Role of PET/CT in muscle-invasive bladder cancer

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Abstract: The purpose of this study covered the diagnostic accuracy and usefulness of positron emission tomography/computed tomography (PET/CT) imaging in muscle invasive bladder cancer patients through previously published literature. Through 30 September, 2019, the PubMed database was searched for eligible articles that evaluated PET/CT imaging in bladder cancer patients. In general, FDG PET/CT, the most commonly used PET/CT imaging, does not show good performance for the detection of primary lesions; however, according to the literature it could accurately assess pelvic lymph node (LN) status better than other imaging technologies and it was especially helpful in determining extra-pelvic recurrences. More recently, non-FDG PET/CT imaging, such as C-11 acetate and C-11 choline, has been introduced. Although further research is required, preliminary results show the potential of these techniques to overcome the drawbacks of FDG. This concise study will overview the role of PET/CT when treating muscle-invasive bladder cancer (MIBC).

Keywords: F-18 fluorodeoxyglucose; C-11 acetate; C-11 choline; positron emission tomography/computed tomography (PET/CT); bladder cancer; lymph node (LN); staging; restaging

Introduction

Bladder cancer is one of the most common urinary tract malignancies, and the majority of cases develop from the uroepithelial tissue. Approximately 30% of bladder cancers shows muscle-invasive bladder cancer (MIBC), which is relevant to a high risk of distant metastases (1,2), while the remainder are superficial tumors. When diagnosing, about 20–30% of bladder cancer patients have MIBC (1).

2-Fluorine-18-fluoro-2-deoxy-d-glucose (FDG) is the most common radiotracer for oncologic positron emission tomography (PET). Most malignancies show increased glucose metabolism and intensely accumulate FDG. However, typical urologic malignancies such as prostate cancer and renal cell carcinoma mildly uptake FDG, and this low glucose metabolic rate hampers the role of FDG PET/CT, whereas in the case of bladder cancer, FDG uptake itself is intense unlike other urinary system malignancy. The physiological urinary excretion of FDG masks FDG accumulation of bladder carcinomas (*Figure 1*). Intense FDG-containing urine that is excreted early, must be flushed using diuresis or delaying acquisition time in order to facilitate the identification of primary bladder cancer and the extravesical spread.

Before any curative treatment is intended, it is necessary to rule out distant metastases. Several regional CT and MRI are the optimal diagnostic techniques to assess lung and liver metastases, respectively. Bone and brain metastases are not common at the time of diagnosing MIBC, and additional skeletal and brain imaging are not routinely indicated without specific symptoms or signs. Metastatic lesions far from the intense FDG-containing urine can be investigated well. Accumulation of evidence in the literature has been suggesting that FDG-PET/CT have clinical potential for staging metastatic bladder cancer; however, currently no consensus has been reached, and further confirmatory studies or trials are necessary for a recommendation.

