

FDG PET–CT for Lymph Node Staging of Bladder Cancer: A Prospective Study of Patients with Extended Pelvic Lymphadenectomy

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ABSTRACT

Background. The purpose of this study was to evaluate the diagnostic accuracy of [¹⁸F] fluorodeoxyglucose (FDG) positron emission tomography–computed tomography (PET–CT) for lymph node (LN) staging of bladder cancer patients undergoing radical cystectomy (RC) with extended pelvic lymphadenectomy compared to conventional CT.

Methods. A total of 61 patients underwent FDG PET–CT before RC and extended pelvic lymphadenectomy. A template for extended pelvic lymphadenectomy to the level of the inferior mesenteric artery was divided into 11 anatomic nodal packets. Definitive pathologic findings of resected LNs were correlated with the results of FDG PET–CT and CT alone in a patient- and nodal packet-based manner.

Results. Among the 61 patients, pathological staging confirmed LN metastasis in 17 patients (27.9 %). In total, 627 LN packets (2580 LNs) were resected and histologically evaluated. The mean number of LNs removed was 42 (median 40; range 22–118). Of the 627 LN packets removed, 27 packets (4.3 %) were positive for LN metastasis based on pathologic analysis. On a patient-based analysis, FDG PET–CT and conventional CT showed a sensitivity of 47.1 and 29.4 %, respectively, specificity of 93.2 and 97.7 %, respectively, positive predictive value (PPV) of 72.7 and 78.2 %, respectively, and negative predictive value (NPV) of 82.0 and 78.2 %, respectively. On a nodal packet-based analysis, sensitivity, specificity,

PPV, and NPV were 14.8, 97.8, 23.5, and 96.2 %, respectively, for PET–CT and 11.1, 98.7, 27.3, and 96.1 %, respectively, for conventional CT.

Conclusions. Combined FDG PET–CT did not improve the diagnostic accuracy of conventional CT for the detection of LN metastasis in bladder cancer patients scheduled for RC.

Urothelial carcinoma of the urinary bladder is the fifth most common malignancy in the United States, with an estimated 72,570 new cases and 15,210 deaths in 2013.¹ Accurate pretreatment staging of bladder cancer is essential for improving patient care because it allows better selection of patients for systemic treatment or curative surgery. The standard treatment of muscle-invasive bladder cancer with no evidence of distant metastasis is radical cystectomy (RC) with pelvic lymph node (LN) dissection. However, the management of bladder cancer is dependent on LN staging, with more advanced tumors requiring aggressive therapy, such as neoadjuvant chemotherapy.^{2,3}

Current standard staging modalities such as computed tomography (CT) or magnetic resonance imaging (MRI), which depend solely on morphologic characteristics and lesion size, have not proven to be highly accurate in LN staging.⁴ The diagnostic accuracy of CT and MRI in terms of LN staging is equally low, with reported rates of 55 and 60 %, respectively.^{5,6}

Positron emission tomography (PET) performed with radiopharmaceutical [¹⁸F] fluorodeoxyglucose (FDG) is a molecular imaging technique that assesses regional glucose metabolism.⁷ It is widely used because most cancers exhibit increased glucose utilization compared to normal tissue. Currently available data indicates that combined PET–CT is more sensitive and specific than either of its

constituent imaging methods alone and probably more so than images obtained separately from PET and CT and viewed side by side for many different tumor types.⁸

To date, there are limited and conflicting data regarding the utility of FDG PET-CT in patients scheduled to undergo RC for muscle-invasive bladder cancer. In addition, there are no previous studies with strict “node-to-node” comparison between FDG PET-CT results and pathology data for LN staging because limited LN tissue is removed during pelvic lymphadenectomy.^{9–17} Therefore, there is no firm consensus regarding the role of FDG PET-CT in nonmetastatic muscle-invasive bladder cancer. Here, we performed a prospective study of FDG PET-CT in patients scheduled to undergo RC and extended pelvic lymphadenectomy for bladder cancer with no evidence of metastatic disease on conventional staging modality.

