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ORIGINAL ARTICLE

Contrast Enhanced Computed Tomography Characterization of Fluorodeoxygluocose-Avid Regional and Non-Regional Lymph Nodes in Patients with Suspicion of Metastatic Bladder Cancer

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ABSTRACT

Objective: The objective of this study is to assess if size alone can predict the presence of metastatic disease within lymph nodes seen on contrast enhanced-computed tomography (CE-CT) in patients with suspicion of metastatic bladder cancer and also to evaluate the nodal distribution and morphological characteristics of fluorodeoxygluocose (FDG) avid lymph nodes on CE-CT. **Materials and Methods:** A retrospective analysis from 2002 to 2009 was performed on patients with suspicion of recurrent disease undergoing restaging FDG-positron emission tomography (PET)/CT. Standardized uptake value (SUVmax) adjusted for lean body mass was recorded in abnormal lymph nodes in the abdominopelvic region. Distribution, size, shape, presence of necrosis and clustering of the FDG-avid lymph nodes was assessed on CE-CT obtained within 4 weeks of the PET/CT. The abnormal nodes were then compared with non-FDG avid lymph nodes on the contralateral side serving as control. **Results:** A total of 103 lymph nodes were found to be FDG-avid in 14 patients on 17 PET/CT examinations. Overall, mean SULmax was 4.7 (range: 1.6-10.7), which is significantly higher than background of 1.5 ($P < 0.05$). Regional pelvic lymph nodes were FDG-avid in 93% of patients and metastatic extra-pelvic in 100% of patients. The overall average size of the FDG avid lymph nodes on CE-CT was 11 mm with a third of these measuring 3-8 mm. The average size of FDG-avid lymph nodes was 11 mm in the paraaortic region 13 mm in the common iliac 9 mm in the internal iliac and 13 mm in the external iliac regions. Nearly 88.4% of lymph nodes were round in shape, clustering was present in 68% and necrosis in 7% and average size of lymph nodes that served as controls was 6 mm with reniform morphology in 92% and absence of clustering and necrosis. **Conclusion:** Overlap in size exists between

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FDG-avid pathological and non-pathological lymph nodes seen on CE-CT in patients with metastatic bladder cancer. Other characteristic such as abnormal morphology and clustering are useful adjuncts in the evaluation of nodal metastatic disease.

Key words: Bladder cancer, contrast-enhanced imaging, fluorodeoxygluocose positron emission tomography/computed tomography

INTRODUCTION

Regional and metastatic nodal disease involvement is a significant prognostic marker in the management of bladder cancer. Patients with higher grade disease are more likely to have occult nodal disease. Up to 27% of surgically treated bladder cancer patients were found to have lymph node metastasis upon histological examination when an extended lymphadenectomy was performed.[1] Therefore, accurate assessment of nodal disease involvement is crucial in optimal management. Currently, the staging assessment of bladder cancer is mainly based on imaging techniques such as contrast enhanced-computed tomography (CE-CT) and magnetic resonance imaging (MRI). Techniques using ultrasmall superparamagnetic iron oxide particles and diffusion weighted imaging with MRI have also been utilized to assess for nodal disease; however, these techniques are not standardized and not available at every center.[2] Conventional anatomical imaging primarily assess nodal enlargement as a marker for nodal disease.[3] However, there is a wide variation in size of non-metastatic lymph nodes, which can substantially overlap with the size of diseased nodes.[4]

Hybrid imaging with fluorodeoxygluocose (FDG) positron emission tomography (PET)/CT has shown utility of FDG PET in the evaluation of bladder cancer. However, the current use is limited to evaluation of systemic disease in patients with higher grade disease and with suspected recurrence and negative or equivocal anatomical imaging findings (e.g.,CE-CT). In recent studies, FDG PET/CT has shown greater sensitivity in detection of loco regional and metastatic nodal disease involvement compared with diagnostic CE-CT.[1] To the best of our knowledge, however, no previous studies have examined the combined utility of CE-CT and FDG PET/CT for the assessment of lymph nodes in bladder cancer.

Thus, in this retrospective analysis, we have sought to evaluate the morphological characteristics (i.e., size, shape and architectural changes) of FDG-avid lymph nodes on CE-CT in patients presenting with suspicion of metastatic bladder cancer and have attempted to increase the accuracy of CT in making an earlier diagnosis of metastatic lymph node involvement.

