BJU Int 2024 doi:10.1111/bju.16363

BJUI
BJU International

Original Article

Use of 18F-fluoro-2-deoxy-D-glucose (18F-FDG) PET/CT for lymph node assessment before radical cystectomy in bladder cancer patients

Mattia Longoni[1,2], Pietro Scilipoti[1,2], Chiara Re[1,2], Giuseppe Rosiello[1,2], Luigi Nocera[1,2], Francesco Pellegrino[1,2], Giuseppe Basile[1,2], Mario de Angelis[1,2], Leonardo Quarta[1,2], Giusy Burgio[1,2], Andrea Necchi[3], Antonio Cigliola[3], Arturo Chiti[4], Maria Picchio[4], Andrea Salonia[1,2], Alberto Briganti[1,2], Francesco Montorsi[1,2] and Marco Moschini[1,2]

[1]*Department of Urology and Division of Experimental Oncology, URI, Urological Research Institute, IRCCS Ospedale San Raffaele,* [2]*Vita-Salute San Raffaele University,* [3]*Department of Genitourinary Medical Oncology, and* [4]*Department of Nuclear Medicine, IRCCS San Raffaele Hospital and Scientific Institute, Milan, Italy*

Objective

To assess the diagnostic performance of 18F-fluoro-2-deoxy-D-glucose (18F-FDG) positron emission tomograpy (PET)/computed tomography (CT) in nodal staging before radical cystectomy (RC) and pelvic lymph node dissection (PLND) for bladder cancer (BCa).

Materials and Methods

This analysis was based on a cohort of 199 BCa patients undergoing RC and bilateral PLND between 2015 and 2022. Neoadjuvant chemotherapy (NAC) or immunotherapy (NAI) was administered after oncological evaluation. All patients received preoperative 18F-FDG PET/CT to assess extravesical disease. Point estimates for true negative, false negative, false positive, true positive, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of conventional imaging and PET/CT were calculated. Subgroup analysis in patients receiving neoadjuvant treatment was performed.

Results

At preoperative evaluation, 30 patients (15.1%) had 48 suspicious nodal spots on 18F-FDG PET/CT. At RC and bilateral PLND, a total of 4871 lymph nodes (LNs) were removed with 237 node metastases corresponding to 126 different regions. Pathological node metastases were found in 17/30 (57%) vs 39/169 patients (23%) with suspicious vs negative preoperative 18F-FDG PET/CT, respectively (sensitivity = 0.30, specificity = 0.91, PPV = 0.57, NPV = 0.77, accuracy = 0.74). On per-region analysis including 1367 nodal regions, LN involvement was found in 19/48 (39%) vs 105/1319 (8%) suspicious vs negative regions at PET/CT, respectively (sensitivity = 0.15, specificity = 0.98, PPV = 0.40, NPV = 0.92, ACC = 0.90). Similar results were observed for patients receiving NAC (n = 44, 32.1%) and NAI (n = 93, 67.9% [per-patient: sensitivity = 0.36, specificity = 0.91, PPV = 0.59, NPV = 0.80, accuracy = 0.77; per-region: sensitivity = 0.12, specificity = 0.98, PPV = 0.32, NPV = 0.93, ACC = 0.91]). Study limitations include its retrospective design and limited patient numbers.

Conclusions

In eight out of 10 patients with negative preoperative 18F-FDG PET/CT, pN0 disease was confirmed at final pathology. No differences were found based on NAC vs NAI treatment. These findings suggest that 18F-FDG PET/CT could play a role in the preoperative evaluation of nodal metastases in BCa patients, although its cost-effectiveness is uncertain.

Keywords

bladder cancer, 18F-FDG, PET/CT, lymph node, staging, radical cystectomy, pelvic lymph node dissection, neoadjuvant therapy

Introduction

Bladder cancer (BCa) affects 573 278 patients worldwide every year and represents a substantial cause of morbidity and mortality worldwide [1]. Muscle-invasive bladder cancer (MIBC) accounts for almost 25% of the cases [2], of which approximately 20% would eventually undergo radical cystectomy (RC) and bilateral pelvic node dissection (pLND) [3]. In this setting, cross-sectional imaging with abdomen CT is considered the standard of care in the evaluation of pelvic node metastases before RC [4]. However, radiological lymph node involvement (LNI) is defined according to only dimensional criteria [5], thus the diagnostic performance of such cross-sectional imaging is affected by a false-negative rate of approximately 25% [6].

Positron emission tomography (PET)/ CT using 18F-fluoro-2-deoxy-D-glucose (18F-FDG) provides functional information based on the increased glucose uptake and glycolysis of cancer cells, highlighting metabolic abnormalities before morphological alterations occur [7] and therefore has been proposed to improve preoperative nodal staging, with preliminary data reporting an accuracy ranging from 60% to 90% [8].