PATIENTS AND METHODS

Study Design

The study population consisted of 61 consecutive patients with bladder cancer who were scheduled to undergo RC and extended pelvic LN dissection with curative intent. Inclusion criteria were histologically proven high-grade T1 cancer ($n = 9$) or muscle-invasive ($n = 52$) bladder cancer. All patients underwent preoperative chest X-ray, conventional CT of the abdomen and pelvis, and bone scan for disease staging, and had no evidence of distant metastasis. Patients with concomitant malignancy as well as those who underwent neoadjuvant chemotherapy were excluded from the study. Patients were also excluded from the data analysis if they did not undergo extended pelvic LN dissection or did not have proven urothelial carcinoma after RC. This prospective study was performed in accordance with the regulations of the local institutional review board and ethics committee, and written informed consent was obtained from all patients before enrollment.

Abdominal CT Protocol and Interpretation All CT data were obtained using a 64-channel CT scanner (Somatom Plus-S, Siemens Medical System, Erlangen, Germany). Initially, an unenhanced scan was performed from the dome of the diaphragm to the bladder with a section thickness of 5 mm. After obtaining unenhanced CT images, intravenous contrast medium was delivered and corticomedullary phase enhanced images were obtained when the Hounsfield unit of the descending aorta reached 100 with a scan delay of 10 s to allow the kidneys to be covered. A delayed pelvic phase scan was conducted 80 s after the injection to cover the bladder, followed by an

excretory phase scan from the liver to the symphysis pubis. The technical parameters of CT imaging at our institute have been previously reported.¹⁸ Before surgery, all CT images were prospectively interpreted by a specialist in genitourinary imaging who was blinded to patient clinical characteristics, and the findings were kept on an electronic medical record. LNs were interpreted as positive for metastatic spread on CT scan if their short-axis diameter exceeded 10 mm or if necrosis, independent of size, was noted.

FDG PET-CT Imaging Protocol and Image Processing

FDG PET-CT scanning was performed using a multislice PET-CT camera system with a Biograph Sensation 16, TruePoint 40 (Siemens Medical Systems, Malvern, PA) or Discovery STE, D690 (GE Healthcare, Waukesha, WI). All patients fasted for ≥ 6 h prior to scanning, and their serum glucose concentration before [¹⁸F] FDG administration was below 150 mg/dl (mean 108 mg/dl; range 68–148 mg/dl). Whole body image acquisition was initiated approximately 1 h after intravenous injection of approximately 555 MBq of [¹⁸F] FDG. CT without contrast enhancement was performed in a spiral mode from the base of the skull to the proximal thigh for attenuation correction and image fusion, followed by a three-dimensional caudocranial PET emission scan. The emission scan time per bed position was 2–3 min, and 5–6 bed positions were employed. CT results were used for PET attenuation correction and fusion. PET results were reconstructed iteratively without and with attenuation correction based on CT results, and then reoriented in axial, sagittal, and coronal slices. FDG PET-CT images were reviewed on a viewing platform (TureD; Siemens Medical Systems) and AW (GE Healthcare) and interpreted by an experienced nuclear medicine physician blinded to the clinical information. LNs were graded as malignant or benign based on functional criteria (increased metabolism relative to the surrounding LNs and blood pool activity) using a maximal standardized uptake value (SUV_{max}) of 2.5 as the cutoff value.

Surgery and Histopathologic Evaluation All operations were performed by a single qualified experienced surgeon (C.S.K.). The standard surgical procedure was RC with extended pelvic LN dissection. Extended pelvic lymphadenectomy was routinely performed, which included bilateral standard pelvic lymphadenectomy template (the distal common iliac, external iliac, hypogastric, obturator, and presacral), as well as LN regions at the level of the proximal common iliac, distal aorta, and vena cava to the level of the inferior mesenteric artery. All nodal tissue removed from each anatomic

location was divided into 11 anatomic nodal packets and submitted as a separate packet.

