Pilot Study of [^{18}F] Fluorodeoxyglucose Positron Emission Tomography (FDG-PET)/Magnetic Resonance Imaging (MRI) for Staging of Muscle-invasive Bladder Cancer (MIBC)

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Abstract

In this pilot study, preoperative staging with [^{18}F] fluorodeoxyglucose-positron emission tomography/magnetic resonance imaging in muscle-invasive bladder cancer detected the primary bladder tumor; however, the determination of lymph node status was limited by few patients with pathologic lymph node involvement. Additional studies are needed to evaluate the potential role for [^{18}F] fluorodeoxyglucose-positron emission tomography/magnetic resonance imaging in the staging of bladder cancer.

Introduction: Computed tomography (CT) has limited diagnostic accuracy for staging of muscle-invasive bladder cancer (MIBC). [^{18}F] Fluorodeoxyglucose positron emission tomography (FDG-PET)/magnetic resonance imaging (MRI) is a novel imaging modality incorporating functional imaging with improved soft tissue characterization. This pilot study evaluated the use of preoperative FDG-PET/MRI for staging of MIBC. **Patients and Methods:** Twenty-one patients with MIBC with planned radical cystectomy were enrolled. Two teams of radiologists reviewed FDG-PET/MRI scans to determine: (1) presence of primary bladder tumor; and (2) lymph node involvement and distant metastases. FDG-PET/MRI was compared with cystectomy pathology and computed tomography (CT). **Results:** Eighteen patients were included in the final analysis, most (72.2%) of whom received neoadjuvant chemotherapy. Final pathology revealed 10 (56%) patients with muscle invasion and only 3 (17%) patients with lymph node involvement. Clustered analysis of FDG-PET/MRI radiology team reads revealed a sensitivity of 0.80 and a specificity of 0.56 for detection of the primary tumor with a sensitivity of 0 and a specificity of 1.00 for detection of lymph node involvement when compared with cystectomy pathology. CT imaging demonstrated similar rates in evaluation of the primary tumor

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(sensitivity, 0.91; specificity, 0.43) and lymph node involvement (sensitivity, 0; specificity, 0.93) when compared with pathology. **Conclusions:** This pilot single-institution experience of FDG-PET/MRI for preoperative staging of MIBC performed similar to CT for the detection of the primary tumor; however, the determination of lymph node status was limited by few patients with true pathologic lymph node involvement. Further studies are needed to evaluate the potential role for FDG-PET/MRI in the staging of MIBC.

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Introduction

An estimated 80,470 (61,700 men and 18,770 women) new cases of bladder cancer and 17,670 (12,870 men and 4800 women) related deaths will occur in the United States in 2019.[1] Although the majority of patients present with non−muscle-invasive bladder cancer (NMIBC), 20% to 40% of patients will require treatment for invasive disease at some point in their disease course. The most important prognostic factor in invasive urothelial carcinoma is the stage, which is based on the depth of invasion and presence of local lymph node and distant metastases.[2] Patients with muscle-invasive bladder cancer (MIBC) undergo staging scans at diagnosis, with either multidetector computed tomography (CT) or magnetic resonance imaging (MRI) of the abdomen and pelvis and chest imaging.[3]

There are several important implications for accurate staging of bladder cancer including the identification of distant metastatic disease, which shifts the goal of treatment from curative to palliative intent and spares patients from the morbidity of radical cystectomy. Phase III randomized trials demonstrating a survival benefit for neoadjuvant cisplatin-based combination chemotherapy have been limited to patients without local lymph node involvement.[4,5] Chemotherapy has also been shown to successfully downstage patients with locally advanced disease and allow for cystectomy in select patients.[6] Assessing the response to chemotherapy is dependent on reliable cross-sectional radiographic assessment.

In a retrospective review of 82 consecutive cases of patients with MIBC who underwent preoperative staging CT of the abdomen and pelvis for detection of lymph node involvement and distant metastases, an accurate diagnosis was made in only 4 (4.9%) and 2 (2.4%) cases, respectively.[7] A more recent retrospective review of 276 patients with pathologic comparison to preoperative staging CT revealed an accuracy of only 49% with 23.4% and 24.7% overstaging and understaging, respectively. Accuracy in predicting lymph node metastases was also poor (54%), with 8.3% and 29.4% overstaging and understaging, respectively.[8] A retrospective review of 2600 patients evaluated for hematuria or a history of bladder cancer with a cystoscopy within 6 months of imaging revealed that CT urogram had a sensitivity of 79% and a positive predictive value of 75% for the detection of a primary bladder cancer lesion.[9]

MRI is also limited in its ability to detect lymph node metastases, with sensitivity reported as low as 50% in a retrospective review of 34 cases of recurrent bladder cancer.[10] It may, however, perform better than CT in the determination of local disease extent, as in this same study, MRI demonstrated a sensitivity of 97% and a specificity of 83% for detecting deep muscle invasion and a sensitivity of 95% and a specificity of 100% for detecting extravesical tumor extension.