The aim of our study was to assess 18F-FDG PET/CT performance in the staging of pelvic node metastasis of BCa patients undergoing RC + PLND, particularly in the subset of patients receiving neoadjuvant therapies, both neoadjuvant chemotherapy (NAC) and immunotherapy (NAI). We hypothesised that PET/CT may exhibit optimal sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy, which may help clinicians to improve preoperative evaluation of disease extent.

Materials and Methods

Study Population

After institutional review board approval, 199 patients with histologically confirmed MIBC or high-risk BCG-unresponsive BCa, receiving RC and bilateral PLND between March 2015 and August 2022 at our tertiary referral centre, were identified (Fig. 1). Eligibility for NAC was granted upon oncological evaluation, while NAI was administered within a clinical trial.

Protocol for PET/CT Acquisition

All patients underwent preoperative standard CT and 18F-FDG PET/CT scans of the chest and abdomen in high-volume centres within 6 weeks before RC. A standard and comparable protocol was used for PET/CT image acquisition. Patients fasted for at least 6 h before imaging, ensuring blood glucose levels were below 10 mmol/L during tracer injection. To minimise muscle 18F-FDG uptake, patients refrained from muscular activity before scans. PET/CT studies were conducted using integrated systems according to institution-specific protocols. PET data, acquired 60 min after 18F-FDG administration, were corrected using CT images and fused into various views. A PET scan was considered positive when abnormal 18F-FDG uptake was observed outside areas of physiological biodistribution, subsequently confirmed by co-registered CT abnormalities.

Pathological Examination and Report

Removed lymph nodes (LNs) were sorted and separately analysed according to anatomical location and side. After fixation, processing and staining using haematoxylin and eosin, pathological specimens were examined by dedicated pathologists at our centre. In cases where metastasis was suspected but not conclusively identified with routine staining, immunohistochemical tests were performed using specific antibodies targeting proteins associated with cancer cells. The 2009 TNM classification was used.

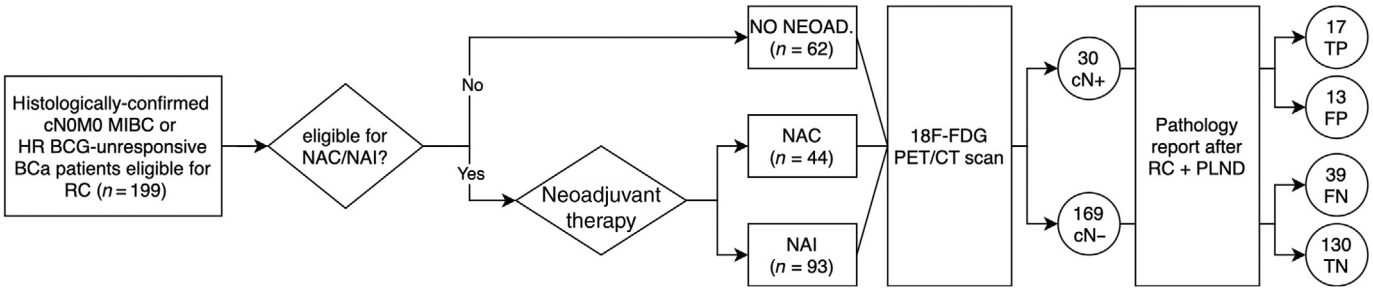
Variables and Outcomes

Demographics and preoperative staging with both 18F-FDG PET/CT and conventional cross-sectional imaging were assessed. The corresponding anatomical location of each positive nodal spot was registered, including right and left obturator, right and left internal iliac, right and left external iliac, right and left common iliac and pre-sacral regions. Pathological features from the most recent transurethral resection of bladder tumour, namely, pathological T stage, histological grade (according to 2016/2022 WHO classifications), and presence of carcinoma *in situ* were retrieved. Administration of chemo- or immunotherapy was noted. Open or robot-assisted RC and bilateral PLND were performed. Retrieved LNs were separately analysed according to the anatomical location, as previously described. Pathological T stage (pT) and N stage (pN), number of LNs removed and positive LNs were included in the final pathological report.

Statistical Analysis

Continuous and categorical variables were displayed as median and interquartile range (IQR) and frequency and proportion, respectively. Using histological report of PLND as the gold standard, point estimates (true positive [TP], true negative [TN], false positive [FP], false negative [FN]), sensitivity, specificity, PPV, NPV, and accuracy of conventional imaging and 18F-FDG PET/CT scan for nodal staging were calculated. Both per-patient and per-region diagnostic performances were evaluated. A subgroup analysis of patients receiving neoadjuvant therapy was also carried out. Corresponding 95% CIs were provided. Analysis was

Fig. 1 Study flow diagram. A total of 199 patients, treated with radical cystectomy and bilateral pelvic lymph node dissection for muscle-invasive or BCG-unresponsive bladder cancer (BCa) between 2015 and 2022 were identified. Neoadjuvant therapy was administered in 137 cases. All patients underwent preoperative 18F-fluoro-2-deoxy-D-glucose (18F-FDG) positron emission tomography (PET)/CT for lymph node involvement (LNI) assessment. Histological findings were used as gold standard for LNI. FN, false negative; FP, false positive; HR, high-risk; MIBC, muscle-invasive bladder cancer; NAC, neoadjuvant chemotherapy; NAI, neoadjuvant immunotherapy; PLND, pelvic lymph node dissection; RC, radical cystectomy; TN, true negative; TP, true positive.



carried out using the R software environment for statistical computing and graphics (version 4.2.1; http://www.r-project.org/).

