer in a 64-year-old woman who was initially treated with radical cystectomy followed by chemoradiation therapy. The axial computed tomography (CT; **a**), fused axial CT and positron emission tomography (PET; **b**), fused sagittal CT and PET (**c**), and fused coronal CT and PET (**d**) images show an intensely hypermetabolic soft-tissue mass in the left posterior pelvis compatible with locally recurrent disease. There is an incidental note of small bowel obstruction

Fig. 2. Metastatic bladder cancer in a 43-year-old man with a history of high-grade papillary transitional cell carcinoma. Fused axial CT and PET images show a hypermetabolic right psoas muscle mass and mediastinal lymph nodes that prompted radiation treatment to the psoas mass in addition to the institution of chemotherapy. The patient's clinical course became complicated with the development of right hydronephrosis, requiring placement of a nephrostomy tube, and complete thrombosis of the inferior vena cava from the level of the right renal vein extending to the right common, internal, and external iliac veins

Fig. 3.
a, b. Metastatic bladder cancer in a 75-year-old man treated initially with cystectomy and Koch pouch placement followed by chemoradiation therapy. The pre- (**a**) and post-therapy (**b**) fused coronal CT and PET images show partial response of the right apical lung lesion to treatment with the development of intralesional relative hypometabolism related to necrosis