


## Original Article

# Staging fluorodeoxyglucose positron emission tomography/computed tomography for muscle-invasive bladder cancer: a nationwide population-based study

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## Objective

To provide insight into the use and staging information on lymph-node involvement added by fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) in patients with muscle-invasive bladder cancer (MIBC), based on a nationwide population-based cohort study.

## Patients and methods

We analysed a nationwide cohort of patients with MIBC without signs of distant metastases, newly diagnosed in the Netherlands between November 2017 and October 2019. From this cohort, we selected patients who underwent pre-treatment staging with CT only or CT and FDG-PET/CT. The distribution of patients, disease characteristics, imaging findings, nodal status (clinical nodal stage cN0 vs cN+) and treatment were described for each imaging modality group (CT only vs CT and FDG-PET/CT).

## Results

We identified 2731 patients with MIBC: 1888 (69.1%) underwent CT only; 606 (22.2%) underwent CT and FDG-PET/CT, 237 (8.6%) underwent no CT. Of the patients who underwent CT only, 200/1888 (10.6%) were staged as cN+, vs 217/606 (35.8%) who underwent CT and FDG-PET/CT. Stratified analysis showed that this difference was found in patients with clinical tumour stage (cT)2 as well as cT3/4 MIBC. Of patients who underwent both imaging modalities and were staged with CT as cN0, 109/498 (21.9%) were upstaged to cN+ based on FDG-PET/CT. Radical cystectomy (RC) was the most common treatment within both imaging groups. Preoperative chemotherapy was more frequently applied in cN+ disease and in FDG-PET/CT-staged patients. Concordance of pathological N stage after upfront RC was higher among patients staged as cN+ with CT and FDG-PET/CT (50.0% pN+) than those staged as cN+ with only CT (39.3%).

## Conclusion

Patients with MIBC who underwent pre-treatment staging with FDG-PET/CT were more often staged as lymph node positive, regardless of cT stage. In patients with MIBC who underwent CT and FDG-PET/CT, FDG-PET/CT led to clinical nodal upstaging in approximately one-fifth. Additional imaging findings may influence subsequent treatment strategies.

## Keywords

Bladder cancer, urothelial carcinoma, muscle-invasive, staging, FDG-PET/CT, radical cystectomy, imaging

## Introduction

Bladder cancer is amongst the 10 most diagnosed cancers in the world [1]. About 25% of patients with bladder cancer present with muscle-invasive disease (MIBC). Pre-treatment staging provides important input to determine optimal

treatment. The standard method to stage patients with MIBC consists of contrast-enhanced CT of the chest, abdomen, and pelvis [2]. In case of non-metastatic MIBC, the standard treatment is a radical cystectomy (RC), with or without preoperative chemotherapy (neoadjuvant chemotherapy [NAC]) [2]. However, recurrences occur in up to 50% of

patients after RC [3], partly due to the presence of (occult) metastases at the time of surgery, as CT is often not sensitive enough to detect systemic disease [4]. This highlights the need to improve pre-treatment staging of MIBC.

In other malignancies, fluorodeoxyglucose-(FDG)-positron emission tomography (PET)/CT has improved detection of lymph node (LN) involvement prior to treatment [5,6]. In MIBC, several studies have shown that FDG-PET/CT generally has a higher sensitivity for the detection of LN metastases than CT with comparable specificity [7–9]. Moreover, FDG-PET/CT has shown to provide important incremental staging information, which potentially influences the treatment of one-fifth of patients with MIBC, but leads to false-positive secondary findings as well [10–13]. Studies on the incremental value of FDG-PET/CT have only been conducted in single-centre settings of specialised cancer hospitals, which may not translate to a broader context. This has contributed to the fact that consensus on the use of FDG-PET/CT for MIBC is lacking, as evidenced by divergent guideline recommendations [14].

In the Netherlands, FDG-PET/CT has been increasingly used for pre-treatment staging of MIBC in recent years, but it is not performed (routinely) in all hospitals. This study aimed to provide insight into the use and added staging information on LN involvement that FDG-PET/CT provides in patients with MIBC, based on a nationwide cohort study.