Until now, reimbursement of FDG PET/CT has been limited in urinary malignancy, and large-scale clinical trials with good evidence are sparse, and studies for bladder cancer are also rare. This short review summarized the role of PET/CT imaging using the currently available knowledge.
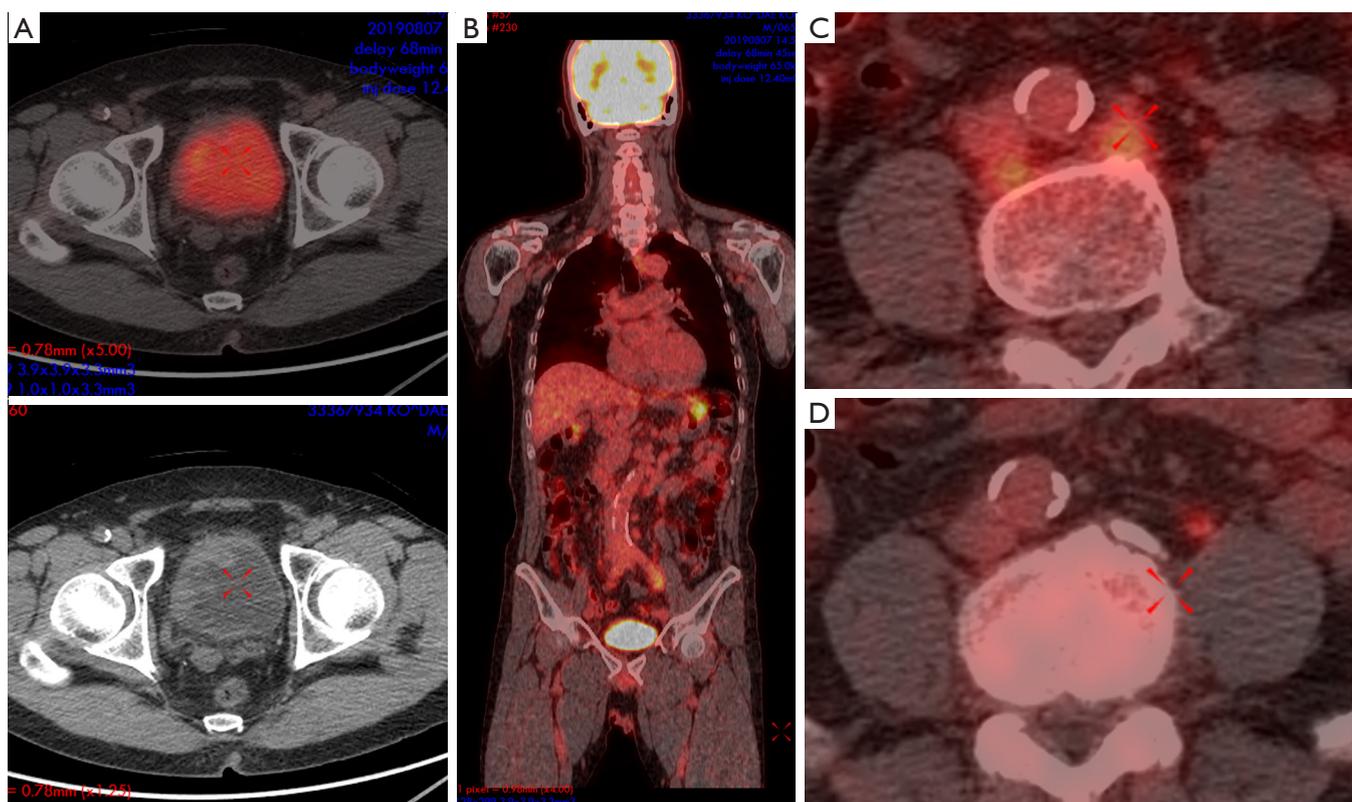
Figure 1 A 65-year-old male with bladder cancer (A). Intense FDG-containing urine obscures FDG uptake in the bladder wall. Histopathologic analysis showed metastatic disease in a left paraaortic lymph node (B,C), which showed F-18 FDG uptake on a PET/CT, coronal, and axial PET/CT fusion image. After transurethral resection and chemotherapy, F-18 FDG avid lymph node enlargement disappeared (D).

Role of imaging for the staging of MIBC

The most common symptom of bladder cancer is hematuria. Cystoscopy or renal tract ultrasound is the initial evaluation step, and both cystoscopy and biopsy remain a key step for the investigation of suspicious bladder cancer. The role of MIBC imaging encompasses diagnosis and differential diagnosis, staging of known tumor, and re-staging after recurrence. In the clinic, CT and MRI are the imaging techniques used routinely in bladder cancer, and both CT and MRI may be used assessing local invasion. The principal reason of CT and MRI is to discover T3b disease or higher because both are unable to accurately detect microscopic invasion of the peri-vesical fat (T2 *vs.* T3a). The European Association of Urology (3) and the National Comprehensive Cancer Network (NCCN) suggests staging confirmed MIBC with CT or MR of the chest, abdomen, and pelvis, if available (4). Occasionally a bone scintigraphy

may be required if there is history, symptom or signs suggesting bony disease.

FDG PET/CT is assumed to be unable to evaluate microscopic peri-vesical fat invasion and adjacent organ involvement. Currently, FDG PET/CT is not recommended as the initial diagnosing or primary staging tool of bladder cancer due to the physiological uptake of FDG in the bladder. In order to overcome these limitations of FDG, profuse water uptake, use of diuretics, and voiding with catheter are known to be helpful (5). According to recent reports, early dynamic FDG images could be helpful for the primary detection of bladder cancer before FDG excrete and collection (6). Several researchers have explored the value of FDG PET or PET/CT when detecting and staging bladder carcinoma, but it remained indecisive and varied. Meta-analysis for diagnostic performance of FDG PET/CT in bladder cancer showed that the pooled sensitivity was 0.82,

Table 1 Diagnostic performance of FDG PET/CT in lymph node staging of bladder cancer