The addition of [^{18}F] fluorodeoxyglucose positron emission tomography (FDG-PET) to CT has demonstrated an improvement in preoperative staging of bladder cancer.[11,12] In a study of 43 patients with negative CT and bone scintigraphy for metastatic disease who also underwent FDG-PET/CT, occult metastatic disease was detected in 7 cases, with a sensitivity of 70% and a specificity of 94%.[11] However, a study of 51 patients with invasive bladder cancer ($\geq$ T2) or recurrent high-risk superficial disease (T1G3 with or without Tis, M0) found no advantage with FDG-PET over CT alone for detection of lymph node involvement prior to cystectomy, suggesting limitations to the addition of FDG-PET.[13] Physiologic accumulation of tracer within the bladder can further limit assessment of bladder cancer; however, diuretic and hydration with delayed FDG-PET/CT imaging has been shown to improve detection.[14]

The optimal imaging modality for nodal staging in bladder cancer is unclear. In a study designed to compare the accuracy of nodal staging in patients using FDG-PET/CT and MRI, 18 patients completed both preoperative studies with results compared with histopathologic findings. There was no demonstrated statistical difference between FDG-PET/CT and MRI, although a trend was observed suggesting an advantage of FDG-PET/CT.[15]

FDG-PET/MRI is a novel hybrid imaging modality designed to combine the anatomical information from MRI, particularly the soft tissue contrast, with the physiologic information from FDG-PET. There are technical challenges related to image acquisition and fusion, including combining free-breathing PET data with breath-holding MRI data, but it has nonetheless shown promise in the detection of both abdominal and pelvic malignancies.[16] This modality has been most widely studied in the evaluation of gynecologic cancers, where FDG-PET/MRI has demonstrated superiority over MRI alone in the detection of recurrent pelvic disease (100% vs. 83.6%; $P < .001$).[17] In small pilot studies, FDG-PET/MRI has also demonstrated superiority over FDG-PET/CT for the detection of the primary gynecologic tumor on restaging scans.[18]

FDG-PET/MRI has also shown promise in the staging of bladder cancer. A recent pilot study comparing FDG-PET/MRI with MRI alone for the staging of bladder cancer found FDG-PET/MRI to have a higher accuracy for the detection of the bladder tumor (86% vs. 77%), metastatic pelvic lymph nodes (95% vs. 76%), and non-nodal pelvic malignancy (100% vs. 91%).[19] The current pilot study was designed to determine the test characteristics of FDG-PET/MRI for

the staging of MIBC and compare these findings with the gold standard pathology as well as the current imaging standard, CT.

Patients and Methods

Patients

This prospective pilot study was approved by the University of North Carolina institutional review board and informed consent was obtained from all participants. Patients 18 years or older with cT2/T3 cN0 M0 urothelial carcinoma of the bladder scheduled to undergo a radical cystectomy with pelvic lymph node dissection were eligible. Women of childbearing potential had a negative serum or urine pregnancy test within 7 days of FDG-PET/MRI. Exclusion criteria included decreased renal function, inability to tolerate MRI and/or PET scans, history of severe reaction to contrast-enhanced CT, poorly controlled diabetes mellitus, presence of pacemaker or intracranial aneurysm clip, body mass index > 35, pregnant or lactating females, and history of a prior malignancy within the last 5 years. Patients who had received neoadjuvant chemotherapy (NAC) were initially excluded but deemed eligible for inclusion after a trial amendment implemented in the setting of slow accrual.

Imaging Studies

Baseline CT. All patients underwent conventional CT post-NAC prior to planned radical cystectomy and pelvic lymph node dissection. Each CT was interpreted by a diagnostic radiologist specializing in body imaging; in patients who received NAC, pre-NAC chemotherapy CT was also available for comparison. Data from the CT reports were used to determine the presence of the primary tumor and any suspected lymph node involvement.

FDG-PET/MRI Technique and Image Analysis. All patients underwent gadolinium-enhanced MRI with simultaneous acquisition of FDG-PET prior to radical cystectomy and pelvic lymph node dissection. In patients undergoing NAC, FDG-PET/MRI was performed after NAC and prior to cystectomy, and imaging findings were then compared with pathology from the cystectomy.

A Biograph mMR (Siemens Healthcare) was used for the hybrid PET/MRI scanner. All patients fasted for 6 hours and did not receive insulin or oral hypoglycemic agents for at least 4 hours before the examination. The blood glucose level was verified to be less than 250 mg/dL before FDG injection. Given the limitations of FDG-PET in the bladder owing to interference by FDG in the urine, patients underwent oral hydration prior to FDG injection and were instructed to void immediately prior to the scan. If incomplete bladder voiding was demonstrated on an initial scan, a Foley catheter was placed to facilitate clearance of urine. The prescribed injected activity was 444 MBq (12 mCi). Simultaneous acquisition of PET with MRI was performed. Iterative three-dimensional (3-D) reconstruction with a full width at half-maximum 4 mm-gaussian filter was used with 3 iterations and 21 subsets. The matrix size was 172×172; axial field of view, 25.8 cm; and transaxial field of view, 59.4 cm. The images were acquired without breath-holding.