Results

Overall, the median (IQR) age at RC and median (IQR) body mass index were 68 (62–74) years and 25 (23–28) kg/m^2, respectively, and 168 of the patients (84.4%) were male. At conventional imaging, cT1-2 and cT3-4 disease was found in 118 (65.2%) and 63 patients (34.8%), respectively, while the cN-positive rate was 19.0%. A total of 137 patients (68.8%) received neoadjuvant therapy, specifically 44 (32.1%) and 93 patients (67.9%) had NAC and NAI, respectively. At preoperative 18F-FDG PET/CT, a total of 48 suspicious pelvic lesions were found in 30 patients (15.1%), while distant metastases were detected by PET/CT in 20 (10.3%). Open and robot-assisted RC was performed in 70 (35.4%) and 128 patients (64.6%), respectively. At bilateral PLND, 4871 LNs were retrieved, with a median (IQR) of 22 (17–31) LNs removed for each patient. Final pathological examination identified 237 positive LNs (median: 2, IQR 1–5), corresponding to 126 positive nodal areas (median: 2, IQR 1–3). Overall, pT3 disease and LNI were found in 50 (25.1%) and 56 patients (28.1%), respectively, and distribution of pN stage was as follows: 19 (9.5%) pN1, 23 (11.6%) pN2 and 14 (7.0%) pN3 (Table 1).

Diagnostic Performance of PET/CT in the Overall Population

All patients were included in the per-patient analysis evaluating diagnostic performance of conventional imaging and PET/CT in LNI detection. Point estimates of TN, FN, FP and TP were 125 vs 130, 36 vs 39, 18 vs 13 and 20 vs 17, respectively, while sensitivity, specificity, PPV, NPV and accuracy were 0.36 (95% CI 0.23–0.50) vs 0.30 (95% CI 0.19–0.44), 0.87 (95% CI 0.81–0.92) vs 0.91 (95% CI 0.85–0.95), 0.53 (95% CI 0.36–0.69) vs 0.57 (95% CI 0.37–0.75), 0.78 (95% CI 0.70–0.84) vs 0.77 (95% CI 0.70–0.83) and 0.73 (95% CI 0.66–0.79) vs 0.74 (95% CI 0.67–0.80), respectively.

Per-region analyses included 1184 vs 1367 nodal regions, which were assessed at conventional imaging vs PET/CT, harvested during PLND and included in the pathological report. Point estimates of TN, FN, FP and TP were 1029 vs 1214, 105 vs 105, 40 vs 29 and 10 vs 19, respectively, corresponding to sensitivity, specificity, PPV, NPV and accuracy of 0.09 (95% CI 0.04–0.15) vs 0.15 (95% CI 0.09–0.23), 0.96 (95% CI 0.95–0.97) vs 0.98 (95% CI 0.97–0.98), 0.20 (95% CI 0.10–0.34) vs 0.40 (95% CI 0.26–0.55), 0.91 (0.85–0.96) vs 0.92 (95% CI 0.90–0.93), and 0.88 (95% CI 0.86–0.90) vs 0.90 (95% CI 0.88–0.92), for standard CT and PET/CT scan, respectively (Tables 2 and 3). Specifically, accuracy of 18F-FDG PET/CT according to anatomical site of the LNs was 0.88 and 0.86 for the right and left obturator, respectively, 0.94 and 0.92 for the right and left internal iliac, respectively, 0.86 for the right and left external iliac, respectively, 0.93 for the right and left common iliac, respectively, and 0.96 for the pre-sacral nodes (Fig. 2).

Diagnostic Performance of PET/CT in the Neoadjuvant Cohort

A subgroup analysis included only patients receiving NAC or NAI (n = 137). Point estimates of TN, FN, FP and TP were 87 vs 92, 19 vs 23, 14 vs 9 and 17 vs 13 for conventional and PET/CT imaging, respectively. Sensitivity, specificity, PPV, NPV and accuracy were 0.47 (95% CI 0.30–0.65) vs 0.36 (95% CI 0.21–0.54), 0.86 (95% CI 0.78–0.92) vs 0.91 (95% CI 0.84–0.96), 0.55 (95% CI 0.36–0.73) vs 0.59 (95% CI 0.36–0.79), 0.82 (95% CI 0.73–0.89) vs 0.80 (95% CI 0.70–0.83) and 0.76 (95% CI 0.68–0.83) vs 0.77 (95% CI

Table 1 Descriptive characteristics of 199 patients treated with radical cystectomy and bilateral pelvic lymph node dissection for muscle-invasive or BCG-unresponsive bladder cancer between 2015 and 2022 undergoing pre-operative 18F-FDG PET/CT for lymph node involvement assessment.