Author/year	Study/N	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	ACC (%)
Kosuda/1997	Pro/12	NR	NR	67	33	NR
Bachor/1999	Pro/64	67	86	NR	NR	80
Drieskens/2005*	Pro/40	50	100	100	89	90
Kibel/2009*	Pro/43	70	94	78	91	NR
Apolo/2010	Pro/57	81	94	NR	NR	NR
Swinnen/2010*	Pro/51	46	97	86	84	84
Hitier-Berthault/2013*	Pro/52	36	87	67	65	65
Girard/2019	Pro/61	29	97	70	85	84
Goodfellow/2014*	Ret/93	46	97	87	81	82
Jeong/2015*	Ret/61	15	98	24	96	NR
Aljabery/2015*	Ret/54	41	86	58	76	NR
Uttam/2016*	Ret/15	100	58	38	100	NR
Pichler/2017*	Ret/70	64	86	NR	NR	83
Lodde/2010*	Ret/70	57	100	13	80	NR
Jensen/2011*	Ret/18	33	93	50	88	NR
Soubra/2016*	Ret/78	56	98	NR	NR	NR
Chakraborty/2014*	Ret/23	88	80	70	92	82
Rouanne/2014*	Ret/102	50	99	72	97	97
Ha/2018	Meta-Analysis/785	57	92			

* included in the meta-analysis by Ha HK *et al.* N, enrolled patients; PPV, Positive Predictive Value; NPV, negative predictive value; ACC, accuracy; Pro, prospective; Ret, retrospective; NR, not reported in the article.

while the specificity was 0.92 in the detection of bladder lesions (7). The analysis included 9 retrospective and 1 prospective study with 433 patients.

Role of FDG PET/CT imaging for lymph nodes (LNs) in MIBC

A 10–30% risk of pelvic LN metastasis are known in patients with MIBC. With extending into the peri-vesical fatty tissue, the risk increases up to 50% (8,9). Assessment of LN metastases is limited on the basis of solely LN size as both CT and MRI could not identify metastases in normal-sized or minimally enlarged nodes. The sensitivity for detecting LN metastases is low, as is the specificity since the nodal enlargement may be due to benign disease. Overall, CT and MR are not sufficiently accurate in the evaluation of preoperative LN involvement in bladder cancer (10,11).

Currently, no evidence is supporting that PET can be routinely used in the nodal staging of bladder cancer. Diverse small-scale trials have been widely undertaken using various imaging protocols. Delayed pelvic images after profuse oral hydration and/or diuretics administration are most commonly used among the various techniques that have been studied to improve the diagnostic performances of FDG PET (12-14). There have been several small prospective (12,15-17) and retrospective trials (18-27) for performance staging LNs, the results of which varied widely. The reported sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy was 15–100%, 80–100%, 13–100%, 33–100%, and 65–97%, respectively (14-16,18-33) (*Table 1*).

Although in some early studies, FDG PET/CT provided relatively good sensitivity and specificity, a very wide range of sensitivity and specificity was shown among whole studies. Overall, the sensitivity ranges from around 50% and the specificity around 90%. High FDG retention in

Table 2 Comparison of diagnostic performance between CT and FDG PET/CT in lymph node staging of bladder cancer

Author/year	Study	Sensitivity		Specificity		Accuracy		PET recommendation
		CT	PET/CT	CT	PET/CT	CT	PET/CT	
Pichler/2017	Ret	5/11	8/11	54/59	48/59	59/70	56/70	Partial
Uttam/2016	Ret	3/3	3/3	6/12	7/12	9/15	10/15	No
Jeong/2015	Ret	5/17	8/17	43/44	41/44	48/61	49/61	No
Aljabery/2015	Ret	7/17	7/17	33/37	32/37	40/54	39/54	No
Goodfellow/2014	Ret	13/28	13/28	64/65	63/65	77/93	76/93	No
Chakraborty/2014	Ret	6/9	7/8	8/14	12/15	14/23	19/23	Yes
Lodde/2010	Ret	5/15	13/23	18/18	20/20	23/33	33/43	Yes
Hitier-Berthault/2013	Pro	2/22	8/22	27/30	26/30	29/52	34/52	Yes
Swinnen/2010	Pro	6/13	6/13	35/38	37/38	41/51	43/51	No
Drieskens/2005	Pro	5/12	6/12	49/51	51/51	54/63	57/63	Yes
Weighted average		57/147 (38.8%)	79/154 (51.3%)	337/368 (91.6%)	337/371 (90.8%)	394/515 (76.5%)	416/525 (79.2%)	

Pro, prospective; Ret, retrospective.

bladder, the extent of LN dissection, small sample size, and study bias could be possible explanations for the low sensitivity. Further research is necessary for substantiating the diagnostic accuracy of FDG PET/CT for this purpose.