## Patients and Methods

### Cohort

This study was approved by the Privacy Review Board of the Netherlands Cancer Registry (NCR), number K22.315. All patients newly diagnosed in the Netherlands with MIBC (i.e., no previous diagnoses of bladder cancer, except for Ta) between 1 November 2017 and 31 October 2019 were identified from the BlaZIB study (acronym of the Dutch words ‘Blaaskankerzorg in beeld’; English: ‘Insight into bladder cancer care’) [15], which is embedded in the NCR. Patients with distant metastases (cM+) were excluded from the analysis.

Stage at diagnosis was based on all available clinical staging information, including physical examination, cystoscopy, transurethral resection (TUR) and CT of the abdomen, pelvis, and chest (with or without FDG-PET/CT). Cancers were staged according to the TNM Classification of Malignant Tumours system (eighth edition) by the Union for International Cancer Control [16].

### Imaging

Pre-treatment imaging was performed and evaluated as part of routine clinical practice according to institutional standards. For this study, CT and FDG-PET/CT were

considered. The percentage of patients who did not undergo adequate imaging (i.e., no CT) was reported, but they were not included in further analysis. The presence of (suspected) lymphadenopathy (clinical nodal stage cN0 vs cN+) on each applied imaging technique was determined at the discretion of the radiologists and nuclear medicine physicians who interpreted images, not blinded to any clinical information.

### Clinical Data

Clinical data on patient characteristics, disease, diagnostic evaluation and treatment were obtained from electronic patient files and entered in the NCR based on strict registration manuals by trained data managers. The date of first histological confirmation (i.e., TUR) of the bladder tumour was considered as the date of diagnosis. For each patient, it was recorded which hospital they were diagnosed at and where they were treated. It was recorded whether the patient was staged with CT and FDG-PET/CT, including the date of imaging and the imaging results in terms of LN stage (cN0 vs cN+). To minimise the risk of natural disease progression being incorrectly measured as imaging-based upstaging, we maintained a maximum interval between imaging modalities of 3 months. Imaging up to 1 month before diagnosis was included.

We presumed that a proportion of hospitals used FDG-PET/CT routinely in patients with potentially curable MIBC, while other hospitals used FDG-PET/CT only in case of suspicious lesions on CT. To elucidate this, we distinguished between patients treated at a hospital where <20% of patients with MIBC were staged with FDG-PET/CT (‘sporadic use’) vs patients staged at a hospital where >20% underwent FDG-PET/CT (‘non-sporadic use’), with the hospitals divided evenly.

Comorbidities from the Charlson Comorbidity Index (CCI) were assessed at diagnosis and a CCI was calculated. Patient fitness was assessed by the Eastern Cooperative Oncology Group Performance Status (ECOG PS), Karnofsky Performance Status and/or American Society of Anesthesiologists (ASA) score. The type of primary treatment was classified as RC without NAC, RC with NAC, induction chemotherapy without subsequent RC, trimodal therapy/chemoradiation (TMT), radiotherapy (RT), systemic therapy (i.e., induction without consolidation or palliative systemic) or no treatment (including only local treatment such as TUR and instillations). Curative treatment options were defined as RC with or without NAC or TMT [17]. The pathological nodal (pN) stage was recorded for patients who underwent RC.

### Analyses

Descriptive summaries of patient and disease characteristics were presented as frequencies and percentages or medians

and interquartile ranges (IQRs), for the full cohort and stratified by the type of imaging. Imaging findings (cN0 vs cN+) and type of treatment within each stratum of imaging were also described through frequencies and percentages. We substratified patients with clinical tumour stage (cT)2 vs cT3/4 MIBC for comparison of cN stage. Chi-square tests were applied to compare distributions of categorical/categorised variables between imaging groups.

In patients who underwent CT and FDG-PET/CT, the disparity and congruence between cN stage on CT and cN stage on FDG-PET/CT was assessed. In the subgroup of patients who underwent RC, the cN stage was assessed and compared with pN stage as determined by histopathology (pelvic LN dissection [PLND] specimens) to calculate diagnostic accuracy (sensitivity, specificity, negative predictive value [NPV], and positive predictive value [PPV]) with corresponding 95% CIs. All analyses were performed in Statistical Analysis System (SAS), version 9.4 (SAS Institute Inc., Cary, NC, USA).