Characteristic	Overall population (*N* = 199)	Neoadjuvant group (*N* = 137)
Gender, *n* (%)		
Female	31 (15.6)	19 (13.9)
Male	168 (84.4)	118 (86.1)
Age, years (IQR)	68 (62, 74)	67 (60, 74)
Body mass index, kg/m^2 (IQR)	25 (23, 28)	25 (23, 27)
Worst stage at TURBT, *n* (%)		
Tis-T1	36 (18.6)	8 (5.8)
T2	162 (81.4)	129 (94.2)
Presence of CIS at TURBT, *n* (%)	51 (25.6)	38 (27.7)
High grade at TURBT, *n* (%)	199 (100)	137 (100)
T stage at CT, *n* (%)		
T0–T2	118 (65.2)	80 (58.4)
T3–T4	63 (34.8)	57 (41.6)
cN+ at CT, *n* (%)	38 (19.0)	31 (22.6)
Neoadjuvant therapy, *n* (%)	137 (68.8)	137 (100)
Neoadjuvant regimen, *n* (%)		
Chemotherapy	44 (22.1)	44 (32.1)
Immunotherapy	93 (46.7)	93 (67.9)
Neoadjuvant immunotherapy regimen (*n* = 93), *n* (%)		
Epacadostat		3 (3.2)
Nivolumab		6 (6.5)
Pembrolizumab		76 (81.7)
Retifanlimib		2 (2.2)
Sacituzumab		3 (3.2)
Others		3 (3.2)
Neoadjuvant chemotherapy regimen (*n* = 44), *n* (%)		
Carboplatin-based		3 (6.8)
Cisplatin-based		23 (52.3)
MVAC		17 (38.6)
Others		1 (2.3)
cN+ at PET/CT, *n* (%)	30 (15.1)	22 (16.1)
PET/CT-positive regions,* *n* (IQR)	1 (1, 2)	1 (1, 2)
cM+ at PET/CT, *n* (%)	20 (10.3)	11 (8.2)
Surgery, *n* (%)		
Open RC	70 (35.4)	39 (28.9)
Robot-assisted RC	128 (64.6)	96 (71.1)
pT stage, *n* (%)		
T0–T2	149 (74.9)	105 (76.6)
T3	50 (25.1)	32 (23.4)
pN+, *n* (%)	56 (28.1)	36 (26.3)
pN stage, *n* (%)		
N0	143 (71.9)	101 (73.7)
N1	19 (9.5)	14 (10.3)
N2	23 (11.6)	11 (8.0)
N3	14 (7.0)	11 (8.0)
Removed LNs, *n* (IQR)	22 (17, 31)	24 (18, 33)
Pathological positive LNs,† *n* (IQR)	2 (1, 5)	2 (1, 4)
Pathological positive regions,† *n* (IQR)	2 (1, 3)	1 (1, 3)

*CIS, carcinoma in situ; IQR, interquartile range; LN, lymph node; PET, positron emission tomography; RC, radical cystectomy; TURBT, transurethral resection of bladder tumour; MVAC, methotrexate-vinblastine-doxorubicin-cisplatin. *Among patients with cN+ disease found at PET/CT (n = 30). †Among patients with pN+ disease at pathology examination (n = 56).*

0.69–0.83), respectively. In this specific cohort, per-region analysis included 879 vs 1010 nodal regions for conventional CT and PET/CT scan, respectively. Point estimates of TN, FN, FP and TP were 773 vs 908, 68 vs 71, 30 vs 21 and 8 vs 10, respectively. Sensitivity, specificity, PPV, NPV and accuracy of conventional imaging and PET/CT were 0.11 (95% CI 0.05–0.20) vs 0.12 (95% CI 0.06–0.22), 0.96 (95% CI 0.95–0.97) vs 0.98 (95% CI 0.97–0.99), 0.21 (95% CI 0.10–0.37) vs 0.32 (95% CI 0.17–0.51), 0.93 (95% CI 0.86–1.01) vs 0.93 (95% CI 0.91–0.94), and 0.89 (95% CI 0.87–0.91) vs 0.91 (95% CI 0.89–0.93), respectively (Tables 2 and 3).