As stated earlier, the diagnostic accuracy of CT and MRI was not sufficient in terms of the evaluation of preoperative LN involvement in bladder cancer. Several reports have dealt with the comparison between FDG PET/CT and CT (*Table 2*), and the results widely varied along studies. A meta-analysis by Soubra *et al.* (26) reported that the pooled sensitivity of FDG PET/CT was 0.565 (95% CI: 0.473–0.653); specificity, 0.954 (95% CI: 0.922–0.976), and those of CT alone was 0.35 (CI: 0.25–0.45); specificity, 0.95 (CI: 0.91–0.98). According to the same study, FDG PET/CT performed better than CT alone; with a pooled sensitivity of 34.5%, CT alone identified 22% fewer patients with LN metastasis correctly than FDG PET/CT, and FDG PET/CT still performed better in the individual studies. According to the current study, to which additional studies were added, the weighted average sensitivity, specificity, and accuracy of FDG PET/CT and CT were 51.3%, 90.8%, 79.2%, and 38.8%, 91.6%, and 76.5%, respectively (*Table 2*). Both FDG PET/CT and CT showed similar high specificity and FDG PET/CT had better sensitivity than CT in the LN evaluation. Although pooled data showed that FDG PET/CT showed better sensitivity than CT alone, the individual study had contradictory conclusions.

In 4 of the 10 studies enrolled in *Table 2*, the use of FDG PET/CT was advocated for LN evaluation, and 5 studies did not. One study partially advocated the use of FDG PET/CT when conventional CT criteria (over 10 mm in maximum short-axis diameter) were used rather than more sensitive criteria as over 8 mm. At this point, in order to establish the clinical or statistically significant superiority of FDG PET/CT over CT in LN staging, more studies are needed.

Detection of extra-pelvic LNs or distant metastatic lesions using FDG PET/CT

The main cause of death of bladder cancer is metastases, and metastatic bladder cancer shows poor prognosis. Metastatic lesions can be detected at the time of diagnosis and local recurrence is common after radical cystectomy, and metastasis develops more commonly in MIBC.

Conventional diagnostic methods such as physical exam, CT, and MRI are not currently able to stage metastatic lesions with high accuracy, and their success rate of clinical staging has been reported as 70% in the literature (34).

Several studies (15,16,23,29,35) found the sensitivity and specificity to be 60%, 88%; 77%, 97%; 70%, 94%; 46%, 97%; 57%, 100%, respectively in small numbers of MIBC patients (<60 patients) who underwent pathological correlation. The diagnostic performances or detection of

Table 3 Patient-based diagnostic performances of FDG PET/CT detecting extra-pelvic lesions in the literature

Author/year	N	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	ACC (%)
Drieskens/2005	55	60	88	75	79	78
Liu/2006	55	77	97	NR	NR	84
Kibel/2009	43	70	94	78	91	88
Swinnen/2010	50	46	97	85	84	84
Lodde/2010	40	57	100	100	80	77
Jensen/2011	18	NR	93	NR	87.5	NR
Apolo/2010	47	87	88	NR	NR	NR
Goodfellow/2014	93	46	97	87	81	82
Ozturk/2015	79	89	78	90	75	86
Lu/2012	NR	89	82	NR	NR	NR

PPV, positive predictive value; NPV, negative predictive value; ACC, accuracy; NR, not reported.

extra-pelvic lesions in the literature were listed in terms of patient-base (*Table 3*).

A systemic review by Lu *et al.* (12) showed sufficient diagnostic accuracy for staging and restaging MIBC and its metastasis (a sensitivity of 89% and specificity of 82%). Other more recent study (36) reported that FDG PET/CT screening in cases of suspected metastatic lesions were retrospectively evaluated and its sensitivity, specificity, accuracy, PPV and NPV were 89%, 78%, 90% (50/55), 75% (18/24), and 86%, respectively, which accorded with Lu *et al.* (12).

In contrast to Lu *et al.* (12) and Öztürk *et al.* (36), Goodfellow *et al.* reported, in a study with 233 patients with MIBC or high-risk non-MIBC, that FDG PET/CT could detect extra-pelvic metastatic lesions with a sensitivity of 54% compared to 41% using CT (20). FDG PET/CT and CT showed similar specificities of 97% and 98%, respectively. The addition of a PET scan can improve the detection of distant metastases comparing CT alone. Although FDG PET revealed 5.6% more patients, PET scans were not routinely recommended because of the small additional clinical advantage and the high financial burden. The pooled diagnostic performance for detecting extra-pelvic lesions were summarized from the lesions reported in the literature (*Table 4*). The pooled sensitivity of FDG PET/CT was demonstrated to be better than that of CT (74.9% *vs.* 43.7%) with similar specificity.

