A pictorial review of bladder cancer nodal metastases

Prasad R. Shankar, Daniel Barkmeier, Lubomir Hadjiiski, Richard H. Cohan

Department of Radiology, Michigan Medicine, Ann Arbor, MI, USA

Contributions: (I) Conception and design: PR Shankar, RH Cohan; (II) Administrative support: PR Shankar; (III) Provision of study materials or patients: PR Shankar, D Barkmeier, RH Cohan; (IV) Collection and assembly of data: PR Shankar, D Barkmeier, RH Cohan; (V) Data analysis and interpretation: PR Shankar; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Prasad R. Shankar, MD. Department of Radiology, Michigan Medicine, 1500 E Medical Center Dr B1-D530H, Ann Arbor, MI 48109, USA. Email: pshankar@med.umich.edu.

Abstract: Lymph node involvement in bladder cancer is common and has prognostic implications. Early and accurate identification of metastatic lymph nodes is, therefore, important in ensuring appropriate patient triage and management. The purpose of this review is to provide a pictorial and educational overview of the staging and imaging appearance of metastatic lymph nodes in bladder cancer. Additionally, a secondary aim of this manuscript is to provide a review of the diagnostic accuracy of common imaging modalities available for detecting metastatic lymph nodes in affected patients.

Keywords: Bladder cancer; lymph node metastasis; nodal metastasis; nodal staging; urothelial cancer

Introduction

Bladder cancer is the 9th most common cause of cancer worldwide and the second most common genitourinary malignancy (behind prostate cancer) (1,2). Most patients with bladder cancer present with hematuria. However, only 10% of patients with gross hematuria and 2% of patients with microscopic hematuria are caused by bladder cancer (3).

Lymph node involvement in bladder cancer occurs in approximately 30% of cases invading the bladder wall (stage T2) and 60% of cases in which the cancer extends into the perivesical tissue (stage T3 or greater) (4,5). Early and accurate identification of metastatic lymph nodes is important in ensuring that the appropriate patients are triaged to surgery. It may also alter the lymphadenectomy template in those patients who do undergo surgery. This can also expedite definite care in cases where the local staging is equivocal, particularly if nodal disease can be definitively identified (4,6,7).

Five-year disease-free survival rates following treatment of bladder cancer can be as great as 89%, depending on the extent of local involvement at presentation (2,6). However, the presence of nodal involvement is associated with a pronounced decrease in 5-year disease-free survival, to approximately 35% (2,6). With this in mind, the role of imaging in assisting in accurate detection and staging of nodal disease in bladder cancer is an important driver in ensuring timely and appropriate patient care and in establishing accurate prognoses (4,8).

The purpose of this review is to provide a pictorial and educational overview of the staging of and imaging appearance of metastatic lymph nodes in bladder cancer and to provide a summary of the diagnostic accuracy of common imaging modalities in detecting metastatic lymph nodes in bladder cancer patients.

Methods

This was an Institutional Review Board-approved Health Insurance Portability and Accountability Act compliant retrospective educational pictorial review. The requirement for informed consent was waived. Images obtained for this review were derived from authors personal teaching files and a retrospective review of lymph node pathology from the electronic medical record at a large academic quaternary care center between 1/1/2010 and 12/31/2017 (9).

Review

Lymphatic drainage of the bladder

The lymphatic drainage from the bladder involves many regions within and beyond the pelvis (10). The specific route of lymphatic spread from the bladder is complex and impacted by the primary location of the tumor (10,11). Roth *et al.* performed a prospective study of 60 patients to assess the primary lymphatic landing site from the bladder and showed that while the major lymphatic landing sites are regional lymph nodes, a small majority of cases showed drainage initially to more distant lymph nodes, such as the common iliac (15%) or paraortic (4%) regions (10). Given this pattern, it is not surprising that the most commonly effected sites of nodal involvement are the obturator and internal iliac regions (10,12,13).