## Results

### Cohort

A total of 2770 patients with newly diagnosed cM0/X MIBC, without a previous diagnosis of high-risk non-MIBC (T1, Tis, Ta+is) were identified from the NCR. For 39 patients, sufficiently detailed data were lacking, leaving 2731 patients in the cohort. Patients had a median age of 74 years and 62.0% had clinical stage T2 (cT2; Table 1).

### Distribution of Imaging Modalities

Of all 2731 patients, the majority ( $n = 1888$  [69.1%]) underwent pre-treatment CT only; 606 patients (22.2%) underwent both CT and FDG-PET/CT; 237 (8.6%) did not undergo CT and were further excluded.

Most CT scans were performed in the 2 weeks prior to (39.3%) or 4 weeks after (39.3%) histological confirmation of the tumour (i.e., TUR). FDG-PET/CT was performed after histological confirmation in 93% of patients, at a median (IQR) of 20 (14–31) days after TUR. Among patients who underwent both, FDG-PET/CT imaging was performed a median (IQR) of 26 (12–42) days after CT.

### Clinical Data

Patients who underwent FDG-PET/CT were significantly younger (median age 70 vs 75 years) and fitter (ECOG PS 0 in 61.1% vs 51.1%; CCI 0 in 50.0% vs 42.4%) than patients who underwent CT only (Table 1B). Also, patients who underwent FDG-PET/CT more often had locally advanced disease (i.e.,  $\geq$ cT3; FDG-PET/CT: 49.2% vs CT only: 34.4%) and suspicion of nodal metastases already on CT.

Patients treated in specialised/teaching hospitals or academic hospitals were relatively more likely to undergo FDG-PET/CT staging compared to patients in general hospitals (proportion of patients with pre-treatment FDG-PET/CT, stratified per type of treatment hospital; general hospital: 10.2%, specialised/teaching hospital: 21.0%, academic hospital: 34.4%).

Of the 606 patients who underwent both CT and FDG-PET/CT, 493 (81.3%) were treated at (one of the 38) Dutch hospitals where FDG-PET/CT was used 'non-sporadically', i.e., in  $>20\%$  of patients with MIBC (Table S1). Of the patients who underwent both CT and FDG-PET/CT, those treated at hospitals where FDG-PET/CT is used only sporadically had more frequent lymphadenopathy on CT compared with patients treated at hospitals where FDG-PET/CT is used non-sporadically, despite an average higher cT stage in this group. In both groups, the cN+ rate, based on CT, was higher than in the CT-only group (10.4%).

### Lymph Node Stage

The clinical LN status (cN0 vs cN+) in patients staged by CT only vs by CT and FDG-PET/CT is presented in Table 2. Patients staged with CT were cN+ in 200/1888 (10.6%) patients, whereas patients staged with CT and FDG-PET/CT were cN+ in 217/606 (35.8%) on at least one imaging modality. The difference was observed both in patients with cT2 disease (6.4% vs 26.9%) and in patients with cT3/4 disease (18.2% vs 45.0%).

In patients who underwent CT and FDG-PET/CT, both modalities gave congruent information about LN involvement in the majority of cases (460/606 [75.9%]). In 109/606 (18.0%) patients, FDG-PET/CT imaging showed cN+ disease, while CT did not. In 37 (6.1%) patients, FDG-PET/CT showed cN0 while CT showed cN+.

### Treatment

Among patients staged with CT only, RC without NAC was the most common treatment, particularly in patients with cN0 (Table 3). Among patients staged with CT and FDG-PET/CT, RC without NAC was the most common treatment as well (48.6%), but RC with NAC was applied relatively more frequently (14.0% vs 21.0%). In this group, the use of NAC varied considerably depending on LN involvement, based on FDG-PET/CT (17.0% vs 28.1% among cN0 and cN+, respectively). Patients who were cN+ on CT, most commonly received no potentially curative treatment.

