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Utility of routine preoperative ^{18}F -fluorodeoxyglucose positron emission tomography-computed tomography (^{18}F -FDG PET/CT) in identifying pathologic lymph node metastases at radical cystectomy

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Abstract

Purpose: To determine the diagnostic performance of ^{18}F -FDG PET/CT for detecting nodal metastases in patients with muscle-invasive urothelial bladder cancer prior to radical cystectomy.

Materials and Methods: Preoperative ^{18}F -FDG PET/CT scans ($n = 208$) were retrospectively reviewed. Scans were routinely performed in 185 patients with muscle-invasive urothelial bladder cancer between August 2012 and February 2017, all of whom underwent radical cystectomy and pelvic lymph node dissection. Analyses were stratified by clinical node involvement and chemotherapy status.

The diagnostic performance of ^{18}F -FDG PET/CT was assessed according to sensitivity, specificity, positive predictive value, and negative predictive value.

Results: Lymph node metastases at time of PLND were present in 21.8% of those without suspicious nodes on computed tomography (clinically node negative) and 52.6% of those with suspicious nodes on CT (clinically node positive). Median metastatic focus size was 5 mm. In clinically node negative patients, ^{18}F -FDG PET/CT rarely detected nodal metastases (sensitivity 7–23%). In clinically node positive patients, a negative ^{18}F -FDG PET/CT was useful in ruling out lymph node metastases (sensitivity 92–100%). This study was limited by its mixed population and focus on pelvic nodal metastases only.

Conclusions: ^{18}F -FDG PET/CT appears to be most useful for better characterization of enlarged nodes identified by CT. Routine preoperative ^{18}F -FDG PET/CT has limited utility in clinically node-negative patients.

Keywords

neoplasm staging; positron emission tomography and computed tomography; cystectomy; lymph node excision; urinary bladder neoplasms

INTRODUCTION

^{18}F -FDG PET/CT is being increasingly used prior to radical cystectomy for staging of high-risk bladder cancer. From 2004 to 2011, the proportion of patients with stage II or III bladder cancer undergoing ^{18}F -FDG PET/CT increased from 1 to 15% in the SEER (Surveillance, Epidemiology, and End Results) registry.¹ This increasing utilization of ^{18}F -FDG PET/CT occurred without endorsement by either the American Urological Association² or European Association of Urology guidelines.³

The utility of ^{18}F -FDG PET/CT rests in its ability to potentially identify lymph node metastases prior to radical cystectomy. In the advanced stage setting, a study from our center previously found ^{18}F -FDG PET/CT to have a sensitivity of 92% with a specificity of 81% for lymph node metastases.⁴ Nonetheless, diagnostic properties in the metastatic setting may not necessarily apply to the radical cystectomy population due to a lower inherent metastatic burden. Current studies of ^{18}F -FDG PET/CT prior to radical cystectomy are summarized in a recent meta-analysis of 13 studies, among which the average number of patients was 49 and the average proportion with pathology-confirmed lymph node metastases was 30%.⁵ Sensitivity ranged from 33% to 100% (n-weighted mean, 55%) and specificity from 58% to 100% (n-weighted mean, 93%). The wide ranges of these values result from the heterogeneous nature of these studies, which generally pooled patients regardless of preoperative chemotherapy status, nodal size on CT, or extent of PLND. Based on this data, it remains unclear whether ^{18}F -FDG PET/CT is useful prior to radical cystectomy and if so under which clinical circumstances.

Uncertainty surrounding the value of ^{18}F -FDG PET/CT in the radical cystectomy candidate led us to perform this study. From 2012 to 2017, the authors began routinely offering ^{18}F -FDG PET/CT prior to radical cystectomy in patients with high-risk invasive bladder cancer. We conducted a re-review of this data set by a dedicated genitourinary radiologist to determine the diagnostic accuracy of ^{18}F -FDG PET/CT in several distinct populations of patients who undergo radical cystectomy. Our goal was to assess whether routine ^{18}F -FDG PET/CT use had value, and if so, to more precisely define the population which would benefit.

METHODS

Eligibility Criteria and Patient Characteristics

Patients were eligible for study inclusion if they had MIBC and underwent ^{18}F -FDG PET/CT prior to radical cystectomy, and received a templated RC-PLND as described above between August 2012 and February 2017. Patients were excluded if they had primary urethral cancer, non-urothelial bladder cancer, concurrent active malignancy other than MIBC, did not receive a templated extended PLND, or underwent ^{18}F -FDG PET/CT >60 days prior to RC-PLND or chemotherapy.