Discussion

Lymph node involvement at final pathology represents an important prognostic factor in patients undergoing RC for MIBC, accounting for a 5-year overall survival rate of 18% [9]. Conventional cross-sectional imaging proved to be

Table 2 Per-patient and per-region diagnostic performance of preoperative standard CT scan in the detection of lymph node involvement in patients treated with radical cystectomy and bilateral pelvic lymph node dissection for muscle-invasive or BCG-unresponsive bladder cancer between 2015 and 2022.

	Overall				Neoadjuvant group			
	Per-patient analysis (*N* = 199)		Per-region analysis (*N* = 1184)		Per-patient analysis (*N* = 137)		Per-region analysis (*N* = 879)	
	Path. –	Path. +	Path. –	Path. +	Path. –	Path. +	Path. –	Path. +
CT –	125	36	1029	105	87	19	773	68
CT +	18	20	40	10	14	17	30	8
	Value	**95% CI**	**Value**	**95% CI**	**Value**	**95% CI**	**Value**	**95% CI**
Sensitivity	0.36	0.23–0.50	0.09	0.04–0.15	0.47	0.30–0.65	0.11	0.05–0.20
Specificity	0.87	0.81–0.92	0.96	0.95–0.97	0.86	0.78–0.92	0.96	0.95–0.97
PPV	0.53	0.36–0.69	0.20	0.10–0.34	0.55	0.36–0.73	0.21	0.10–0.37
NPV	0.78	0.70–0.84	0.91	0.85–0.96	0.82	0.73–0.89	0.93	0.86–1.01
Accuracy	0.73	0.66–0.79	0.88	0.86–0.90	0.76	0.68–0.83	0.89	0.87–0.91

Path., pathological report; PNV, negative predictive value; PPV, positive predictive value.

Table 3 Per-patient and per-region diagnostic performance of preoperative 18F-fluoro-2-deoxy-D-glucose (18F-FDG) PET/CT scan in the detection of lymph node involvement in patients treated with radical cystectomy and bilateral pelvic lymph node dissection for muscle-invasive or BCG-unresponsive bladder cancer between 2015 and 2022.

	Overall				Neoadjuvant group			
	Per-patient analysis (*N* = 199)		Per-region analysis (*N* = 1367)		Per-patient analysis (*N* = 137)		Per-region analysis (*N* = 1010)	
	Path. –	Path. +	Path. –	Path. +	Path. –	Path. +	Path. –	Path. +
PET/CT –	130	39	1214	105	92	23	908	71
PET/CT +	13	17	29	19	9	13	21	10
	Value	**95% CI**	**Value**	**95% CI**	**Value**	**95% CI**	**Value**	**95% CI**
Sensitivity	0.30	0.19–0.44	0.15	0.09–0.23	0.36	0.21–0.54	0.12	0.06–0.22
Specificity	0.91	0.85–0.95	0.98	0.97–0.98	0.91	0.84–0.96	0.98	0.97–0.99
PPV	0.57	0.37–0.75	0.40	0.26–0.55	0.59	0.36–0.79	0.32	0.17–0.51
NPV	0.77	0.70–0.83	0.92	0.90–0.93	0.80	0.72–0.87	0.93	0.91–0.94
Accuracy	0.74	0.67–0.80	0.90	0.88–0.92	0.77	0.68–0.83	0.91	0.89–0.93