MRI of the whole body was performed covering from the level of skull base to the level of symphysis pubis with the specific protocol described in Supplemental Table 1 (in the online version). Three-D T2-weighted imaging was performed for the pelvis including the bladder. Postgadolinium 3D-gradient echo (GE) sequences were acquired by an automated injector (Medrad) administering 2 mL/sn of intravenous contrast followed by 20 mL saline. The gadolinium-based contrast agent was Multihance (Bracco). Dynamic contrast enhanced imaging was performed for the pelvis including the bladder on the arterial phase (between 30 and 60 seconds after the contrast administration), venous phase (between 60 and 120 seconds), and interstitial phase (120 and 180 seconds) for the pelvis. Additionally, contrast enhanced imaging of the upper abdomen, chest, and neck were also acquired with 3D-GE sequences after the pelvic post-gadolinium imaging.

Two independent teams, each consisting of 1 nuclear radiologist and 1 diagnostic radiologist (JKL and AS, EA and TZW), all of whom had at least 10 years of experience in PET imaging or body MRI, performed combined reads in consensus, resulting in 2 combined reads for every FDG-PET/MRI. Two different sets of reviewers were used to increase accuracy of image analysis and decrease potential bias resulting from reviewer's experience. Cases were read by consensus to decrease the subjectivity of individual assessments. Unlike the CT imaging, radiologists were blinded to prior pathologic, radiographic, and cystoscopic findings.

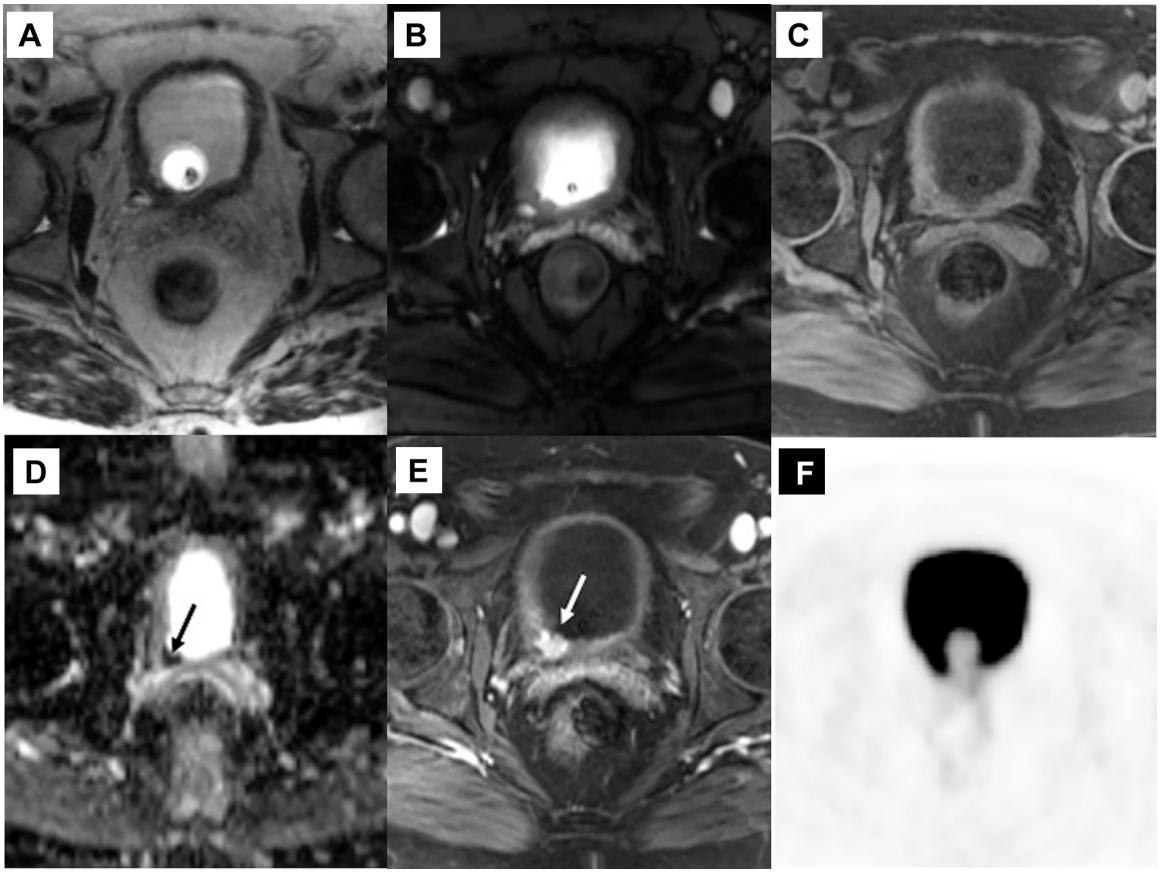
Each team recorded the presence or absence of primary tumor, pathologic lymph nodes, and any evidence for distant metastatic disease on the respective imaging studies, and the 2 combined reads