Planned stratifications for this study included clinical node status (cN0 or cN+), and timing of ^{18}F -FDG PET/CT relative to chemotherapy (pre-, post, and no chemotherapy).

cN+ disease was defined as the presence of an enlarged pelvic lymph node with short-axis diameter of 10 mm or greater on a conventional CT with contrast performed prior to PET/CT scan. Both conventional CT and ^{18}F -FDG PET/CT were interpreted by a genitourinary radiologist at our institution.

^{18}F -FDG-PET/CT

^{18}F -FDG was administered intravenously approximately 60 min prior to imaging on dedicated PET/CT scanners (GE Medical Systems, Waukesha, WI, USA) from the mid-skull to the mid-thigh. Images were obtained for 3–5 min per bed position depending on patient size. All ^{18}F -FDG PET/CT studies were reviewed and annotated in detail for the purpose of this study by an experienced genitourinary radiologist using picture-archiving workstations that display CT, PET emission, and PET/CT fusion image sets in various orthogonal planes. SUVmax, normalized to patient lean body mass, were recorded using a three-dimensional tool placed over sites of abnormal ^{18}F -FDG uptake. ^{18}F -FDG PET/CT findings were characterized as abnormal/suspicious for malignancy if uptake intensity was greater than that of adjacent blood pool or normal gluteal muscle activity (background) and not explained by physiologic processes (e.g. urinary ^{18}F -FDG excretion in the ureters/bladder). The locations of all areas of suspicious radiotracer uptake were recorded and catalogued.

Pathologic Assessment of Lymph Nodes

All patients underwent RC-PLND. The templated PLND involved bilateral removal of all nodal tissue with associated fibro-adipose tissue and skeletonization of vessels from the genitofemoral nerve laterally, node of Cloquet caudally, pelvic floor inferiorly, and cranially to include at least the aortic bifurcation. Additional lymph nodes in the presacral space and fossa of Marcille were also removed. Lymph nodes were sorted by anatomic region (right common iliac, left common iliac, right pelvic, left pelvic, presacral and paraaortic nodes) and submitted for pathology separately to ensure detailed evaluation and accurate mapping.

Pathologic specimens were processed and reviewed in the standard fashion by an experienced genitourinary pathologist. The number of positive lymph nodes in addition to the total number of lymph nodes were reported in each anatomic region. The diameter of the largest metastatic lesion in each region was also measured.

Statistical Analysis

The sensitivity, specificity, positive predictive value, and negative predictive value were calculated for ^{18}F -FDG PET/CT's detection of pathologic positive lymph nodes on both a per-patient (a positive PET in a patient with pN+) and per-anatomical region (whether the site on PET positive finding was in the region of a pathologically positive node) basis among clinically node-negative patients, defined as lymph nodes < 10 mm short axis on pre-operative CT scan. The regional analysis was conducted to more accurately identify the diagnostic properties of PET/CT by reducing chance-associations that might relate to analysis on a patient level. Confidence intervals were estimated based on the Rao-Scott method to take into account multiple scans per patient.⁶ We did not re-review the baseline CT scans of patients included in our previous report on the diagnostic properties of ^{18}F -

FDG PET/CT for patients with nodal metastatic disease,⁴ nor did we perform a per-region analysis among cN+ patients. All statistical analyses were performed in software packages SAS 9.4 (SAS Institute Inc., Cary, NC, USA) or R version 3.4 (The R Foundation for Statistical Computing).

RESULTS

Patient Characteristics

The study cohort comprised 185 patients, from whom a total of 208 ¹⁸F-FDG PET/CT scans were collected and analyzed. Baseline characteristics are detailed in Table 1. Most (170; 82%) scans were from patients classified as cN0 based on CT and 38 (18%) were from patients classified by CT as cN+.

Among patients with cN0 disease, nodal metastases were pathologically confirmed (pN+) after surgery in 21.8%, compared with 52.6% of those with cN+ disease. In pN+ patients, the median metastatic focus size was 5 mm and a median of 2 nodes were positive.

Diagnostic Characteristics of ¹⁸F-FDG PET/CT

Among patients with cN0 disease (n = 170 scans), ¹⁸F-FDG PET/CT had very poor sensitivity for detecting nodal metastases, ranging from 7% in patients who had received chemotherapy prior to imaging to 23% in patients who had not yet received chemotherapy. However, its specificity was high, ranging from 89% to 99% (table 2). This finding was consistent across all subgroups of patients regardless of chemotherapy status or whether the analysis was conducted on a per-patient or per-region basis. Similarly, its positive predictive value was low (25–37%) and its negative predictive value was modest (75–83%) on a per patient level.