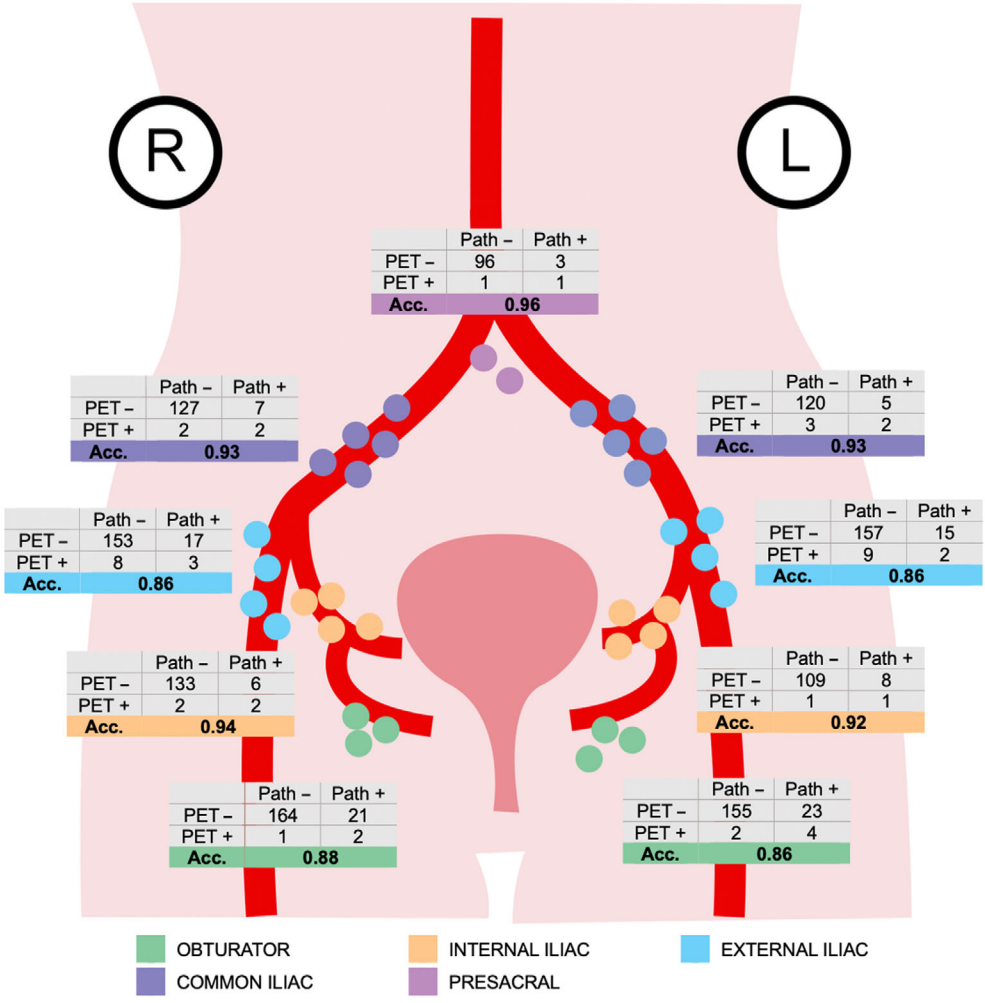
Path., pathological report; PET, positron emission tomography; PNV, negative predictive value; PPV, positive predictive value.

insufficient to detect LN metastases preoperatively, with 54% accuracy [10]. In this regard, preliminary but encouraging results support the role of 18F-FDG PET/CT scan for loco-regional and systemic staging in MIBC [11–14].

Our study led to several noteworthy observations. First, in patient-based analysis, 18F-FDG PET/CT showed low sensitivity (0.30) and high specificity (0.91) for LNI detection, with a PPV, NPV and accuracy of 0.57, 0.77 and 0.74, respectively. These results are consistent with those published in previous reports. Specifically, Bacchiani et al. performed a systematic review on this topic and highlighted the diagnostic accuracy of PET/CT for nodal staging and re-staging after neoadjuvant therapy in BCa patients [15]. Notably, heterogenous results were found and lower sensitivity and specificity were reported (33% and 72% in the staging setting, and 70% and 67% in the re-staging setting, respectively). In a recent systematic review and meta-analysis of the literature including 14 studies (six prospective, eight retrospective), PET/CT showed a pooled sensitivity and specificity of 0.57 and 0.92, respectively, among newly diagnosed BCa patients [12]. However, the use of neoadjuvant therapy and its impact on diagnostic performance was not investigated.

Second, 1367 nodal regions were included in a per-region analysis, of which 126 (9.2%) were pathologically confirmed LN metastases. These findings resulted in sensitivity, specificity, PPV, NPV and accuracy of PET/CT of 0.15, 0.98, 0.40, 0.92 and 0.90, respectively. These results are in line with those published by Girard et al. [14] in a prospectively collected cohort of 61 patients with clinically localised MIBC who underwent RC + PLND. Overall, LNI was found in 17 patients (28%), corresponding to 24 out of 122 nodal regions (20%). In a region-based analysis, Girard et al. found that preoperative PET/CT had an overall accuracy of 84%, with 29% sensitivity, 97% specificity, 70% PPV and 85% NPV. In

Fig. 2 Per-region analysis showing diagnostic accuracy of 18F-fluoro-2-deoxy-D-glucose positron emission tomography/CT for lymph node involvement detection according to pelvic lymph node anatomical regions. Acc., accuracy; L, left; Path, pathological report; R, right.



our study, the diagnostic accuracy of PET/CT stratified according to anatomical site ranged from 0.86 in external iliac and left obturator LNs to 0.96 in pre-sacral LNs. Compared to the per-region diagnostic performance of conventional cross-sectional imaging found in a large retrospective study by Lonati et al. [16], our results showed that PET/CT is considerably superior in discriminating LNI according to LN site.

Finally, subgroup analysis including 137 patients receiving neoadjuvant therapy before PET/CT found slightly higher sensitivity (0.36), with comparable specificity (0.91) for LNI detection. Similar results were found in a study by Fitoussi et al. [17] in a cohort of 45 patients undergoing NAC before RC, in which 18F-FDG PET/CT showed 97% sensitivity and 30% specificity, suggesting that PET/CT can be used for early response evaluation after NAC. With regard to NAI, Marandino et al. [18] evaluated the diagnostic value of preoperative PET/CT in BCa patients receiving pembrolizumab within the PURE-01 trial (NCT02736266). With a pathological LNI rate of 14%, sensitivity and specificity were 27% vs 37.5% and 97% vs 98% in the staging and re-staging settings, respectively.