Lymph node staging of bladder cancer

Staging of nodal metastases from bladder cancer is based on the current TNM guidelines from the American Joint Committee on Cancer, eight edition staging manual (AJCC 8th edition) (8,14,15). Definitive lymph node staging is based on post-operative histology and should only be suggested on imaging studies when lymph node involvement is obvious. Nodal staging, which is provided in *Figure 1*, is also summarized as follows:

(I)   N0 disease is defined as no lymph node involvement;

(II) N1 disease is defined as bladder cancer involvement of one regional pelvic lymph node. Regional lymph nodes include: inguinal, hypogastric (internal iliac chain), obturator, external iliac chain, perivesical, and presacral lymph nodes, all of which are located below the level of the common iliac arteries (*Figure 1*) (8,14-16);

(III) N2 disease is defined as involvement of more than one regional lymph node. It should be noted that in previous staging classification systems, differences in involved lymph node size were also used to differentiate N1 from N2 disease; however, lymph node size is no longer considered part of the staging system (*Figure 1*) (8,15).

(IV) N3 disease is defined as a positive lymph node along either or both of the common iliac chains (*Figure 1*) (8,14,15);

(V)   Importantly, involved lymph nodes, above the level of the aortic bifurcation, are now considered to be

distant metastases and classified as M1a disease. Metastases to other organs are now classified as M1b disease) (*Figure 1*) (8,14,15).

The location and number of involved lymph nodes can be helpful in predicting the prognosis for patients with advanced disease (8).

Lymph node evaluation on CT

The most commonly used first line imaging study for evaluation of patients with suspected or known newly diagnosed bladder cancer is CT of the abdomen and pelvis, typically in the form of a CT urogram (5,17,18). The CT urogram, performed without and with intravenous contrast material, is considered the appropriate first line test for the detection of suspected bladder cancer in patients with either microscopic or gross hematuria and is also considered an appropriate first step in staging for those patients in whom invasive bladder cancer (stage T2 or greater) has been diagnosed at cystoscopy (17-19).

While the use of lymph node size alone (measured in maximal short axis diameter) had historically been a marker of nodal involvement and was used as a measure of nodal staging in prior iterations of the AJCC TNM criteria (5), size criteria alone, as a marker of disease involvement is imprecise due to the wide range of normal lymph node sizes and the potential for metastatic bladder cancer occurring within non-enlarged lymph nodes (*Figures 2,3*) (12). Acknowledging these limitations, recommended size thresholds that have been utilized are ≥8 mm in short axis for suspected abnormal pelvic lymph nodes and ≥10 mm in short axis for abdominal lymph nodes (*Figure 4*) (12).

For the previously provided reasons, some investigators have found that identification of suspected metastatic lymph nodes on CT is most accurate when lymph node features, in addition to size, are assessed. This includes lymph node shape and internal architecture/attenuation (12). Normal lymph nodes generally have a reniform shape, as they frequently contain a central fatty hilum. The loss of this normal appearance and a more rounded (*Figure 2*) or irregular configuration should be concerning for involvement with metastatic tumor (*Figure 5*) (12,20). Another alteration of internal nodal architecture, is central low attenuation due to necrosis, which should be considered suspicious for metastatic disease when a primary pelvic neoplasm is present (21).