Table 1 Baseline Characteristics (n = 18)

Characteristic	%
Median age at diagnosis, y (range)	63.5 (50-76)
Race	
White	94.4
Black	5.6
Gender	
Male	83.3
Female	16.7
cT status at diagnosis	
cT2	88.9
cT3	11.1
Histology (predominant)	
Urothelial carcinoma	100
Variant histology present	39.0
Micropapillary	11.1
Squamous	11.1
Plasmacytoid	5.6
Glandular	5.6
Glandular/squamous	5.6
Neoadjuvant chemotherapy	
Yes	72.2
Neoadjuvant regimen	
GC	84.6
ddMVAC	7.7
GC + pembrolizumab	7.7

Abbreviations: ddMVAC = dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin; GC = gemcitabine + cisplatin; GC + pembrolizumab on clinical trial: NCT02690558.

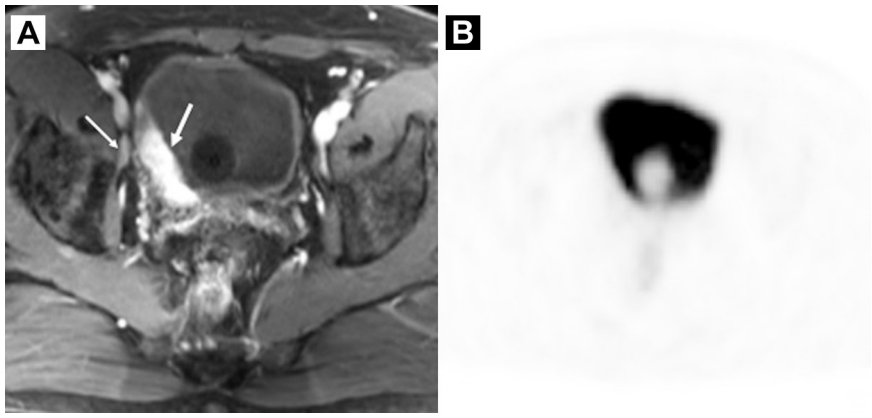
Figure 1 Transverse 3-dimensional T2-weighted SPACE (A), T2-Weighted Fat-suppressed SS-ETSE (B), T1-weighted 3-dimensional Fat-suppressed Gradient Echo (C), Apparent Diffusion Coefficient Map (D), T1-weighted Post-gadolinium Fat-suppressed 3-dimensional Gradient Echo (E), and Attenuation Corrected Positron Emission Tomography (PET) Image (F). An Invasive Urothelial Cancer (*arrows*) Is Present Adjacent to the Right Ureterovesical Junction. The Lesion Is Isointense to the Bladder Wall on T2-weighted Images (A and B) and T1-weighted Precontrast Image (C) and Not Well Seen, although Mild Asymmetrical Wall Thickening Is Detected at This Location. The Lesion Restricts the Diffusion and Therefore Is Seen as a Hypointense Lesion on the Apparent Diffusion Coefficient Map (*black arrow*, D). The Lesion Also Shows Prominent Enhancement on the Postgadolinium T1-weighted Image (*white arrow*, E), Which Involves the Whole Muscular Layer. There Is Also Associated Right Hydroureter. However, the Lesion Is Not Seen on the [^{18}F] Fluorodeoxyglucose-PET Image (F) owing to the Presence of Significant [^{18}F] Fluorodeoxyglucose Activity in the Bladder Lumen. Please Also Note the Foley Balloon in the Bladder Lumen on Magnetic Resonance and PET Images



from each paired team were then used for data analysis. The imaging assessment of the primary bladder cancer on MRI relied on the detection of focal or diffuse abnormal wall thickening, which is greater than 5 mm, or focal polypoid lesions, regardless of size, extending into the lumen. Additional MRI features including the presence of restricted diffusion on diffusion-weighted MRI sequence and/or arterial phase enhancement on dynamic contrast enhanced 3-D GE post-gadolinium imaging sequences with or without the presence of abnormal high T2 signal on T2-weighted images were the other required MRI features for the diagnosis of bladder cancer. The detection of abnormal FDG uptake on PET images was also accepted as the sign of bladder cancer; however, the absence of abnormal FDG uptake was not accepted as a negative sign for bladder cancer in the presence of abnormal corresponding MRI findings on consensus reading because the presence of intraluminal FDG uptake can prevent the detection of FDG uptake on the bladder wall. The presence of abnormal FDG uptake without any corresponding MRI findings was also accepted as a sign of bladder cancer on consensus reading. FDG uptake evaluation on PET was evaluated qualitatively on imaging, and no quantitative standardized uptake value assessment was performed for diagnostic purposes.