### Pathological Nodal Status

A total of 814 patients who were staged with CT only, underwent RC; of whom 550 without NAC (Table S2). The

**Table 1** (A) Baseline patient and clinical tumour characteristics of patients with non-metastatic MIBC ( $n = 2731$ ) diagnosed between November 2017 and October 2019 in the Netherlands. (B) Patient and disease characteristics by imaging modalities applied.

Variable	Value			
<b>(A)</b>				
All, $N$ (%)	2731 (100)			
Age, years				
Median (IQR)	74 (66–81)			
0–60, $n$ (%)	364 (13.3)			
61–70, $n$ (%)	691 (25.3)			
71–80, $n$ (%)	993 (36.4)			
$\geq 81$ , $n$ (%)	683 (25.0)			
Sex, $n$ (%)				
Male	1898 (69.5)			
Female	833 (30.5)			
CCI, $n$ (%)				
0	1202 (44.0)			
1	751 (27.5)			
2	412 (15.1)			
$\geq 3$	366 (13.4)			
Clinical T stage*, $n$ (%)				
T2	1692 (62.0)			
T3	734 (26.9)			
T4a	305 (11.2)			
Morphology, $n$ (%)				
Urothelial carcinoma	2492 (91.2)			
Non-urothelial carcinoma	239 (8.8)			
Imaging applied, $n$ (%)				
CT only	1888 (69.1)			
CT and FDG-PET/CT	606 (22.2)			
No CT or FDG-PET/CT only	237 (8.6)			
Variable	No CT, $n$ (%)	CT only, $n$ (%)	CT and FDG-PET/CT, $n$ (%)	$P$
<b>(B)</b>				
All (row %)	237 (8.7)	1888 (69.1)	606 (22.2)	
Age, years				<0.001
0–60	15 (6.3)	221 (11.7)	128 (21.1)	
61–70	48 (20.3)	460 (24.4)	183 (30.1)	
71–80	76 (32.1)	694 (36.8)	223 (36.8)	
$\geq 81$	98 (41.4)	513 (27.2)	72 (11.9)	
Sex				0.890
Men	167 (70.5)	1307 (69.2)	424 (70.0)	
Women	70 (29.5)	581 (30.8)	182 (30.0)	
ECOG PS				<0.001
0	87 (36.7)	967 (51.2)	370 (61.1)	
1	37 (15.6)	330 (17.5)	117 (19.3)	
2	72 (30.4)	454 (24.0)	91 (15.0)	
3/4	16 (6.8)	65 (3.4)	15 (2.5)	
Unknown	25 (10.5)	72 (3.8)	13 (2.1)	
CCI				0.005
0	98 (41.4)	801 (42.4)	303 (50.0)	
1	62 (26.2)	528 (28.0)	161 (26.6)	
2	33 (13.9)	303 (16.0)	76 (12.5)	
$\geq 3$	44 (18.6)	256 (13.6)	66 (10.9)	
Clinical T stage				<0.001
cT2	–	1219 (64.6)	308 (50.8)	
cT3	–	477 (25.3)	214 (35.3)	
cT4	–	192 (10.2)	84 (13.8)	
Clinical N stage (CT)				<0.001
cN0	–	1688 (89.4)	498 (82.2)	
cN+	–	200 (10.6)	108 (17.8)	
Morphology				0.001
Urothelial carcinoma	211 (89.0)	1739 (92.1)	542 (89.4)	
Neuroendocrine carcinoma	8 (3.4)	61 (3.2)	35 (5.7)	
Squamous cell carcinoma	5 (2.1)	44 (2.3)	19 (3.1)	
Adenocarcinoma	2 (0.8)	6 (0.3)	5 (0.8)	
Undifferentiated carcinoma	1 (0.4)	6 (0.3)	3 (0.5)	
Other/undetermined	10 (4.2)	32 (1.7)	2 (0.3)	

\*Based on all available staging information, including imaging. The green column displays the patients staged with CT only. The blue column display the patients staged by CT and FDG-PET/CT.