As previously demonstrated in a similar study by Aljabery et al. [19], when compared to conventional imaging, 18F-FDG PET/CT scan showed slightly better patient-based performances, except for lower sensitivity rates (0.30 vs 0.36 and 0.36 vs 0.47 overall and after neoadjuvant therapy, respectively). Conversely, on per-region analysis, PET/CT outperformed CT, in particular with lower FP rates and higher NPV (0.40 vs 0.20 and 0.32 vs 0.21 overall and after neoadjuvant therapy, respectively). While the improved performance may be beneficial for patient outcomes and future research, the incremental benefits may not justify the higher costs associated with PET/CT compared to conventional imaging techniques. We believe that a comprehensive cost-effectiveness analysis would be necessary

to weigh the real clinical benefits against the economic costs. Taken together, our findings show that 18F-FDG PET/CT had high specificity and NPV for LNI detection in BCa patients, albeit with low sensitivity and mediocre accuracy. These results were confirmed in the subgroup of patients receiving NAC or NAI. Per-region analyses demonstrated even higher specificity and NPV, also compared to conventional imaging, which is crucial to guide urologists in their management of these patients. However, cost-effectiveness assessment against CT is warranted to justify the use of PET/CT in this setting.

Implications for clinical practice are of utmost significance. First, with a higher per-region NPV as compared to conventional imaging, PET/CT could be a useful tool in identifying a complete response in LN metastases after neoadjuvant therapy and therefore selecting those patients that would benefit from RC in terms of oncological outcomes [20]. Moreover, although PET/CT findings alone are inadequate to alter patients' treatment, they could be implemented – along with other relevant variables – into novel or existing nomograms that predict LNI risk [21]. In this regard, since strong evidence supporting the therapeutic role of extended PLND is lacking [22], and ongoing RCTs – such as SWOG S1011 – are unlikely to identify substantial differences in oncological outcomes [23,24], 18F-PET/CT information, given its high per-region specificity and PPV, may be integrated to discern those patients that would profit from a more extended PLND, while opting for a standard template in the remaining cases.

Despite its interesting findings, several study limitations need to be acknowledged. First, our study is limited by its retrospective design, potentially leading to selection biases. Second, we relied on a heterogenous population in terms of baseline characteristics, namely, worst pT stage (≤pT1 vs ≥pT2), presence of LNI at conventional imaging (cN0 vs cN+) and neoadjuvant regimen used (NAI vs NAC vs no therapy). Moreover, information on basal PET/CT was not always available, thus this were not included in the analysis. Third, concerning the PET/CT results, for the majority, these were taken from medical reports when original images were not available. Finally, although we acknowledge the significance of investigating complications, peri-operative mortality and oncological outcomes of patients undergoing RC and bilateral PLND for BCa, our primary focus remained the evaluation of PET/CT diagnostic performances in nodal staging. Consequently, data related to those aspects were not collected as part of our study protocol.

In conclusion, 18F-FDG PET/CT showed high specificity and NPV for LNI detection among BCa patients undergoing RC and PLND, in both per-patient and per-region analyses. These results were confirmed by subgroup analyses including only patients receiving NAC or NAI. Our findings suggest that physicians can safely use preoperative PET/CT to rule out nodal disease, as the absence of LNI would be confirmed in eight out of 10 patients at final pathology. However, sensitivity is still suboptimal and further efforts are necessary to understand whether 18F-FDG PET/CT findings could safely guide clinicians in tailoring patient treatment, with additional evaluation of its cost-effectiveness vs conventional imaging.

Disclosure of Interests

All the authors have no conflict of interest to declare.

References

1 **Sung H, Ferlay J, Siegel RL et al.** Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021; 71: 209–49

2 **Lobo N, Afferi L, Moschini M et al.** Epidemiology, screening, and prevention of bladder cancer. *Eur Urol Oncol* 2022; 5: 628–39

3 **Gore JL, Litwin MS, Lai J et al.** Use of radical cystectomy for patients with invasive bladder cancer. *JNCI J Natl Cancer Inst* 2010; 102: 802–11

4 **Witjes JA, Bruins HM, Carrión A et al.** EAU guidelines on muscle-invasive and metastatic bladder cancer. 2023

5 **Dorfman RE, Alpern MB, Gross BH et al.** Upper abdominal lymph nodes: criteria for normal size determined with CT. *Radiology* 1991; 180: 319–22

6 **Karl A, Carroll PR, Gschwend JE et al.** The impact of lymphadenectomy and lymph node metastasis on the outcomes of radical cystectomy for bladder cancer. *Eur Urol* 2009; 55: 826–35