Kibel *et al.* (16) found 7 patients with occult metastatic disease in a total of 42 patients, and FDG PET/CT

influenced the treatment decision prior to radical cystectomy. In the study by Apolo *et al.* (32) that evaluated 47 patients and 135 individual metastatic lesions, FDG-PET/CT led to change the therapeutic plan in 68% of the patients because it was able to detect 40% more cases than CT and MRI imaging conducted together. They concluded that FDG PET/CT provided additional diagnostic information that improved clinical management compared to CT or MRI alone.

Reports advocated that FDG PET/CT revealed extra-pelvic metastatic lesions in MIBC with superior sensitivity and specificity (37). Moreover, it has been disclosed that FDG PET/CT provides additional changes in treatment of the disease.

Survival and FDG PET/CT

Drieskens *et al.* prospectively revealed that the median survival of PET negative patients was longer than PET negative ones (32.0 *vs.* 13.5 months) in 55 MIBC or high-grade bladder cancer patients (29). The patients with at least one positive or equivocal lesion were categorized as positive; 12 patients showed PET positivity (21.8%) and the remaining 43 showed negativity. PET-negative patients showed 85% of the 2-year overall survival and PET-positive did 37%. Although the 6-month overall survival was not reported, the figures could be interpolated from the graph (*Table 5*), and the 6-month overall survival in PET-positive and negative were 93 and 97, respectively.

Table 4 Lesion-based diagnostic performance of FDG PET/CT and CT detecting extra-pelvic lesions*

Author/year	Sensitivity		Specificity		Accuracy	
	CT	PET/CT	CT	PET/CT	CT	PET/CT
Drieskens/2005	1/8	4/8	48/52	49/52	49/60	53/60
Liu/2006		10/13		33/34		43/47
Apolo/2010		25/31		15/16		40/47
Goodfellow/2014	23/56	30/56	148/151	147/151	171/207	177/207
Ozturk/2015		50/56		18/23		68/79
Soubra/2016		8/8				8/8
Pichler/2017**	7/7	7/7			7/7	7/7
Weighted average	31/71 (43.7%)	134/179 (74.9%)	196/203 (96.6%)	262/276 (94.9%)	227/274 (82.8%)	396/455 (87.0%)

*, all lesions, which were remarked as the extra-pelvic lymph nodes and distant metastatic lesions, were pooled; **, Pichler *et al.* includes secondary malignancies.

Table 5 Overall survival rates in terms of PET positivity

Author	Patients number	Median survival (months)		24 months OS (%)		6 months OS (%)	
		PET +	PET −	PET +	PET −	PET +	PET−
Drieskens/2005	55	13.5	32.0	37	85	93*	97*
Kibel/2009	42	6*	33*	23	58	63	93
Mertens/2014	211	14	50	38*	70*	72*	94*

*, the numbers, which were not reported in detail, were extracted from the survival curve charts in the literature using WebPlotDigitizer (https://automeris.io/WebPlotDigitizer/). +, positive on PET scan; −, negative on PET scan.

In another study by Kiebel *et al.*, PET-positivity was defined visually and semi-quantitatively (16). In total, 42 MIBC patients were enrolled, and PET-positivity was 21.4% (n=9), while 33 patients showed PET-negativity. The overall survival at 6 and 24 months of PET-positive and negative patients was 63%, 23% and 93%, 58%, respectively. The recurrence free survival rates at 6 and 24 months were 50%, 0% and 89%, 55% for PET-positive and negative patients, respectively. The disease specific survival rates at 6 and 24 months were 63%, 23% and 100%, 62% for PET-positive and negative patients, respectively.

PET-positive patients showed significantly poorer results in term of recurrence free survival, disease specific survival rates and overall survival rates than PET-negative patients. The median survival was not reported.

In a recent relatively large study conducted in 2014 by Mertens *et al.* (38), 211 MIBC patients were evaluated for the relationship of FDG PET/CT results with mortality.

In total, 98 patients (46%) showed PET positivity and 113 were negative. The median overall survival rate was 14.0 months with PET positivity and 50.0 months with PET negativity. Overall survival rate between patients with regional or distant PET/CT lesions was not different significantly. The median disease specific survival rates with PET-positive and PET-negative patients were 16.0 and 50.0 months, respectively.

In multivariate survival analyses, a PET-positivity remained an independent predictor of shortened overall survival (38). None of the other variables were associated with overall survival rate, and extravesical lesions on conventional CT was not significant on multivariate survival analysis.