Statistical Analysis Continuous variables are expressed as the median (and range) or the mean \pm SD. Categorical variables are expressed as numbers and percentages. Definitive pathologic findings of resected LN were correlated with the results of FDG PET-CT and CT alone in a patient- and nodal packet-based manner. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of FDG PET-CT and CT were evaluated. All statistical analyses were performed using the SPSS software version 21.0 (IBM, Armonk, NY).

RESULTS

Between June 2009 and April 2012, 69 patients were consecutively enrolled in this study. Patients were prospectively included in the study if histological diagnosis indicated muscle-invasive bladder cancer or high-grade T1 disease on previous transurethral resection. Of the 69 patients, 61 had RC with extended pelvic LN dissection after FDG PET-CT, and these patients were included in the final data analysis (Fig. 1).

Demographic and pathologic characteristics of the patients are shown in Table 1. Most of the patients underwent surgery within a range of 1–25 days (median 6 days) after undergoing FDG PET-CT. Among the 61 patients, pathological staging confirmed LN metastasis in 17 patients (27.9 %). In total, 627 LN packets (2580 LNs) were resected and histologically evaluated. The 11 anatomical LN packets during extended pelvic LN dissection are shown in Fig. 2a. The mean number of LNs removed

TABLE 1 Patient characteristics

No. of patients	61
Mean age \pm SD (median, range)	63.7 \pm 10.1 (65, 31–79)
No. gender (%)	
Male	46 (75.4)
Female	15 (24.6)
No. primary tumor status (%)	
pT0–T2	29 (47.5)
pT3–T4	32 (52.5)
No. nodal status (%)	
pTxN0	44 (72.1)
pTxN1	6 (9.8)
pTxN2	7 (11.5)
pTxN3	4 (6.6)
No. grade (%)	
Low	3 (4.9)
High	58 (95.1)
No. lymphovascular invasion (%)	
Positive	30 (49.2)
Negative	31 (50.8)
Mean total LN packets removed \pm SD (median, range)	10.3 \pm 0.8 (11, 8–11)
Mean positive LN packets removed \pm SD (median, range)	0.4 \pm 0.8 (0, 0–4)
Mean LN removed \pm SD (median, range)	42.3 \pm 15.1 (40, 22–118)
Mean positive LN removed \pm SD (median, range)	0.7 \pm 1.8 (0, 0–10)

SD standard deviation, LN lymph node

was 42 with a median of 40 (range 22–118). Of the 627 LN packets removed, 27 packets (4.3 %) showed LN metastasis by pathological analysis. The mean (range) number of LNs removed from each nodal packet and the location of the 27 positive nodal packets are shown in Fig. 2b and c.

The predictive accuracy of FDG PET-CT and that of conventional CT alone are shown in Table 2. On a patient-based analysis, FDG PET-CT and conventional CT showed a sensitivity of 47.1 and 29.4 %, respectively, specificity of 93.2 and 97.7 %, respectively, PPV of 72.7 and 83.3%, respectively, and NPV of 82 and 78.2 %, respectively. On a nodal packet-based analysis, sensitivity, specificity, PPV, and NPV were 14.8, 97.8, 23.5, and 96.2 %, respectively, for FDG PET-CT and 11.1, 98.7, 27.3, and 96.1 %, respectively, for conventional CT.