Our cohort included 38 patients with cN+ disease (table 1). Among the 13 patients who did not receive preoperative chemotherapy, ¹⁸F-FDG PET/CT had a sensitivity of 100% (95% CI, 47.8–100) and a specificity of 62.5% (95% CI, 20.8–91) for detecting nodal metastases. We did not evaluate the diagnostic performance of pre- and post-chemotherapy scans due to the potential confounding effects of chemotherapy exposure on imaging findings and final pathology in the setting of a limited number of events (supplementary table 1).

Pre- and Post-chemotherapy PET/CT Analysis

To determine if either stability or a change in metabolic response could predict negative final pathology, we analyzed the ¹⁸F-FDG PET/CT scans of 23 patients who underwent imaging prior to and after preoperative chemotherapy (supplementary figure 1). We found no evidence that either metastatic lesion stability or change in metabolic response correlated with pN+ status. In this exploratory analysis, the rate of discrepant findings ranged from 33% (pathologically confirmed metastases following stable negative PET/CT scans) to 100% (no metastatic lymph nodes after conversion from negative to positive PET/CT scans).

Incidental Findings

To better understand the implications of routinely performing ^{18}F -FDG PET/CT prior to RC-PLND, we assessed the incidental findings identified in patients not receiving chemotherapy ($n = 69$). We excluded patients receiving chemotherapy because these patients received multiple imaging tests and we could not ascribe the origin of the incidental findings. Numerous investigations and procedures were prompted by ^{18}F -FDG PET/CT-detected lesions (supplementary table 2). Two unrelated malignancies were diagnosed and it is uncertain if these would have been detected by conventional modalities.

DISCUSSION

In this study, we found that routine ^{18}F -FDG PET/CT was not useful in identifying lymph node metastases in patients who were cN0 on CT. This finding arises from the observed low sensitivity (7–23%) in this group. The low sensitivity likely is a result of the low burden of disease in these patients, where the median metastatic focus size within the involved LN was only 5 mm.

The main use of ^{18}F -FDG PET/CT is likely in better evaluating clinically suspicious lymph nodes identified by conventional CT. We found that a negative ^{18}F -FDG PET/CT in this group ruled out lymph node metastases due to the high sensitivity of ^{18}F -FDG PET/CT in this group. Our findings corroborate those of an earlier study from our center supporting the high sensitivity of ^{18}F -FDG PET/CT in patients with lymph node metastases. Among 51 suspicious lymph nodes on ^{18}F -FDG PET/CT, sensitivity was 92% (95% CI 74–99) and specificity was 81% (95% CI 61–93).⁴ Together, these results indicate that a suspicious lymph node identified on CT that is not PET-avid can be presumed to be pathologically negative. Management of a PET-avid suspicious node is less clear – other risk factors along with the degree of certainty required for clinical decision making will influence whether this is presumed to be truly positive or a percutaneous biopsy is performed. Alternatively, those with a PET-avid node could receive a preoperative chemotherapy regimen that does not differ based on suspicion of metastatic disease, such as 6 cycles of dose-dense gemcitabine and cisplatin.⁷

We did not find any suggestion that ^{18}F -FDG PET/CT had clinical utility in any other scenarios that we studied. Post-chemotherapy scans have exceedingly low sensitivity and positive predictive value, preventing their use to inform decisions on whether to perform consolidative RC-PLND. Additionally, we saw no evidence that either stable ^{18}F -FDG PET/CT findings pre- and post-chemotherapy or conversion from positive to negative predicted pN+ status. These findings all reaffirm extended PLND as the only accurate lymph node staging method presently available for patients with MIBC.

Data prior to our study was presented in a recent meta-analysis of 13 studies, finding a wide range of sensitivities, from 33% to 100%, and specificities, from 58% to 100%.⁵ We hypothesize that these heterogeneous findings are likely attributable to differences in study design. By separately analyzing data from cN0 and cN+ patients, we identified major differences in sensitivity, allowing clear conclusions regarding clinical utility in these distinct settings. This is a practical stratification because clinical nodal status is generally

known prior to ^{18}F -FDG PET/CT. Other strengths of our investigation included the lack of selection bias resulting from routine use of ^{18}F -FDG PET/CT during this period and consistent re-review of all scans by a dedicated genitourinary radiologist.

This study was limited by the mixed population with respect to chemotherapy exposure and the timing of ^{18}F -FDG PET/CT relative to chemotherapy. Chemotherapy could impact our findings if lymph nodes completely responded, leading to pN0 status despite positive ^{18}F -FDG PET/CT findings. Nonetheless, we do not feel that this limitation impacts our overall conclusions. We were also limited in our ability to assess the utility of ^{18}F -FDG PET/CT in detecting distant metastases prior to RC-PLND. This limitation arises from the fact that these patients would ultimately not undergo radical cystectomy and thus not be included in our study cohort. Finally, we were limited in our ability to assess the value of SUVmax in distinguishing positive from negative lymph nodes because of study size. As a higher SUVmax PET lesion is more likely to be pathologically positive,⁸ a higher cutoff could improve specificity. The ideal SUVmax cutoff should be defined in future research.