MATERIALS AND METHODS

A retrospective analysis from 2002 to 2009 was performed on all patients with suspicion of recurrent disease who were undergoing restaging 18F-FDG PET/CT scan. The study was reviewed and approved by our institutional review board. All patients were imaged using our standard clinical PET/CT protocol.[5] Scanning was performed using a Discovery LS or ST-RX PET/CT scanner (GE Health-care) using a standard whole body oncology protocol (base of the skull to mid-thighs). Scans were acquired from the thighs up to minimize the effect of excreted FDG in the bladder.

SUVmax (standardized uptake value) adjusted for lean body mass (SULmax) was recorded in abnormal lymph nodes in the abdomino-pelvic region. Lymph nodes with uptake higher than the background (measured from the liver) on more than one slice were considered to be abnormal. A 3 cm volume of interest was drawn over the right hepatic lobe to determine SULavg (SUVmean adjusted for lean body mass) according to PET Response Criteria In Solid Tumors, or PERCIST 1.0 guidelines to determine background activity.[6]

CE-CT performed within 4 weeks of 18F-FDG PET/CT without intervening treatment was included in the analysis. Distribution, size (short dimension), shape (round vs. reniform), presence of necrosis and clustering (defined as the presence of three or more adjacent lymph nodes) of the FDG-avid lymph nodes was assessed on CE-CT. CE-CT and FDG PET/CT images were assessed visually side-by-side. Lymph nodes were grouped into four regions (para-aortic, common iliac, external iliac and internal iliac regions). FDG-avid para-aortic lymph nodes were considered metastatic, while diseased common, external and internal iliac lymph nodes were considered regional. The largest non-FDG-avid lymph node in each nodal region on the contralateral side served as a control; measurements of the short dimension were made. Both CE-CT and 18F-FDG PET/CT were reviewed by a nuclear medicine physician and a radiologist with 7 years of CT interpretation experience each and findings were recorded by consensus.

RESULTS

A total of 17, 18F-FDG PET/CT and CE-CT examinations performed in 14 patients between 2002 and 2009 were included in this analysis. These patients had a history of various treatments including radical cystoprostatectomy, transurethral tumor resection, chemoradiation and treatment with Bacillus Calmette-Guerin followed by radical cystoprostatectomy for recurrent disease [Table 1].

A total of 105 (n = 16) FDG-avid lymph nodes were found. One gastrohepatic and one right pelvic lymph node were not included in the detailed analysis as they were not clearly identified on CE-CT. Detailed analysis was performed on 103 lymph nodes among 14 patients.

Region-wise distribution of lymph nodes was as follows: Para-aortic (n = 62), external iliac (n = 12), common iliac (n = 25) and internal iliac (n = 4). Regional lymph nodes were FDG-avid in 93% of patients (n = 13) and metastatic lymph nodes were positive in 100% patients (n = 14). Overall, mean SULmax was 4.7 (range: 1.6-10.7) while mean hepatic SULavg was 1.5 (range: 1.1-1.9).

The average size of all regional and metastatic FDG-avid lymph nodes was 11 mm (range: 3-26 mm). Average size and range for all lymph nodes was as follows; para-aortic 11 mm (range: 3-26 mm), common iliac 13 mm (range: 5-24 mm), internal iliac 9 mm (range: 6-23 mm) and external iliac 13 mm (range: 9-23 mm) [Table 2]. Approximately, 42% of these lymph nodes were <10 mm in size (n = 43) with a size range of 3-9 mm.

Based on morphological analysis, 88.4% (n = 91) lymph nodes were round, while 12 lymph nodes were reniform in shape. Two thirds (68%) of the lymph nodes had clustering (n = 70) [Figure 1]. Necrosis was only evident in 8 lymph nodes (approx. 8%) [Table 3 and Figure 2].

Table 1: Demographics and clinical characteristics of the patient cohort

Characteristics	Number (n)
Age	65 years (mean)
Gender	12 males, 2 females
Histology	
TCC	14
Grade	
Poorly differentiated	14
Moderately differentiated	0
Well-differentiated	0
Treatment history	
Radical cystoprostatectomy	7
Transurethral resection	5
Chemotherapy	1
Chemo-radiotherapy	1
Biopsy	1
BCG	1

TCC: Transitional cell carcinoma, BCG: Bacillus calmette-guerin

A total of 25 lymph nodes were characterized as controls with an average size of 6 mm (range: 3-8 mm). 92% (n = 23) of lymph nodes were reniform in shape while the round nodes were of 4 mm and 6 mm in size. None of the controls had clustering or necrosis.