**Table 2** Clinical nodal status in patients staged by CT only and by CT and FDG-PET/CT. Clinical nodal status (cN0 vs cN+) stratified by pre-treatment imaging modality in all 2385 patients who underwent CT ( $n = 1888$ ) or CT and FDG-PET/CT ( $n = 606$ ).

	Nodal status		P
	cN0, n (%)	cN+, n (%)	
<b>All cT stages</b>			<0.001
CT only	1688 (89.4)	200 (10.6)	
CT and FDG-PET-CT	389 (64.2)	217 (35.8)	
Based on CT alone	498 (82.2)	108 (17.8)	
Based on FDG-PET alone	426 (70.3)	180 (29.7)	
<b>cT2 only</b>			<0.001
CT only	1141 (93.6)	78 (6.4)	
CT and FDG-PET-CT	225 (73.1)	83 (26.9)	
Based on CT alone	268 (87.0)	40 (13.0)	
Based on FDG-PET alone	242 (78.6)	66 (21.4)	
<b>cT3/4 only</b>			<0.001
CT only	547 (81.2)	122 (18.2)	
CT and FDG-PET-CT	164 (55.0)	134 (45.0)	
Based on CT alone	230 (77.2)	68 (22.8)	
Based on FDG-PET alone	184 (61.7)	114 (38.3)	

*The green column displays the patients staged with CT only. The blue rows display the patients staged by CT and FDG-PET/CT; here a distinction is made between lymphadenopathy detected on CT vs lymphadenopathy detected on FDG-PET/CT.*

proportion of patients with pN+ disease was highest among cN+ patients who did not receive preoperative therapy (39.3% pN+) and CT and FDG-PET/CT (50.0% pN+).

In the RC group without NAC, the sensitivity of CT only was 7.1% (95% CI 3.6–12.4) vs 40% (95% CI 26–26) of CT and FDG-PET/CT. Specificity was 96% (95% CI 93–97) vs 85% (95% CI 78–91), respectively; PPV 39% (95% CI 22–59) vs 50% (95% CI 33–67), respectively and NPV 73% (95% CI 69–76) of CT only vs 80% (95% CI 71–86) of CT and FDG-PET/CT.

## Discussion

Pre-treatment staging of patients with MIBC needs to be improved, as LN metastases are often missed. FDG-PET/CT

can provide additional information to guide treatment. However, studies on the incremental value of FDG-PET/CT have only been conducted in single-centre settings and consensus of its use is lacking. For this reason, we performed a nationwide population-based study, to gain insight the use and outcomes of pre-treatment FDG-PET/CT on the LN status in patients with MIBC. We found that a quarter of Dutch patients with MIBC underwent FDG-PET/CT between 2017 and 2019. Among patients with MIBC staged with CT and FDG-PET/CT, LN involvement was reported approximately three times more frequently than in patients who underwent CT only. This difference persisted regardless of cT stage. Moreover, within the group of patients staged with both CT and FDG-PET/CT, FDG-PET/CT found suspected LN involvement in almost one-fifth of patients staged cN0 by CT.

Prior to the present study, the use of FDG-PET/CT for LN staging in MIBC had only been investigated in monocentric patient series. In a review of 19 studies, it was summarised that the sensitivity of FDG-PET/CT for LN assessment is superior to CT with comparable specificity [7]. In particular, previous literature showed that FDG-PET/CT can detect smaller LN metastases than CT [8,9]. In the present study, patients were significantly more frequently diagnosed as cN+ based on FDG-PET/CT compared to CT. Histopathology of upfront RC and PLND was available as a reference standard in a quarter of patients and in this subgroup, sensitivity and NPV were significantly higher than of CT only. Despite this improvement, the sensitivity of both imaging modalities in this study was relatively low.

In the present study, patients underwent imaging as part of clinical practice, and treatment decisions were usually based on all available information; hence, this is not a diagnostic accuracy study. Therefore, we cannot exclude the possibility that a proportion of additional FDG-PET/CT findings may be false positives. False-positive results can occur due to  $^{18}\text{F}$ -

**Table 3** Treatments and clinical nodal status by imaging findings based on CT and FDG-PET/CT among patients with MIBC.