One of the broader implications of this study is that routine ^{18}F -FDG PET/CT in the radical cystectomy candidate particularly with clinically negative LN's is unnecessary. Most patients with MIBC will have already undergone conventional CT, which is more widely available, less expensive, involves lower radiation exposure, and has a shorter acquisition time compared with ^{18}F -FDG PET/CT. Additionally, ^{18}F -FDG PET/CT leads to a higher rate of incidental findings, prompting more invasive investigations, anxiety, and costs. ^{18}F -FDG PET/CT use should thus be limited to patients in whom it has clinical utility, namely those with abnormal nodes on CT scan.

CONCLUSIONS

^{18}F -FDG PET/CT should not be used as a routine test prior to radical cystectomy. Its main utility is in evaluating equivocal lymph nodes seen on conventional CT scan. Further research is required to clarify the role of ^{18}F -FDG PET/CT in assessing chemotherapy response.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key of Definitions for Abbreviations

^{18}F -FDG PET/CT	^{18}F -fluorodeoxyglucose positron emission tomography-computed tomography
cN0	clinical node negative
cN+	clinical node positive

RC	radical cystectomy
PLND	pelvic lymph node dissection
MIBC	muscle invasive bladder cancer
SUV_{max}	maximum standardized uptake value
pN+	pathologic node positive

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Table 1.

Patient, disease, and preoperative chemotherapy characteristics.

	cN- (n = 170)	cN+ (n = 38)
Patient characteristics		
Median age, years (IQR)	67 (59–74)	67 (59–74)
Female gender, n (%)	32 (19)	8 (21)
Disease characteristics		
Pathologic tumor stage at cystectomy, n (%)		
T0	28 (16)	3 (8)
Tis	18 (11)	3 (8)
Ta	2 (1)	1 (3)
T1	5 (3)	1 (3)
T2	37 (22)	6 (16)
T3	77 (45)	23 (61)
T4	3 (2)	1 (3)
Median LN count, n (IQR)	28 (20–37)	36 (23–49)
Patients with pN+ disease, n (%)	37 (22)	20 (53)
Median positive node count, n (IQR)	2 (1–6)	2 (2–5)
Median size of largest metastatic focus in pN+ patients, cm (IQR)	0.5 (0.2–0.9)	0.6 (0.3–0.8)
Preoperative chemotherapy characteristics		
Preoperative chemotherapy received, n (%)	114 (67)	25 (66)
Chemotherapy regimen, n (%)		
Gemcitabine and cisplatin	97 (85)	18 (72)
Other	17 (15)	7 (28)
Timing of scan relative to chemotherapy, n (%)		
No chemotherapy	56 (33)	13 (34)
PET/CT prior to chemotherapy	60 (35)	18 (47)
PET/CT following chemotherapy	54 (32)	7 (18)
Median time from PET/CT to first chemotherapy dose, days (IQR)	13 (7–21)	15 (10–22)
Median time from last chemotherapy dose to PET/CT, days (IQR)	28 (14–42)	32 (24–51)

Abbreviations: IQR, interquartile range; cN-, clinically node negative; cN+, clinically node positive; pN+, persistent nodal disease; PET/CT, positron emission tomography/computed tomography

Diagnostic properties of ¹⁸F-FDG PET/CT for detecting nodal metastases in patients without abnormal nodes on CT scan (n = 170 scans) on a per patient (A) and per region (B) basis.

Table 2.

A. Per patient							
	Sensitivity (%)	95% CI	Specificity (%)	95% CI	Positive predictive value (%)	95% CI	Negative predictive value (%)
No chemotherapy	10.0	0.8 – 58.0	93.5	80.9 – 98.0	25.0	0.4 – 96.0	82.7
Post-chemotherapy	7.1	0.7 – 44.0	95.0	81.1 – 99.0	33.3	0.0 – 100.0	74.5
Pre-chemotherapy	23.0	6.3 – 57.0	89.4	76.2 – 96.0	37.5	8.6 – 79.0	80.8
B. Per region							
	Sensitivity (%)	95% CI	Specificity (%)	95% CI	Positive predictive value (%)	95% CI	Negative predictive value (%)
No chemotherapy	9.0	0.8 – 53.0	98.7	96.6 – 100.0	33.3	2.0 – 92.0	93.9
Post-chemotherapy	N/A	N/A	99.0	96.9 – 100.0	N/A	N/A	91.3
Pre-chemotherapy	10.0	0.9 – 55.0	98.5	96.0 – 99.0	20.0	0.7 – 89.0	96.6