7 **Almuhaideb A, Papathanasiou N, Bomanji J.** 18F-FDG PET/CT imaging in oncology. *Ann Saudi Med* 2011; 31: 3–13

8 **Apolo AB, Riches J, Schöder H et al.** Clinical value of fluorine-18 2-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography in bladder cancer. *J Clin Oncol* 2010; 28: 3973–8

9 **Darwish C, Sparks A, Amdur R et al.** Trends in treatment strategies and comparison of outcomes in lymph node positive bladder cancer: an analysis of the national cancer database. *Urology* 2020; 146: 168–76

10 **Moussa M, Chakra MA, Saad W et al.** The role of 18F-FDG PET/CT scan compared to CT-scan alone for lymph node staging before radical cystectomy in patients with bladder cancer. *Urol Oncol* 2021; 39: 833.e9–17

11 **Omorphos NP, Ghose A, Hayes JDB et al.** The increasing indications of FDG-PET/CT in the staging and management of invasive bladder cancer. *Urol Oncol* 2022; 40: 434–41

12 **Ha HK, Koo PJ, Kim SJ.** Diagnostic accuracy of F-18 FDG PET/CT for preoperative lymph node staging in newly diagnosed bladder cancer patients: a systematic review and meta-analysis. *Oncology* 2018; 95: 31–8

13 **Zhang H, Xing W, Kang Q et al.** Diagnostic value of [18F] FDG-PET and PET/CT in urinary bladder cancer: a meta-analysis. *Tumour Biol* 2015; 36: 3209–14

14 **Girard A, Rouanne M, Taconet S et al.** Integrated analysis of 18F-FDG PET/CT improves preoperative lymph node staging for patients with invasive bladder cancer. *Eur Radiol* 2019; 29: 4286–93

15 **Bacchiani M, Salamone V, Massaro E et al.** Assessing the performance of 18F-FDG PET/CT in bladder cancer: a narrative review of current evidence. *Cancers (Basel)* 2023; 15: 2951

16 **Lonati C, Mordasini L, Afferi L et al.** Diagnostic accuracy of preoperative lymph node staging of bladder cancer according to different lymph node locations: a multicenter cohort from the European Association of Urology – Young Academic Urologists. *Urol Oncol* 2022; 40: 195.e27–35

17 **Fitoussi O**, **Roche JB**, **Riviere J et al.** Accuracy of FDG-PET/CT for response evaluation of muscle-invasive bladder cancer following neoadjuvant or induction chemotherapy. *Urol Int* 2023; 107: 239–45
18 **Marandino L**, **Capozza A**, **Bandini M et al.** [18F]Fluoro-deoxy-glucose positron emission tomography to evaluate lymph node involvement in patients with muscle-invasive bladder cancer receiving neoadjuvant pembrolizumab. *Urol Oncol* 2021; 39: 235.e15–21
19 **Aljabery F**, **Lindblom G**, **Skoog S et al.** PET/CT versus conventional CT for detection of lymph node metastases in patients with locally advanced bladder cancer. *BMC Urol* 2015; 15: 87
20 **Flaig TW**, **Spiess PE**, **Agarwal N et al.** Bladder cancer, version 3.2020, NCCN clinical practice guidelines in oncology. *J Natl Compr Cancer Netw* 2020; 18: 329–54
21 **Moschini M**, **Afferi L**, **Gandaglia G et al.** Prediction of the need for an extended lymphadenectomy at the time of radical cystectomy in patients with bladder cancer. *Eur Urol Focus* 2021; 7: 1067–74
22 **Bruins HM**, **Veskimae E**, **Hernandez V et al.** The impact of the extent of lymphadenectomy on oncologic outcomes in patients undergoing radical cystectomy for bladder cancer: a systematic review. *Eur Urol* 2014; 66: 1065–77
23 **Katims AB**, **Bochner BH**. Extended pelvic lymph node dissection in muscle invasive bladder cancer. *Curr Opin Urol* 2023; 33: 252–7
24 **Lerner SP**, **Tangen C**, **Svatek RS et al.** SWOG S1011: a phase III surgical trial to evaluate the benefit of a standard versus an extended lymphadenectomy performed at time of radical cystectomy for muscle invasive urothelial cancer. *J Clin Oncol* 2023; 41: 4508

Correspondence: Marco Moschini, Via Olgettina 60, 20132 Milano, Italy.

e-mail: marco.moschini87@gmail.com

Abbreviations: BCa, bladder cancer; FN, false negative; FP, false positive; IQR, interquartile range; LN, lymph node; LNI, lymph node involvement; MIBC, muscle-invasive bladder cancer; NAC, neoadjuvant chemotherapy; NAI, immunotherapy; NPV, negative predictive value; PET, positron emission tomography; PLND, pelvic lymph node dissection; PPV, positive predictive value; RC, radical cystectomy; TN, true negative; TP, true positive.