Based on a patient-based analysis, nodal staging was correctly determined by both FDG PET-CT and CT alone in 44 (72.1 %) of the 61 patients. The remaining 2 (3.3 %) and 16 (26.2 %) of the 61 patients were overstaged or understaged, respectively, on FDG PET-CT. When patients were analyzed by conventional CT alone, 4 (6.6 %) and 13 (21.3 %) of the 61 patients were overstaged

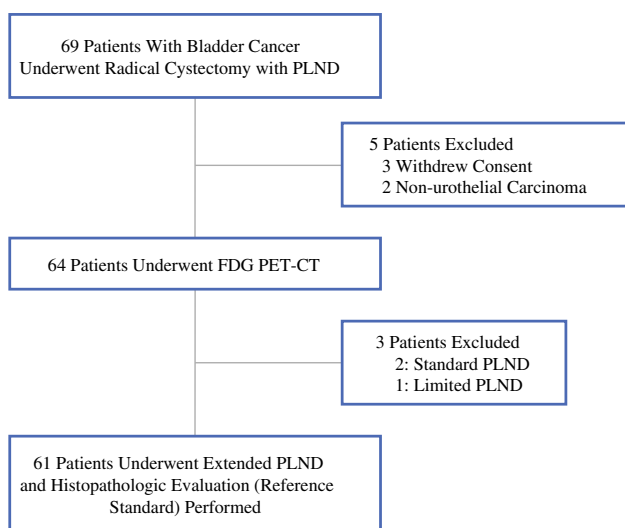


FIG. 1 Study flow diagram

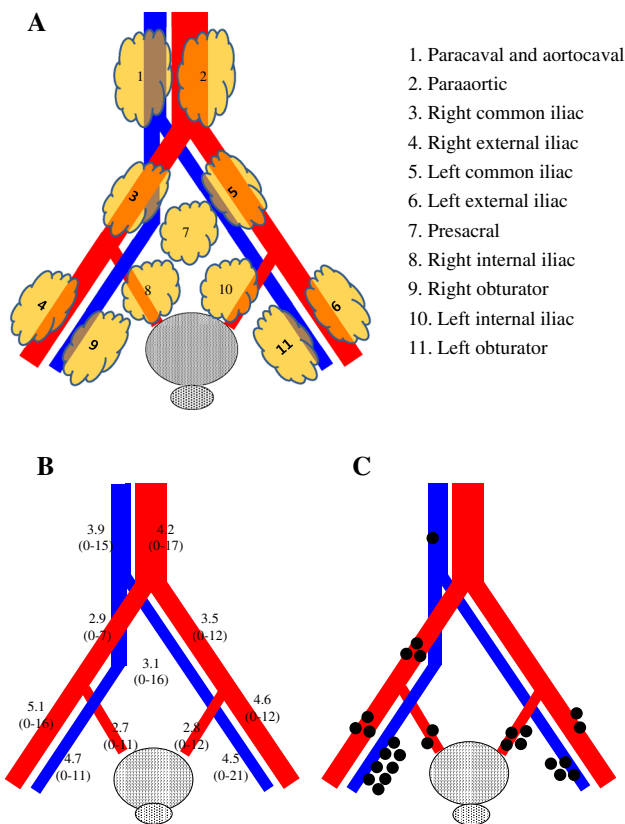


FIG. 2 Eleven anatomical lymph node packets during extended pelvic lymphadenectomy (a) The mean (range) number of lymph nodes removed from each nodal packet (b) and the location of 27 positive nodal packets (c)

or understaged, respectively. The detailed clinical, radiographic, and pathologic characteristics of the 17 LN-positive patients are shown in Table 3.

DISCUSSION

In this study, we found that combined FDG PET-CT did not improve the diagnostic accuracy of conventional CT alone for the detection of LN metastasis in bladder cancer patients scheduled for RC. Although our study included only 61 patients with bladder cancer, to the best of our knowledge, it represents the largest study published on extended pelvic LN dissection and preoperative FDG PET-CT imaging directly comparing to surgically removed LNs (Table 4).