The summary of literature is listed in *Table 5*. In spite of very limited patient numbers and several weaknesses in study design, the presence of PET-avid lesions was shown to be an independent variable for reduced survival rate without exception.
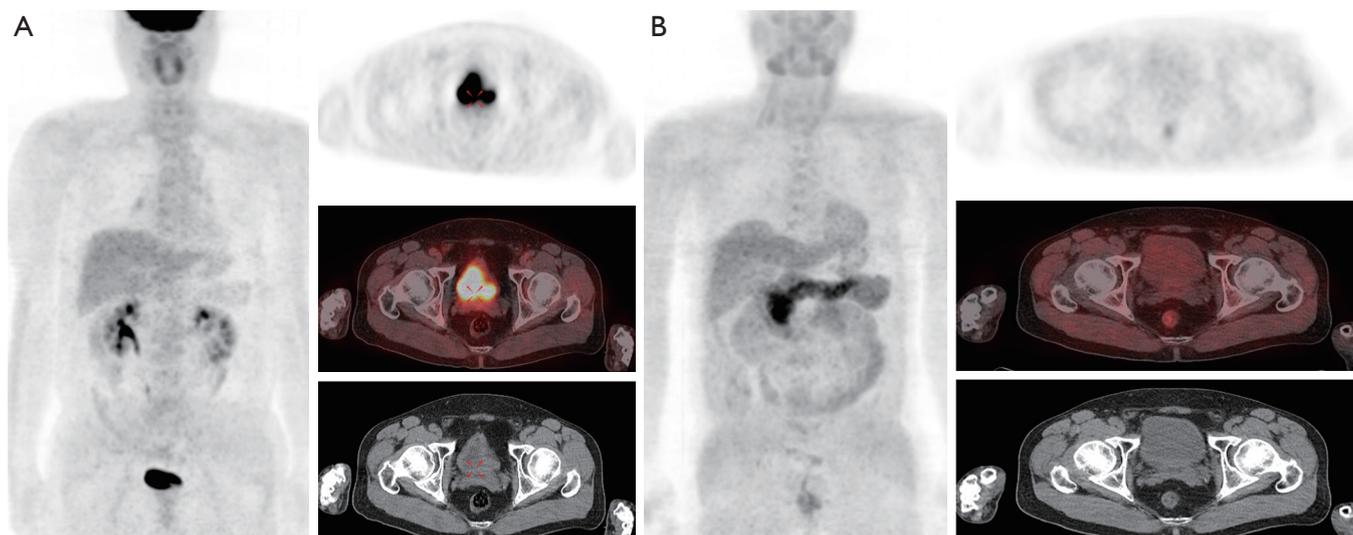
Figure 2 Biodistribution of F-18 FDG (A) and C-11 acetate (B). (A) FDG was excreted into the urine and intense activity is seen in the bladder; (B) physiologic tracer activity is seen in the liver, spleen, and pancreas; excreted activity is seen in the intestines. Myocardial and renal uptake are also shown. Only faint activity is seen in the bladder.

PET/CT using a non-FDG radiotracer

It is difficult to overcome the innate weakness of FDG for assessing urinary tract tumors. Several C-11 radiotracers with different uptake mechanisms, such as C-11 choline (CHOL), C-11 methionine, and C-11 acetate (ACET), are rarely excreted through the urinary system and are advantageous for the evaluation of the bladder itself (*Figure 2*). The performance to assess primary lesions (39,40) and regional LN status (41) has been reported in small studies. C-11 radiotracer PET/CT possesses the advantage of providing both anatomic and metabolic information in a single whole-body examination for bladder cancer and involved LNs.

Conventionally, ACET was developed and used for cardiac imaging, and was recently introduced in tumor imaging. The increased ACET uptake and retention in cancer cells is explained by enhanced fatty acid metabolism for cell membranes. As a tumor imaging agent for urinary malignancy, ACET has a critical advantage in that is not excreted into urine. In healthy persons, there is no remarkable ACET uptake except physiologic tracer activity in the liver, spleen, and pancreas.

In three studies (17,42,43), ACET PET/CT were evaluated for their use in bladder cancer and LN metastases, and in one study (44), ACET PET/MR was investigated. In the study by Schöder *et al.*, 17 patients (only 5 patients were over T2, the other were T0–T1) were evaluated (43). Six