LIMITATIONS

Our study is not without limitations. First, the data was analyzed retrospectively, which renders out of our control the availability and accuracy of medical records. Secondly, our patient population had already undergone lymph node dissection. This explains why most of the recurrence seemed to have been in the para-aortic regions and not in the pelvis. Finally, as we did not obtain pathologic samples, we cannot definitively report that nodes truly harbored disease. However, the high SUVs are suggestive

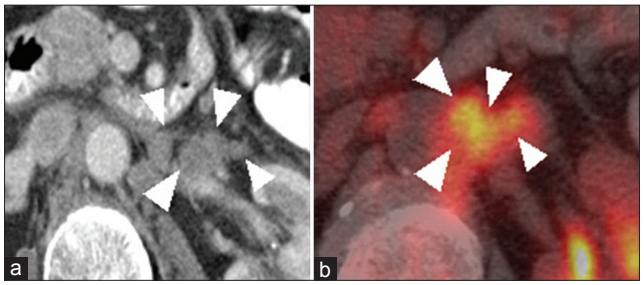

Figure 1: 58-year-old male, with urothelial cancer, initially treated with radical cystoprostatectomy and adjuvant chemotherapy. Follow-up bone scan was suspicious for osseous metastases. a) Contrast enhanced-computed tomography (CT) and b) fused 18F-fluorodeoxygluocose (FDG) positron emission tomography/CT show clustering of enlarged FDG-avid lymph nodes in left para-aortic region, SULmax 6.9 (arrow heads).

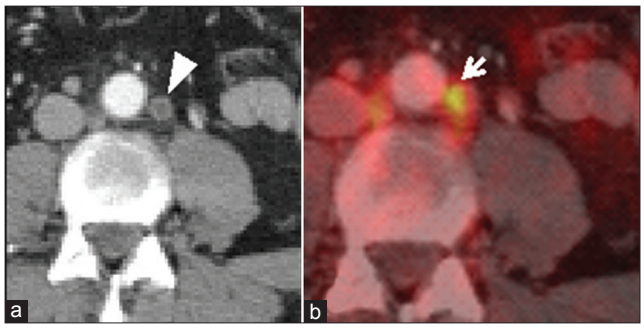

Figure 2: 71-year-old male, initially diagnosed with metastatic urothelial cancer, presenting with biopsy proven recurrent disease.a) Contrast enhanced-computed tomography (CT) shows a round para-aortic node measuring 10 mm with central necrosis (arrowhead). b) Fused 18F-fluorodeoxygluocose (FDG) positron emission tomography/CT (right) shows FDG-avidity with SULmax 5.6 (white arrow).

Table 2: Regional distribution, size, and SULmax characteristics of analyzed lymph nodes

Region	Number (n)	SULmax (mean)	Mean size (range, mm)
Para-aortic	62	4.4	11 (3-26)
Common iliac	25	4.5	12 (5-24)
External iliac	12	5.6	13 (9-23)
Internal iliac	4	5.5	9 (6-23)
Total	103	5	11 (3-26)

SULmax: Standardized uptake value adjusted for lean body mass

of metastatic disease. Although the literature is limited with regards to the correlation between histopathology and PET/CT predictive value in bladder cancer, studies have reported a sensitivity of 86% for PET/CT for the detection of lymph nodes.[7] Furthermore, it was reported that 85% of findings considered suspicious for cancer on PET/CT had an SUV of >4, while 97% of histologically proven negative lesions had an SUV of <4.[8] In our study population, the overall SUV, adjusted for lean body mass, was 4.7 (range: 1.6-10.7). Therefore, there seems to be a positive association between the presence of disease in lymph nodes and FDG SUV measurements.