Variable	CT only, N = 1888			FDG-PET/CT, N = 606		
	All, N (%)	cN-, n (%)	cN+, n (%)	All, N (%)	cN-, n (%)	cN+, n (%)
Total		1688 (89.4)	200 (10.6)		389 (64.2)	217 (35.8)
Treatment						
RC - NAC	550 (29.1)	522 (30.9)	28 (14.0)	167 (27.6)	131 (33.7)	36 (16.6)
RC + NAC*	264 (14.0)	231 (13.7)	33 (16.5)	127 (21.0)	66 (17.0)	61 (28.1)
Induction chemotherapy, no RC†	51 (2.7)	34 (2.0)	17 (8.5)	34 (5.6)	11 (2.8)	23 (10.6)
TMT	178 (9.4)	172 (10.2)	6 (3.0)	108 (17.8)	72 (18.5)	36 (16.6)
RT	374 (19.8)	350 (20.7)	24 (12.0)	80 (13.2)	57 (14.7)	23 (10.6)
Systemic treatment	44 (2.3)	31 (1.8)	13 (6.5)	27 (4.5)	14 (3.6)	13 (6.0)
Other/none‡	427 (22.6)	348 (20.6)	79 (39.5)	63 (10.4)	38 (9.8)	25 (11.5)

\*Including induction chemotherapy and subsequent RC. †Palliative or induction therapy has been initiated with planned subsequent RC, but RC was not performed. ‡Including local treatment (e.g., TUR, coagulation) or no tumour-directed treatment. cN-, no visual nodal involvement; cN+, (suspected) lymphadenopathy. The green columns display the patients staged with CT only. The blue columns display the patients staged by CT and FDG-PET/CT. A distinction is made between patients with or without visual lymph node involvement.

FDG uptake in infectious or inflammatory tissue. In this study, FDG-PET/CT was performed at a median of 3 weeks after TUR, which may have impacted the results as well. Another pitfall of FDG-PET/CT in MIBC imaging is the extraction of FDG, which can hinder adequate visualisation of urinary tract tumours. Nevertheless, most studies have found that the specificity of FDG-PET/CT for the detection of LN metastases is comparable to that of CT [7]. Given the previously reported comparable specificity, we assume that there is a balanced proportion of false positives within both the CT group and the FDG-PET/CT group, with nevertheless a marked increase in detection of cN+ disease based on FDG-PET/CT.

We observed considerable differences in patient and tumour characteristics between patients staged with CT only compared to those who received both CT and FDG-PET/CT. The latter group was younger and had a better performance status, but more often had a higher cT stage. Nevertheless, within the group who received both imaging techniques, we observed 18% of upstaging with FDG-PET/CT as compared to CT. In addition, among those who underwent upfront RC, the NPV of CT and FDG-PET/CT was considerably higher than that of CT only. Most importantly, the significant difference in cN+ stage applied to both cT2 and cT3/4 disease. Taken together, this indicates a significant proportion of imaging-induced upstaging caused by adding FDG-PET/CT to the diagnostic evaluation in a nationwide cross-sectional cohort.

We noted not only a difference in LN stage, but also in treatment. There was a clear difference in applied treatment between patients staged with CT vs CT and FDG-PET/CT. This may be related to the imaging modality, but also to a variety of other factors, such as patient and hospital characteristics. Nonetheless, we observed differences between imaging results and treatment, e.g., the percentage of patients who received NAC before RC was 74% in CT-negative and FDG-PET/CT-positive patients and 34% in 'double-negative' patients. In CT-positive FDG-PET/CT-negative patients, this was only 41%. This could reflect a potential effect of imaging on treatment, as has also been described in previous single-centre series [8–11]. For instance, Voskuilen *et al.* [10] found that FDG-PET/CT influenced the treatment of almost one-fifth of patients with MIBC. Due to the retrospective design of our study, we could not examine treatment changes per individual patient, nor could we determine whether changes in treatment were a direct consequence of imaging. Hence, no definitive conclusions regarding the impact of FDG-PET/CT on treatment can be drawn. At the same time, since LN-positive MIBC is associated with poor outcomes [18] and should be treated with systemic therapy rather than surgery [2], higher sensitivity and nodal upstaging likely lead to treatment changes. However, how the extent and how this affects oncological outcome is not yet known.