There has been limited study of the diagnostic accuracy

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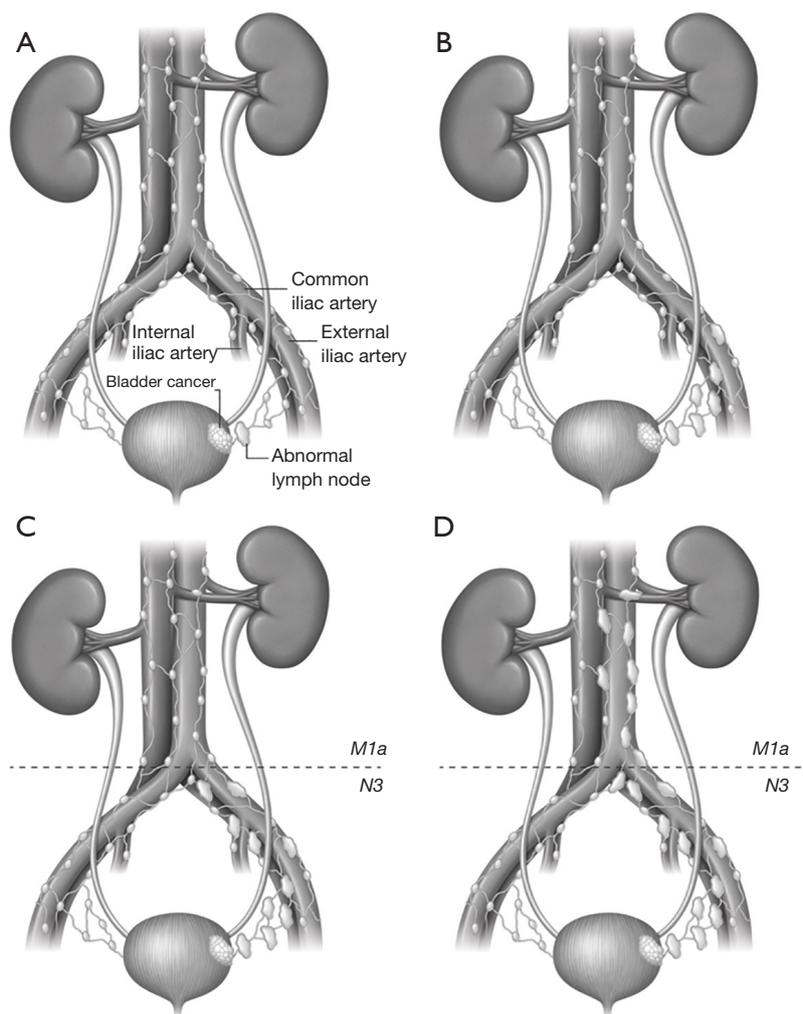
Figure 1 *Schematic of bladder cancer lymph node staging (15). Nodal staging of bladder cancer detailed for N1–M1a (A-D). N1 disease depicted as a single abnormal left perivesical lymph node (A). N2 disease depicted as multiple abnormal left regional lymph nodes (B). N3 disease depicted as abnormal lymph nodes involving the left common iliac distribution (C). M1a disease depicted as abnormal lymph nodes involving the para-aortic region above the level of the aortic bifurcation (D). Abnormal lymph nodes are depicted with irregular margins for illustrative purposes.*

of CT in nodal staging of bladder cancer over the past 10 years (6,22-25), with the few recent publications having found that even with current techniques, the sensitivity of CT in detecting metastatic bladder cancer in lymph nodes is highly variable, but generally limited, ranging from 30% to 75%. The limited sensitivity is likely primarily due to the presence of metastases within normal sized lymph nodes (high proportion of false negatives). There has been a wide range in reported specificities, from 56% to 100% (6,22-25). Overall diagnostic accuracy in identifying N1, N2, or N3 bladder cancer has recently been reported at between 61% and 97% (4). Overall, CT can be viewed as more specific

than sensitive for the detection of nodal involvement.

Lymph node evaluation on multiparametric magnetic resonance imaging (MRI)

MRI of the of the abdomen and pelvis is an alternative, but less commonly utilized, modality for evaluating lymph nodes in patients with suspected or known bladder cancer (18). When consideration is made as to whether or not to obtain an MRI, the potential benefits of multiparametric assessment of nodal characteristics, should be weighed against a number of potential contraindications,

Figure 2 Contrast enhanced CT abdomen/pelvis—positive perivesical lymph node. A 68-year-old man with known invasive urothelial bladder cancer (asterisk) presents for staging. Contrast enhanced CT images reveal a round non-enlarged right perivesical lymph node suspicious for metastatic involvement (arrow). The patient underwent radical cystoprostatectomy, pelvic lymph node dissection, and ileal loop urinary diversion, with pathology confirming involvement of the perivesical node and final histologic stage of T3b N1 M0 bladder cancer.

Figure 3 Contrast enhanced CT abdomen/pelvis—false negative right external iliac lymph node. A 59-year-old man presented with left groin and flank pain, without hematuria, and was found to have an invasive (T3) bladder urothelial mass obstructing the right ureter. A staging CT showed no evidence of metastatic disease, with the largest visible lymph node in the right external iliac station measuring just 5 mm short axis (arrow). However, radical cystoprostatectomy with pelvic lymph node dissection performed less than one month later yielded multiple bilateral pelvic lymph nodes positive for malignancy.

including the patient's ability to lie still for a prolonged period of time, claustrophobia, the presence of regional orthopedic hardware, and potential MR incompatibility of any implantable medical devices that the patient may have (7).

The role of MRI in assessment of nodal involvement is an area of active investigation (26). Similar to CT, metastatic lymph nodes are conventionally identified when short axis diameter lymph node exceeds 8–10 mm (12);

however, assessment of nodal size by MRI suffers from the same limitations as CT, in that normal sized lymph nodes may still harbor metastatic disease (4,13,20).