The imaging assessment of lymph nodes on MRI primarily relied on the size of lymph nodes. Lymph nodes that measured 1.0 cm or larger in short axis were accepted as enlarged lymph nodes. The presence of round morphology, increased T2 signal, or prominent restricted diffusion compared with the remaining other lymph nodes were accepted as additional MRI findings that could be suggestive of metastatic disease; however, these findings were not accepted as positive findings for metastatic disease in the absence of an enlarged lymph node. Increased FDG uptake of the lymph nodes

Figure 2 Transverse T1-weighted Post-gadolinium Fat-suppressed 3-dimensional Gradient Echo (A) and Attenuation-corrected Positron Emission Tomography (PET) Image (B). There Is an Invasive Urothelial Carcinoma (*thick arrow*, A) Along the Right Lateral Wall of the Bladder, Which Does Not Show Any [^{18}F] Fluorodeoxyglucose (FDG) Uptake Owing to the Presence of Significant FDG Activity in the Bladder Lumen on the FDG-PET Image. There Is Also an Ellipsoid Lymph Node that is Subcentimeter in Size Along the Right External Iliac Chain on T1-weighted Magnetic Resonance Image (*thin arrow*, A) which Does Not Show Any Abnormal FDG Uptake on the FDG-PET Image (B)



on PET imaging was accepted as a sign of metastatic disease, and this assessment was performed qualitatively but no quantitative standardized uptake value assessment was performed for lymph node evaluation.

Statistical Analysis

This pilot study planned for an enrollment of 30 patients with the primary objective of estimating the test characteristics of FDG-PET/MRI for staging of MIBC, using pathology from the cystectomy and lymph node dissection as the gold standard. Analyses included calculating the accuracy between imaging modalities and pathology ([true positive + true negative]/[true positive + true negative + false positive + false negative]) as well as estimating the sensitivity, specificity, positive predictive value, and negative predictive value for both the detection of the primary tumor and lymph node involvement with FDG-PET/MRI as compared with the cystectomy pathology and the pre-cystectomy CT scan. A clustered analysis was performed, combining the 2 paired reads with additional analyses including test statistics, accuracy, and concordance between the paired reads. Given the limited number of cases and concordance evaluation performed between paired reads, inter-team variability was not assessed.

Results

Patients

Baseline characteristics are summarized in Table 1. Only 21 of a planned 30 patients were enrolled between June 2012 and December 2016 owing to slow accrual, with 18 patients included in the final analysis. One MRI was determined to be not evaluable owing to artifact from hip prosthesis, and 2 patients had data corruption during processing and storing, resulting in loss of all attenuation-corrected FDG-PET images. The median age was 63.5 years. Most patients enrolled were white (94.4%), male (83.3%), and had cT2 disease (88.9%). Most patients received NAC (72.2%), and the most common regimen was gemcitabine and cisplatin (84.6%). Eight (61.5%) of 13 patients who underwent NAC achieved a pathologic response (≤ ypT1) at the time of cystectomy. An average of 20.1 lymph nodes were removed at cystectomy. FDG-PET/MRI were performed as close to cystectomy and staging CT scan to allow for accurate correlation; the average duration between FDG-PET/MRI and cystectomy was 23.6 days,

Table 2 Clinical, Pathologic, and Imaging Characteristics of Trial Participants

Pt.	cT at Diagnosis	pTNM at Cystectomy	FDG-PET/MRI Characteristics
1	cT2	pT2 pN0	True positive
2	cT2	pT2 pN0	True positive
3	cT2	pT3 pN3	False negative LN and primary
4	cT2	ypT0 pN0	True positive
5	cT2	ypT0 pN0	False positive primary
6	cT2	ypT3a pN0	False negative primary
7	cT3	ypT0 pN0	False positive primary
8	cT2	ypT0 pN0	False positive primary
9	cT2	pT0 pN0	True positive
10	cT2	ypTis pN0	True positive
11	cT2	ypT0 pN0	False positive primary
12	cT2	ypT2 pN0	True positive
13	cT2	ypT3 pN0	False negative primary
14	cT2	pT3a pN0	True positive
15	cT2	ypT0 pN0	False positive primary
16	cT2	ypT2b pN2	False negative LN
17	cT2	ypT2a pN0	True positive
18	cT2	ypT3a pN3	False negative LN

Abbreviations: FDG = [^{18}F] fluorodeoxyglucose; LN = lymph node; MRI = magnetic resonance imaging; PET = positron emission tomography.