patients had previously received intravesical BCG therapy and 10 had received neoadjuvant chemotherapy prior to ACET PET/CT. ACET PET/CT correctly identified 80% of residual bladder cancers (8/10), and two small residual TiS lesions (20%) were missed, which are attributed to the spatial detection limitation. Of the ACET uptake in the bladder wall, false positive lesions were identified secondary to proliferative cystitis after recent transurethral resection of the bladder or granulomatous cystitis after BCG instillation. The sensitivity and specificity of ACET PET/CT for LN metastasis was 100% and 87%. Three patients showed true positive uptake in the LN. False positive uptake occurred in 14 LN regions secondary to granulomatous disease after prior intravesical BCG therapy. Vargas *et al.* (17) reported that ACET accumulated in nine patients within the bladder wall; the ACET accumulation was true-positive in 7 patients and false-positive in 2 patients. Of the remaining ACET-negative 7 patients, 5 had true-negative and 2 had false-negative results for cancer in the bladder wall. Before ACET PET/CT, 4/16 patients received intravesical BCG treatment, 6/16 did systemic chemotherapy, 3/16 did both, and 3 did neither. Orevi *et al.* (42) demonstrated in 13 patients that ACET was taken up in all bladder cancers and involved LNs, but it could not detect *in situ* bladder cancer. ACET PET/CT showed positivity in 10 LNs, of which 5 were malignant, which gave a specificity of 50%.

In all three previous studies (17,42,43), ACET PET/

Table 6 C-11 acetate PET/CT for bladder cancer detection and lymph node staging

Author/year	Purpose	Study	Patients/lesions	Sensitivity (%)	Specificity (%)	PPV	NPV	ACC (%)
Vargas/2012	BC	Pro	16	100 (2/2)	71 (10/14)	NR	NR	75
Schoder/2012	BC	Pro	16	80 (8/10)	60 (3/5)	NR	NR	65
	LN	Pro	17, 109 lesions	100 (3/3), 100 (3/3)	64 (9/14), 87 (92/106)	NR	NR	
Orevi/2012	LN	Pro	14	50 (5/10)				
Salminen/2018	LN	Pro	175 lesions	20	96			80

BC, bladder cancer detection; LN, lymph node evaluation; PPV, positive predictive value; NPV, negative predictive value; ACC, accuracy; NR, not reported.

Table 7 Diagnostic performance of C-11 choline PET/CT

Author/Year	Purpose	Study/N	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	ACC (%)
Ceci/2015	Staging	Ret/59	59	90	84	81	71
de Jong/2002	LN	Pro/18	67	100	NR	NR	94
Picchio/2006	LN*	NR/27	62	100	NR	NR	89
Brunocilla/2014	LN**	Ret/26	42	84	NR	NR	NR
Maurer/2012	LN	Pro/44	58	66	39	81	64
Graziani/2015	LN***	Ret/25	67	85	80	73	76
	DIS***	Ret/25	90	93	90	93	92

*, study was done after cystectomy; **, patient-based diagnostic performance was calculated; ***, restaging. N, enrolled patients; PPV, positive predictive value; NPV, negative predictive value; ACC, accuracy; Pro, prospective; Ret, retrospective; LN, lymph node evaluation; DIS, distant lesion evaluation; NR, not reported in the article.

CT demonstrated that it has potential, in term of sensitivity and specificity, detecting bladder tumor in comparison with pathology. ACET PET/CT found all MIBC cases and ACET PET/CT seemed to outperform FDG PET/CT due to poor accuracy of FDG for the detection of primary site of bladder cancer. Although these studies showed over-staging affecting accuracy, over-staging seems a less clinically significant than under-staging, which might cause treatment delay. For LN detection, it showed good sensitivity but low specificity. Unfortunately, in the population with prior BCG or transurethral resection of bladder, staging accuracy was negatively affected. ACET PET/CT had the lowest specificity for the detection of nodal metastases due to the high rate of false positive LNs. It remains to be further investigated whether ACET have high positive predictive value in detecting involved LNs.

ACET PET is severely negatively affected by prior neoadjuvant chemotherapy (44). The sensitivity, specificity, and accuracy of ACET PET/MRI detecting MIBC was 1.00, 0.69, and 0.73 in patient base and 0.20, 0.96 and 0.80

in LN region level, respectively (44). For most imaging modalities including CT and MR, staging accuracy was hampered by previous intravesical and/or systemic chemotherapy. ACET PET was also disappointing until now. It does not seem that ACET PET/MRI is not a satisfactory solution for detecting metastatic pelvic LNs due to limited accuracy after chemotherapy.

MRI, CT, and ACET PET/CT were compared in most previous reports using ACET PET/CT before cystectomy and PLND. These three modalities had similar accuracy for MIBC, although these require further investigation. The pooled data for ACET PET/CT are listed in *Table 6*.