Accurate clinical LN staging can identify patients most likely to benefit from systemic treatment before definitive surgery. Great effort has been made to improve the accuracy of preoperative LN staging before RC using various imaging modalities.^{4,19} PET-CT is one of these imaging modalities and has undergone explosive growth because of recent technical improvement in PET-CT scanners and the development of better PET tracers.¹⁴ However, conflicting data currently exists on the utility of preoperative FDG PET-CT in patients with muscle-invasive bladder cancer. Some studies advocate the use of FDG PET-CT, which has higher sensitivity and equal specificity compared to conventional CT alone.^{9,12,16} However, other studies do not support the incremental benefit of this imaging modality over conventional CT scan or MRI.^{10,17} Various factors including patient population, extent of LN dissection, and the staging sequence as well as the interpretation of FDG PET-CT imaging data, such as different cutoff values of standardized uptake value (SUV) to distinguish benign from malignant FDG uptake, may underlie the institutional discrepancies in the diagnostic performance of FDG PET-CT imaging for the detection of LN metastasis.

TABLE 2 Predictive accuracy

	FDG PET-CT	CT alone
Patient-based analysis		
Sensitivity (%)	47.1 [8/17] (23.0–72.1)	29.4 [5/17] (10.4–56.0)
Specificity (%)	93.2 [41/44] (81.3–98.5)	97.7 [43/44] (87.9–99.6)
Positive likelihood ratio	6.9 (2.1–23.0)	12.9 (1.6–102.9)
Negative likelihood ratio	0.6 (0.4–0.9)	0.7 (0.5–1.0)
Positive predictive value (%)	72.7 [8/11] (39.1–93.7)	83.3[5/6] (36.1–97.2)
Negative predictive value (%)	82.0 [41/50] (68.6–91.4)	78.2 [43/55] (65.0–88.2)
Nodal packet-based analysis		
Sensitivity (%)	14.8 [4/27] (4.3–33.8)	11.1 [3/27] (2.5–29.2)
Specificity (%)	97.8 [587/600] (96.3–98.8)	98.7 [592/600] (97.4–99.4)
Positive likelihood ratio	6.8 (2.4–19.6)	8.3 (2.3–29.7)
Negative likelihood ratio	0.9 (0.7–1.0)	0.9 (0.8–1.0)
Positive predictive value (%)	23.5 [4/17] (7.0–49.9)	27.3 [3/11] (6.4–60.9)
Negative predictive value (%)	96.2 [587/610] (94.4–97.6)	96.1 [592/616] (94.3–97.5)

TABLE 3 Characteristics of 17 node-positive patients

Patient no.	Age	Sex	LN removed (positive/total)	pN stage	Positive LN site	CT N stage	PET-CT N stage
1	61	Male	1/22	pN1	LO	cN0	cN0
2	73	Female	1/29	pN1	LI	cN0	cN0
3	59	Male	1/30	pN1	RO	cN0	cN0
4	60	Male	1/41	pN1	RE	cN0	cN0
5	73	Female	1/45	pN1	LI	cN0	cN1
6	74	Female	1/61	pN1	RO	cN2	cN2
7	67	Male	1/38	pN3	PC	cN0	cN0
8	56	Male	2/40	pN2	RO	cN0	cN0
9	40	Male	2/50	pN2	RI, RO	cN0	cN0
10	75	Male	2/38	pN2	RE	cN0	cN0
11	43	Male	2/44	pN2	RO	cN1	cN2
12	60	Female	2/41	pN3	LO, RC	cN2	cN1
13	52	Male	2/27	pN2	LE, RE	cN0	cN1
14	72	Male	3/44	pN2	LI, LO, RO	cN2	cN2
15	68	Male	5/41	pN3	RO, RC	cN0	cN0
16	63	Male	7/58	pN3	LE, RI, RO, RC	cN2	cN2
17	70	Male	10/118	pN2	LI, LO	cN0	cN1

LO left obturator, LI left internal iliac, RO right obturator, RE right external iliac, PC paracaval, RI right internal iliac, RC right common iliac, LE left external iliac

TABLE 4 FDG PET-CT studies for lymph node staging in patients with bladder cancer