Table 3 Test Characteristics of Paired Radiologist Reads of FDG-PET/MRI as Compared With Pathology at Cystectomy

Team One

		Primary Tumor				Lymph Node	
		Surgical Pathology				Surgical Pathology	
		Positive	Negative			Positive	Negative
PET/MRI	Positive	9	5	PET/MRI	Positive	0	0
	Negative	1	3		Negative	3	15
	Sensitivity	0.90			Sensitivity	0	
	Specificity	0.38			Specificity	1.00	
	PPV	0.64			PPV	0	
	NPV	0.75			NPV	0.83	
	Accuracy	0.67			Accuracy	0.83	

Team Two

		Primary Tumor				Lymph Node	
		Surgical Pathology				Surgical Pathology	
		Positive	Negative			Positive	Negative
PET/MRI	Positive	7	2	PET/MRI	Positive	0	0
	Negative	3	6		Negative	3	15
	Sensitivity	0.70			Sensitivity	0	
	Specificity	0.75			Specificity	1.00	
	PPV	0.78			PPV	0	
	NPV	0.67			NPV	0.83	
	Accuracy	0.72			Accuracy	0.83	

Clustered Analysis of Paired Reads

		Primary Tumor				Lymph Node	
		Surgical Pathology				Surgical Pathology	
		Positive	Negative			Positive	Negative
PET/MRI	Positive	16	7	PET/MRI	Positive	0	0
	Negative	4	9		Negative	6	30
	Sensitivity	0.80			Sensitivity	0	
	Specificity	0.56			Specificity	1.00	
	PPV	0.70			PPV	0	
	NPV	0.69			NPV	0.83	
	Accuracy	0.69			Accuracy	0.83	
	Concordance	0.72			Concordance	1	

Abbreviations: FDG = [^{18}F] fluorodeoxyglucose; MRI = magnetic resonance imaging; NPV = negative predictive value; PET = positron emission tomography; PPV = positive predictive value.

and the average duration between FDG-PET/MRI and staging CT scan was 31.3 days. Figures 1 and 2 demonstrate representative images of FDG-PET/MRI imaging.

FDG-PET/MRI

Comparison With Cystectomy Pathology. Radiologic presence of the primary tumor and lymph node involvement from PET/MRI were compared with the pathology at the time of cystectomy; however, harvested nodes were not directly correlated with nodes assessed on imaging. Seven (38.9%) of 18 patients had no pathologic evidence of disease (ypT0), and 15 (83.3%) of 18 patients had no pathologic lymph node involvement at cystectomy (ypN0). Detailed clinical, pathologic, and imaging information are summarized in Table 2. Combined analyses had a sensitivity and specificity of 80% and 56% for evaluation of the primary tumor, with an overall accuracy of 69%. Combined analyses had a sensitivity and specificity of 0% and 100% for evaluation of lymph node involvement, with an overall accuracy of 83%. There was a 72% and 100% concordance rate for evaluation of the primary tumor and lymph node involvement on PET/MRI between the 2 teams. Additional test characteristics are summarized in Table 3. The positive predictive value for FDG-PET/MRI in detecting lymph node involvement was 0%;

however, evaluation was limited with only 3 (16.7%) patients having pathologic lymph node involvement at the time of cystectomy. Complete staging information at time of study enrollment, at time of cystectomy, and FDG-PET/MRI findings are summarized in Table 2.

Comparison With Conventional CT. All 18 patients underwent preoperative conventional CT imaging in addition to FDG-PET/MRI. Conventional preoperative CT had a sensitivity and specificity of 91% and 43%, with an overall accuracy of 72% for the detection of the primary tumor. The sensitivity and specificity for the detection of lymph node involvement was 0% and 93%, respectively, with an overall accuracy of 78%. FDG PET/MRI and CT had similar test characteristics for the detection of the primary tumor and lymph node involvement (Table 4), recognizing that the small number of patients with positive lymph node involvement limited the analysis.

Discussion

Current imaging modalities for the detection and staging of MIBC have significant limitations. Direct visualization via cystoscopy cannot always distinguish benign masses from malignant lesions, CT imaging cannot differentiate NMIBC from MIBC, both CT and MRI have low sensitivity for nodal staging, and PET/CT has limitations in differentiating normal and pathologic structures.[20] FDG-PET/MRI is an emerging imaging modality with limited data to guide its clinical application at present. The current study enrolled a total of 21 patients with MIBC, of which 18 patients had evaluable FDG-PET/MRI images to compare with surgical pathology. Two studies were not interpretable owing to errors in attenuation correction, a well-described challenge for this novel imaging modality, with incorrect attenuation resulting in underestimation of FDG avidity in PET/MRI compared with PET/CT.[16] This FDG-PET/MRI accurately detected primary tumor in 25 (69%) of 36 combined radiologist assessments when compared with surgical pathology. This was similar to the preoperative CT imaging accuracy in evaluation of the primary bladder tumor in 13 (72%) of 18 assessments. FDG-PET/MRI in this study performed worse than prior published experiences with FDG-PET/MRI for detection of primary bladder tumors (85%); however, differences in patient populations likely account for differences in diagnostic accuracy.[19] The largest study published to date examined 22 patients with MIBC who were staged with both FDG-PET/MRI and MRI alone, revealing an improved accuracy in the detection of pelvic lymph node metastases with FDG-PET/MRI.[19] The incremental improvement with FDG-PET/MRI was most pronounced for the detection of pathologic lymph nodes. When FDG-PET imaging was added to MRI, the suspicion for pathologic lymph node involvement was changed (high to low suspicion or low to high suspicion) in 52% of the imaging studies, with 95% of the changes based on FDG-PET/MRI being correct when compared with the cystectomy pathology.