DISCUSSION

Patients with more advanced disease undergo routine and frequent imaging within the first 2-3 years as 90% of recurrences following cystectomy occur during this time period. CT, being the routine imaging modality for patient surveillance, is used to detect T3b disease or higher and especially, the presence of locoregional lymph node metastases, which are treated with systematic chemotherapy. Therefore, accurate post treatment surveillance is important for selection of appropriate clinical management. Size is currently the most commonly used criterion to assess nodal involvement. However, presence of disease cannot be predicted reliably because small lymph nodes may harbor micrometastases and enlarged nodes may be reactive without tumor. Sensitivity and specificity for assessing lymph nodes based on their size is low due to a lack of agreement regarding the size limit for diagnosing pelvic nodal metastasis.[9] As such, size is not a reliable tool for distinguishing metastatic from non-metastatic enlarged nodes. Furthermore, assessing lymph nodes by clinical examination might also yield false-negative results; for example, studies have shown that patients with head-and-neck cancer who have been categorized as clinically N0 neck may harbor metastatic disease as identified by PET/CT.[10] Furthermore, very little nodal enlargement is frequently seen in metastases from the bladder and other pelvic cancers.[11] FDG-PET/CT has recently shown greater sensitivity in the detection of locoregional and metastatic nodal disease involvement compared with CE-CT. With similar high specificity, FDG-PET/CT has demonstrated almost twice the sensitivity of CE-CT (57% vs. 33%) for detecting pelvic nodal disease.[1]

Of clinical importance is the early detection of disease recurrence by FDG PET/CT that allows for early treatment and may, subsequently, increase the survival of patients.[12] Giannarini et al., assessed whether the diagnosis of asymptomatic recurrence by routine follow-up post-radical cystectomy increased the survival benefit in 479 patients with transitional cell carcinoma of the bladder.[13] The authors found that patients in whom recurrence was detected by routine follow-up had a significantly higher survival probability in comparison to patients with symptomatic recurrence.[13] Interestingly, the majority of recurrent long-term survivors had extrapelvic lymph node metastasis, confirming the importance of early detection and treatment of lymph node metastasis. Furthermore, regular surveillance allowed for the early detection of non-invasive recurrences, which are typically associated with good prognosis.[13] The authors concluded that follow-up to detect early disease recurrence after radical cystectomy offers a significant survival benefit.

Conventional anatomical imaging studies have been used to assess lymph nodes in pelvic and extra-pelvic regions. The accuracy range for lymph node staging is 70-90% for CT with false-negative rates of 25-40%, while MRI yields accuracy of 64-92%.[2,14-16] Nodal spread in bladder cancer is most common to the external iliac (especially the obturator node) and the internal iliac nodes. It is highly unlikely to have more cranial nodal involvement, if these lymph nodes are not diseased.[5]

In our population, the mean size of FDG positive lymph nodes above aortic bifurcation was 11 mm (range: 3-26 mm) with 25% of para-aortic lymph nodes <8 mm in size. In our control group [Figure 3], the mean overall size was 6 mm, demonstrating an overlap in the size of normal and abnormal nodes [Figure 1]. Vinnicombe et al., established the size criteria for normal pelvic and abdominal lymph

Table 3: Region-wise morphological analysis (shape, clustering, and necrosis) of FDG-avid lymph nodes

Region	Number	Shape (round)	Cluster	Necrosis
Para-aortic	62	54	48	5
Common iliac	25	22	11	2
External iliac	12	12	9	1
Internal iliac	4	3	2	0
Total (%)	103	91 (88.4)	70 (68)	8 (8)

FDG: Fluorodeoxygluocose

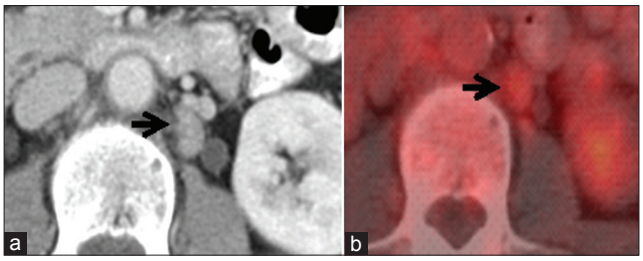

Figure 3: 66-year-old female, with initial diagnosis of infiltrating high grade urothelial cancer, with metastases to lymph node. She was initially treated with chemoradiation therapy. Computed tomography (CT) shows indeterminate retroperitoneal lymph nodes. a) Contrast enhanced-CT and b) fluorodeoxygluocose (FDG) positron emission tomography/CT fused images illustrate control lymph nodes. The images show a 8 mm reniform shaped left para-aortic lymph node with normal FDG uptake , SULmax 1.6 (liver SUVavg 1.5) (arrow).