Study	No. patients	Mean no. LN removed	No (%) of patients positive LNs	Sensitivity (%) (patient)	Specificity (%) (patient)
Kibel et al. ⁹	42	NA	10 (23.8)	70	94
Lodde et al. ¹²	44	NA	22 (50.0)	57	100
Swinnen et al. ¹⁰	51	16.3	13 (25.5)	46	97
Jensen et al. ¹⁷	18	NA	3 (16.7)	33	93
Hitier-Berthault et al. ¹⁶	52	16.5	22 (42.3)	36	86.7
Goodfellow et al. ¹⁵	93	17	28 (30.1)	68	95
Present study	61	42	17 (27.9)	47	93

LN lymph node, NA not applicable

Removal of regional LNs during RC is important to optimize disease-specific outcomes.²⁰ The extent of LN dissection is one of the most important determinants of the accuracy of imaging for the detection of LN metastasis for several reasons. First, LN dissection according to an extended template with subsequent pathologic evaluation is the gold standard for accurate LN staging. For example, presacral or common iliac LN metastasis cannot be identified using a limited LN dissection template. Second, pelvic LN dissection performed with a limited template or LN sampling for positive findings on preoperative imaging increases the accuracy of FDG PET-CT for LN staging. However, none of the studies that advocate the use of FDG PET-CT for LN staging included patients who had undergone extended pelvic LN dissection during RC.^{9,12,16}

FDG PET-CT for bladder cancer patients who are scheduled to undergo RC can also be used to identify metastatic disease undetectable by conventional imaging, such as CT scan or chest X-ray. In patients planned to undergo curative treatment with RC, surgery can be replaced with systemic chemotherapy based on FDG PET-CT findings. In a study by Apolo et al. 21 % of patients scheduled to receive organ-confined treatment or local radiotherapy for bladder cancer had a change in treatment to metastatic treatment or systemic chemotherapy as a result of FDG PET-CT data.¹¹ However, in this study, we did not detect new metastatic lesions on FDG PET-CT in any patient with no evidence of metastasis on conventional imaging.

In addition to FDG, new PET tracers, such as radio labeled choline and acetate, have been used as tracers in

LN staging of patients with bladder cancer prior to undergoing RC and have the advantage of minimal urinary excretion. However, studies showed inconsistent results, likely attributable to small patient populations, nonstandardized LN dissection, and differing patient population with diverse spectrum of disease.^{21,22} Although a recent study using combined ultrasmall super paramagnetic particles of iron oxide MRI showed an improved detection of metastasis in normal-sized pelvic LNs of bladder cancer in 19 patients with bladder cancer, external validation on a large cohort of bladder cancer patients is needed.¹⁹ Further development of more reliable methods for preoperative LN staging in bladder cancer is needed.

Our study results were strengthened by the standardization of patients. All bladder cancer patients undergoing RC with extended pelvic LN dissection at our institute underwent FDG PET-CT before surgery, which eliminates any potential selection bias. Also, because this study was conducted prospectively, all FDG PET-CT imaging findings were interpreted by specialists in genitourinary FDG PET-CT imaging who were blinded to conventional imaging as well as final pathology results.

However, this study has several limitations. First, our study includes a relatively small number of patients and includes patients with LN metastasis. However, to the best of our knowledge, this is the largest study on the use of FDG PET-CT in patients with bladder cancer who underwent extended pelvic LN dissection. Additionally, because there is no specific SUV number that distinguishes between benign and malignant lesions, we choose an SUV of ≥ 2.5 as the cutoff point according to a previous study on FDG PET-CT.²³

In conclusion, our study demonstrates that FDG PET-CT has a low sensitivity for LN staging in muscle-invasive bladder cancer. Combined FDG PET-CT did not improve the diagnostic accuracy of conventional CT alone for the detection of LN metastasis in bladder cancer patients scheduled for RC. Considering the cost, routine use of FDG PET-CT for LN staging of bladder cancer is not recommended. Further studies are needed on the use of other PET tracers and/or the resolution of PET scanners for the LN staging of bladder cancer.

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