Notably, preoperative CT imaging in our study performed significantly better than historical series in evaluation of the primary tumor (72% vs. 49% accuracy) and lymph nodes (78% vs. 54% accuracy).[8] Potential explanations for the improved accuracy with CT in the current study include technological advances in CT image acquisition as well as more experienced and dedicated body radiologists. CT scans were also evaluated with the benefit of access to the medical record, whereas the FDG-PET/MRI reads were done with the readers blinded to all other clinical and imaging studies. Neither CT nor FDG-PET/MRI was able to detect pathologic lymph node disease in the 3 cases with documented pathologic lymph node involvement.

Owing to slow accrual, enrollment was expanded to include patients undergoing NAC, which resulted in improved patient accrual and likely contributed to a high rate of patients without pathologic lymph node involvement at the time of cystectomy. NAC is the standard of care for patients with MIBC, based on the results of SWOG 8710 demonstrating an improvement in survival and pathologic complete response (pCR) (38% vs. 15%; $P < .001$) for those undergoing NAC followed by cystectomy compared with those undergoing cystectomy alone.[4] NAC is also effective in downstaging patients with lymph node-positive disease. One study enrolling patients with isolated MIBC and patients with lymph node-positive disease demonstrated that administration of neoadjuvant accelerated M-VAC (methotrexate, vinblastine, doxorubicin, and cisplatin) resulted in a pCR of 38%, downstaging to NMIBC in 14%, and a total of 65% of patients downstaged to a

Table 4 Test Characteristics of Conventional CT for Detection of Primary Tumor and Lymph Node Involvement as Compared With Pathology at Cystectomy

	Primary Tumor				Lymph Node		
		Surgical Pathology				Surgical Pathology	
		Positive	Negative			Positive	Negative
CT	Positive	10	4	CT	Positive	0	1
	Negative	1	3		Negative	3	14
	Sensitivity	0.91			Sensitivity	0	
	Specificity	0.43			Specificity	0.93	
	PPV	0.71			PPV	0	
	NPV	0.75			NPV	0.82	
	Accuracy:	0.72			Accuracy	0.78	

Abbreviations: CT = computed tomography; NPV = negative predictive value; PPV = positive predictive value.

lower pathologic stage at cystectomy.[21] A similar study found that 82% of patients with lymph node-positive disease were downstaged to ypN0 at time of cystectomy.[22] In our study, patients who received NAC had a better than predicted ypT0 rate (61.5%), suggesting that patient selection may have contributed to few patients with pathologic lymph nodes at the time of cystectomy, thus limiting our ability to determine the test characteristics of FDG-PET/MRI for the detection of lymph node involvement. The PET portion of the scan may be particularly susceptible to the effects of chemotherapy as there could be a functional response in the primary lesion or lymph nodes, with less or no response on the CT or MRI images.[23]

FDG-PET/MRI is a promising new combined imaging modality harnessing the improved soft-tissue contrast of MRI with the molecular imaging of PET; however, accurate evaluation of urothelial malignancies is confounded by the physiologic renal excretion of FDG into the ureters and the urinary bladder. Although forced diuresis protocols, in which patients are requested to void or undergo Foley catheterization prior to imaging, has been shown to improve study quality and tumor detection in pelvic malignancies, it is not effective in all cases.[24] The optimal method for bladder evaluation on MRI is with full bladder distension and therefore imaging with combined modality FDG-PET/MRI may only allow optimization of one modality.

Several new radiotracers are also in development for use in PET imaging, including ^{11}C-choline, ^{11}C-methionine, and ^{11}C-acetate. ^{11}C-choline is of particular interest for imaging urothelial malignancies as it is minimally excreted in urine. In a small study of 25 patients found to have residual bladder cancer at the time of cystectomy, preoperative ^{11}C-choline PET imaging was found to have comparable accuracy with CT in detecting residual bladder cancer and a superior accuracy in detecting lymph node metastases ($P < .01$).[25] ^{11}C-choline PET/CT has similarly demonstrated a modest improvement in sensitivity for detection of lymph node metastases in bladder cancer compared with FDG-PET alone or CT alone.[26,27]

FDG-PET/MRI and CT had similar accuracy in the detection of the primary bladder tumor, but given the low number of patients with pathologic lymph node involvement at time of surgery, this study was unable to meaningfully assess the accuracy of FDG-PET/MRI for the detection of lymph node involvement. Additional studies enrolling more patients with lymph node involvement, including patients ineligible for NAC, are needed to better evaluate a potential role for FDG-PET/MRI in the staging of MIBC.