Other than ACET PET/CT, CHOL PET/CT was evaluated in several studies (40,45) (*Table 7*). Exogenous choline is phosphorylated into phosphatidylcholine, which is essential component of the cell membrane (46). Cancer is associated with increased cellular proliferation. Following up-regulation of choline kinase, which catalyzes the phosphorylation of choline, provides the rationale using CHOL as an oncological radiotracer (47). Because CHOL

is not excreted into urine, it was reported as a new PET radiotracer for urinary tumors. de Jong *et al.* (45) showed in their early work that CHOL avidly accumulates in bladder cancer with virtually absent urinary CHOL. Furthermore, no uptake of ACET was observed in premalignant lesions.

The use of CHOL PET/CT, which was mostly evaluated in the literature, is metastatic nodal assessment of MIBC with reference to the pathological specimens. In the study of de Jong *et al.* (45), CHOL PET/CT showed good performance with a sensitivity of 67%, specificity of 100%, and accuracy of 94% in 18 patients with bladder cancer. A patient-based analysis by Brunocilla *et al.* (48) reconfirmed these results with a sensitivity of 42%, specificity of 84%, and accuracy of 73% in the setting of LN staging (26 patients).

Picchio *et al.* (40) reported that diagnostic efficacy of CHOL PET/CT was higher than contrast enhanced CT for assessing LN involvement in bladder cancer staging. On the other hand, Maurer *et al.* (49) asserted that CHOL PET/CT did not give additional diagnostic benefit during preoperative LN staging, in comparison with contrast enhanced CT. 27% patients revealed LN metastasis (12/44), and the sensitivity, specificity, PPV, NPV, and accuracy for CHOL PET/CT were reported as 58%, 66%, 39%, 81%, and 64%, respectively, analyzing on patient-base; and for CT those were 75%, 56%, 39%, 86%, and 61%, respectively.

CHOL PET/CT may supply more diagnostic information in preoperative LN staging of bladder cancer patients and be considered a useful tool for restaging patients suspecting bladder cancer relapse. In bladder cancer population, CHOL PET/CT had a sensitivity, specificity, PPV, NPV and accuracy of 59%, 90%, 71%, 84%, and 81%, respectively (50). CHOL PET/CT is helpful for the restaging of BC patients suspected of relapse. In particular, CHOL PET/CT offered appropriate sensitivity, specificity, accuracy, PPV, and NPV for the identification of LN or distant metastases. CHOL PET/CT showed a sensitivity, specificity, accuracy, PPV, and NPV of 66.7%, 84.6%, 76%, 80%, and 73.3% for local relapse and 90%, 93.3%, 92%, 90%, and 93.3% for LNs and distant relapse, respectively (51).

In a prospective trial, neither CT nor CHOL PET/CT were able to sufficiently predict overall survival or cancer specific death in bladder cancer patients treated with radical cystectomy, although trends and moderately increased hazard ratios could be demonstrated without significant differences between CT and CHOL PET/CT (52). In summary, CHOL PET/CT demonstrates good sensitivity and specificity detecting LN metastasis in bladder cancer with some discrepancy in the results. It could be helpful for restaging bladder cancer patients with a high risk of relapse after primary therapy.

The C-11 radiotracer has a disadvantage compared to FDG because of its need for an expensive on-site cyclotron and its short physical half-life of 20 minutes, whereas, CHOL and ACET have the advantage of minimal urinary excretion and thus a higher sensitivity for the detection of local relapse compared to FDG (40). The tumoral uptake of ACET and CHOL are similar in bladder cancer. The mean tumor-to-background ratios (TBR) for the bladder tumor on ACET and CHOL were 4.5 (range, 1.9–8.7) and 6.0 (range, 2.0–12.7), respectively, and those for LNs were 9.8 (range, 2.6–44.0) and 13.2 (range, 4.3–50.0), respectively (42). SUVs of CHOL accumulation were slightly higher in bladder cancers, which was not statistically significant, than ACET whereas ACET accumulates more in LNs than CHOL. TBR of CHOL was not significantly higher than ACET for bladder cancers but significantly higher for LNs. The higher TBR for CHOL and ACET may be due to a lower background uptake rather than a higher tumoral uptake, and there may be an advantage for C-11 radiotracer imaging of bladder cancer and metastatic LNs. It should be noted that these results relate only to CHOL and ACET, as the corresponding FDG are excreted into urine and cannot reveal primary bladder cancers.

Conclusions

Recently, FDG and non-FDG PET/CT imaging have been increasingly studied as additive tools for the management of select bladder cancer patients. Several retrospective and prospective studies supported its superiority to CT in the staging of LN and extra-pelvic metastases, as well as re-staging, although there were some discrepant results. There are promising results for the use of new non-FDG radiotracer as an alternative to FDG, which causes a high degree of difficulty in the assessment of the genitourinary tract, despite its limited availability. This short review outlined the role of PET/CT imaging in bladder cancer.

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