Lastly, this study shows that there is ambiguity regarding the use of FDG-PET/CT in patients with MIBC. In some hospitals in the Netherlands, FDG-PET/CT is part of routine pre-treatment staging, while in other hospitals it is not used or only in exceptional cases, e.g., in suspicious LN lesions on CT. To gain insight into a potential selection bias, we separately analysed patients who were staged at hospitals where FDG-PET/CT was used 'sporadically' (based on a pre-defined cut-off). Indeed, we found that these patients were more likely to have suspicious LNs on CT, despite a generally lower cT stage. This suggests that in a minority of patients who underwent FDG-PET/CT, physicians decided on this additional imaging after the CT result. The 'non-sporadic' group, on the other hand, more closely resembled the CT population; hence, the majority was not selected. On the other hand, ~8% of patients with MIBC did not undergo adequate staging. Although not according to guidelines [2], this is consistent with the observation that a proportion of (mostly older and prognostically unfavourable) patients with non-metastatic MIBC remain untreated [19].

Key strengths of this study include its nationwide population-based design with a large number of patients included in a recent period, reflecting contemporary MIBC care in the Netherlands. Limitations include its observational, retrospective design. For example, this allowed us to distinguish only between cN0 vs cN+ (instead of cN1–3) for each imaging modality separately. Moreover, imaging evaluation was not standardised across readers or centres. Another limitation is the fact that we did not have a reference standard for patients who were not treated with RC (e.g., repeated imaging), which would allow for a more direct assessment of sensitivity and specificity of both imaging techniques. Furthermore, only patients without distant metastases as determined by either CT or FDG-PET/CT were included, which means that we could not register upstaging to distant metastatic disease (cM1) based on FDG-PET/CT.

Despite these limitations, this study provides relevant insight into the nationwide application of, and staging information obtained by FDG-PET/CT in MIBC, which has not been previously described. Future prospective studies are required to assess the impact of FDG-PET/CT and FDG-PET/CT-induced treatment changes on survival. This requires consideration of a potential 'Will Rogers phenomenon' [20] or 'stage migration', as was observed in head-and-neck cancer [21]. At the same time, the impact of imaging-induced changes in treatment on quality of life warrants further attention. Furthermore, cost-effectiveness and the financial burden of additional staging should be thoroughly assessed.

In conclusion, results of this large nationwide population-based study show that a quarter of Dutch patients with MIBC

are staged with FDG-PET/CT and confirm that patients with MIBC who underwent pre-treatment staging with FDG-PET/CT were more often classified as LN positive, regardless of cT stage. In patients with MIBC who underwent CT and FDG-PET/CT, FDG-PET/CT leads to clinical nodal upstaging in approximately one-fifth. Additional imaging findings may influence subsequent treatment strategies.

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## Disclosure of Interests

None.

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Abbreviations: CCI, Charlson Comorbidity Index; cN, clinical nodal stage; cT, clinical tumour stage; ECOG PS, Eastern Cooperative Oncology Group Performance Status; FDG-PET, fluorodeoxyglucose positron emission tomography; IQR, interquartile range; LN, lymph node; MIBC, muscle-invasive bladder cancer; NAC, neoadjuvant chemotherapy; NCR, the Netherlands Cancer Registry; NPV, negative predictive value; PLND, pelvic lymph node dissection; pN, pathological nodal stage; PPV, positive predictive value; RC, radical cystectomy; RT, radiotherapy; TMT, trimodal therapy/chemoradiation; TUR, transurethral resection.

## Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Table S1** Patient and disease characteristics of the 606 patients who underwent FDG-PET/CT in hospitals where FDG-PET/CT is used in <20% of patients with MIBC

(‘sporadic use’) vs hospitals where FDG-PET/CT is used in >20% of patients with MIBC (‘non-sporadic use’).

**Table S2** Pathological nodal status of RC patients, stratified by imaging modality based on CT and FDG-PET/CT among patients with MIBC.