Clinical Practice Points

- Current standard imaging modalities for patients with MIBC have relatively poor predictive accuracy for the detection of both the primary tumor and lymph node metastases. Novel imaging modalities such as FDG-PET/MRI may improve the diagnostic accuracy for the staging of bladder cancer.
- This pilot study was designed to determine the test characteristics of FDG-PET/MRI for staging MIBC and to compare these findings with pathologic evaluation and standard CT imaging. In 18 patients with MIBC, FDG-PET/MRI had a sensitivity of 0.80 and specificity of 0.56 for detection of the primary tumor when compared with cystectomy pathology. Evaluation of lymph node status was limited by few patients with pathologic lymph node involvement, in part owing to the use of NAC.
- Further studies are needed to evaluate the potential role for FDG-PET/MRI in the staging of MIBC.

CRediT authorship contribution statement

Patrick J. Eulitt: Data curation, Formal analysis, Investigation, Methodology, Writing - original draft, Writing - review & editing. **Ersan Altun:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Resources, Software, Validation, Visualization, Writing - original draft, Writing - review & editing. **Arif Sheikh:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Resources, Software, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing. **Terence Z. Wong:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Resources, Software, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing. **Michael E. Woods:** Data curation, Formal analysis, Investigation, Methodology, Writing - original draft, Writing - review & editing. **Tracy L. Rose:** Data curation, Formal analysis, Investigation, Methodology, Writing - review & editing. **Eric M. Wallen:** Data curation, Formal analysis, Investigation, Methodology, Writing - review & editing. **Raj S. Pruthi:** Data curation, Formal analysis, Investigation, Methodology, Writing - review & editing. **Angela B. Smith:** Data curation, Formal analysis, Investigation, Methodology, Writing - review & editing. **Matthew E. Nielsen:** Data curation, Formal analysis, Investigation, Methodology, Writing - review & editing. **Young E. Whang:** Data curation, Formal analysis, Investigation, Methodology, Writing - review & editing. **William Y. Kim:** Data curation, Formal analysis, Investigation, Methodology, Writing - review & editing. **Paul A. Godley:** Data curation, Formal analysis, Investigation, Methodology, Writing - review & editing. **Ethan M. Basch:** Data curation, Formal analysis, Investigation, Methodology, Writing - review & editing. **Grace U. David:** Data curation, Project administration, Resources, Software, Supervision, Validation, Visualization. **Juanita Ramirez:** Data curation, Project administration, Resources, Software, Supervision, Validation, Visualization. **Allison M. Deal:** Data curation, Formal analysis, Investigation, Methodology, Writing - review & editing. **W. Kimryn Rathmell:** Data curation, Formal analysis, Investigation, Methodology, Writing - review & editing. **Ronald C. Chen:** Data curation, Formal analysis, Investigation, Methodology, Writing - review & editing. **Marc A. Bjurlin:** Data curation, Formal analysis, Investigation, Methodology, Writing - review & editing. **Weili Lin:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing. **Joseph K. Lee:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing. **Matthew I. Milowsky:**

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Disclosure

The authors have stated that they have no relevant conflicts of interest.

Supplemental Data

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Supplemental Data

Supplemental Table 1 Magnetic Resonance Imaging Protocol

Sequence	Plane	TR	TE	Flip Angle	Thickness/Gap	FOV	Matrix
T2-weighted SS-ETSE	Coronal	1500[b]	85	170	6 mm/20%	350-400	192 × 256
T2-weighted SS-ETSE	Axial	1500[b]	85	170	6 mm/20%	350-400	192 × 256
T2-weighted SS-ETSE	Sagittal	1500[b]	85	170	6 mm/20%	350	192 × 256
T2-weighted STIR[a]	Axial	3980[b]	54	180 to >90	5 mm/20%	350-400	139 × 256
T2-weighted STIR	Coronal	3600	54	180 to >90	5 mm/20%	350-400	154 × 256
T1 SGE in/out-of-phase	Axial	170	2.2/4.4	70	7 mm/20%	350-400	192 × 320
T2 3D TSE	Axial	1200	120	150	1.5 mm	250	256 × 256
T2 TSE	Axial/coronal/sagittal	5000	80	90	3 mm	230	256 × 256
Diffusion-weighted imaging	Axial	4500	88	90	3 mm	270	128 × 128
T1 3D GE FS pre	Axial	3.8	1.7	10	3 mm	350-400	160 × 256
Post-gadolinium sequences							
T1 3D GE fat-suppressed	Axial/coronal/sagittal	3.8	1.7	10	3 mm	350-400	160 × 256

Abbreviations: FOV = field of view; 3D GE: 3-dimensional gradient echo; SGE = spoiled gradient echo; SS-ETSE = single shot echo train spin echo; TE = echo time; TI = inversion time; TR = repetition time.
[a]TI = 220.
[b]TR between slice acquisitions.