nodes.[3] Para-aortic and para-caval lymph nodes had an approximate length of 9-11 mm, lymph nodes at the level of the common iliac arteries and pre-sacral lymph nodes had a maximum length of 8 mm and nodes distally located within the pelvic region close to the bladder had a maximum length of 9-12 mm; all measured from the short dimension. The size criteria of >10 mm for abnormal lymph nodes has led to a low accuracy in imaging studies. Furthermore, the presence of enlarged lymph nodes is not a sensitive measure of malignant involvement. In a recent pathological analysis of a large sample of patients for nodal disease involvement, median diameter measured from the short dimension of the most frequently involved nodal regions was as follows; external iliac measured 8 mm, obturator measured 8 mm and internal iliac measured 6 mm.[17] The average size of FDG-avid lymph nodes in the external iliac region in our study was 13 mm with a range of 9-23 mm and 9 mm for the internal iliac group (range: 6-23 mm). In another study by Jensen et al., analyzing nodal groups in patients undergoing lymphadenectomy, a greater overlap of size between pathological and non-pathological lymph nodes was noted; 1-35 mm for non-pathological and 3-20 mm in pathological lymph nodes.[4] Jensen et al., demonstrated that transverse diameter was a better predictor for metastatic disease involvement compared with longitudinal diameter and nodal volume.[4] A cut-off value of 8 mm or greater for lymph nodes above aortic bifurcation had a predictive value of only 29%, with a sensitivity of 25%. Furthermore, a greater overlap was seen in the size of positive and negative lymph nodes.[4] For example, size of the para-aortic lymph nodes ranged from 3 to 5 mm for positive lymph nodes and 1-10 mm for negative lymph nodes.[4]

Identification of metastases in lymph nodes that are not enlarged continues to be an additional challenge for imaging. Since size alone cannot predict the presence of metastatic disease within lymph nodes, we sought to evaluate other features along with size; that is, nodal distribution and morphological characteristics of FDG avid lymph nodes on CE-CT. In our study, 88% of all FDG-avid lymph nodes were found to be round in shape compared to only 8% round lymph nodes present in the control population. The round nodes in the control group were small in size measuring 4-6 mm. These round lymph nodes were non-FDG avid and are thus presumably benign in nature. Lymph node clustering was present in approximately 68% of nodal regions, with central necrosis present in only 8% of lymph nodes [Figure 1]. Furthermore, there was a significant difference in clustering between control nodes and involved nodes, $P < 0.01$. CE-CT surveillance of these lymph node features (i.e., round shape and clustering) may decrease the threshold for further evaluation with PET-CT. In some imaging studies performed for evaluation of pathological nodal morphology, round shape, and central necrosis have been characterized as adjunct feature.[18,19] Fukuya et al., (1995) found that nodes with higher short-axis-to-long-axis ratio were more likely to be malignant. In this study, the mean short-axis-to-long-axis ratio of malignant nodes was 0.81 compared with 0.57 for benign ones.[9] Furthermore, round nodes are more likely to be metastatic than are ovoid nodes; in a study by Jager et al., metastasis was accurately predicted because lymph nodes were round.[16] Some malignant lymph nodes may also undergo central necrosis and may therefore demonstrate peripheral enhancement following contrast administration.[20] Central necrosis in a node can be seen with metastatic involvement.[9] In a study by Yang et al., central necrosis was noted in 27% of all abnormal lymph nodes on helical CT and 17% on MRI and had a positive predictive value of 100%.[18]

To summarize, lymph nodes that are FDG-avid, round in shape, clustered and present with central necrosis, are indicative of regional metastatic disease involvement. Each of the morphological characteristics described in the present study was more likely to be associated with malignant lymph nodes than with the benign control group (for example, non-FDG-avid ovoid nodes). The presence of two or more of these characteristics in a lymph node may increase the diagnostic accuracy of malignancy in regional lymph nodes, especially when compared to using only size for defining suspicious nodes.

CONCLUSION

Overlap in size exists between pathological and non-pathological lymph nodes seen on CE-CT in patients with metastatic bladder cancer. Careful evaluation and search for other characteristic findings such as abnormal morphology and clustering in the internal iliac, external iliac, and para-aortic nodal groups are useful adjuncts in the evaluation of nodal metastatic disease. Evaluating different types of morphological characteristics simultaneously will further increase the accuracy of diagnosing lymph nodes associated with regional metastasis. To the best of our knowledge, this is the first study to demonstrate the utility of CE-CT for the evaluation of different morphological characteristics of FDG-avid lymph nodes arising from bladder cancer. This may help in making an earlier diagnosis of nodal metastatic disease by decreasing the threshold for further evaluation with PET-CT, which may lead to an improved survival of patients with bladder cancer.

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