Compared with CT, the use of multiple pulse sequences in MRI allows for evaluation of a large number additional lymph node features independent of size, potentially aiding in the identification or exclusion of metastatic disease (7). Some of the many other multiparametric MRI lymph node features that can be evaluated include: lymph node shape, T1 and T2 signal intensity, diffusion characteristics, and the temporal nature of gadolinium-based contrast material enhancement. On MRI, normal lymph nodes often demonstrate a reniform configuration with a preserved central T1-hyperintense fatty hilum (*Figure 6*). Metastatic lymph nodes are more likely to demonstrate heterogeneous and/or increased peripheral enhancement (*Figures 7,8*) and heterogeneous central T1-hypointensity and T2-hyperintensity, corresponding to necrosis (*Figure 9*) (21). To date, no routinely acquired MRI sequence (T1-weighted, T2-weighted, diffusion weighted or gadolinium-enhanced) has been shown to be superior to the others in terms of increasing sensitivity or specificity in the detection of metastatic lymph nodes (7,13,26).

Despite the potential advantages of MRI over CT in assessing lymph nodes in bladder cancer patients, studies evaluating the ability of MRI to detect metastatic lymph nodes have not shown significant diagnostic benefits, especially with respect to sensitivity. A recent meta-analysis by Woo *et al.* showed a pooled sensitivity of MRI for identifying metastatic lymph nodes from bladder cancer to be 56%, although the specificity was 94% (26). In another meta-analysis, Salminen *et al.* showed a sensitivity range of 40.7–86% and a specificity of 31–92% (with 5/6 included studies having a specificity >80%) (7).

The use of intravenous lymphotropic ultrasmall superparamagnetic particles of iron oxide (USPIO) in further characterization of metastatic lymph nodes has been suggested as a possible alternative technique for improving accuracy in detection of metastatic lymph nodes (12,27,28). USPIO functions by being taken up in benign lymph nodes, which appear diffusely hypointense on T2-weighted and gradient echo sequences (12,27-29). In contrast, metastatic lymph nodes remain relatively hyperintense on these sequences. The use of USPIO has been shown in a recent meta-analysis by Woo *et al.* to improve pooled sensitivity to 86% (from 56%), while pooled specificity is relatively unchanged at 93%, with similar trends having been shown in other studies (7,26,29-31). However, USPIO is not
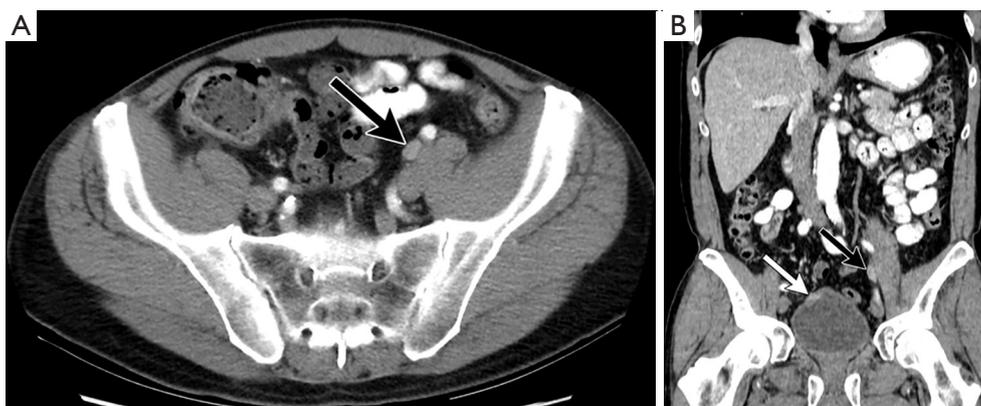
Figure 4 Contrast enhanced CT abdomen/pelvis—positive left common iliac lymph node. A 67-year-old man was initially diagnosed with T1 bladder cancer and treated with mitomycin and BCG. One year later, he developed a recurrent bladder mass. A follow-up CT at that time revealed an abnormal left common iliac lymph node (black arrows) seen in axial (A) and coronal (B) planes on contrast-enhanced CT. This was excised and positive for urothelial metastasis on pathology. The primary bladder mass is visible on the coronal image (B, white arrow). BCG, Bacillus Calmette-Guerin.
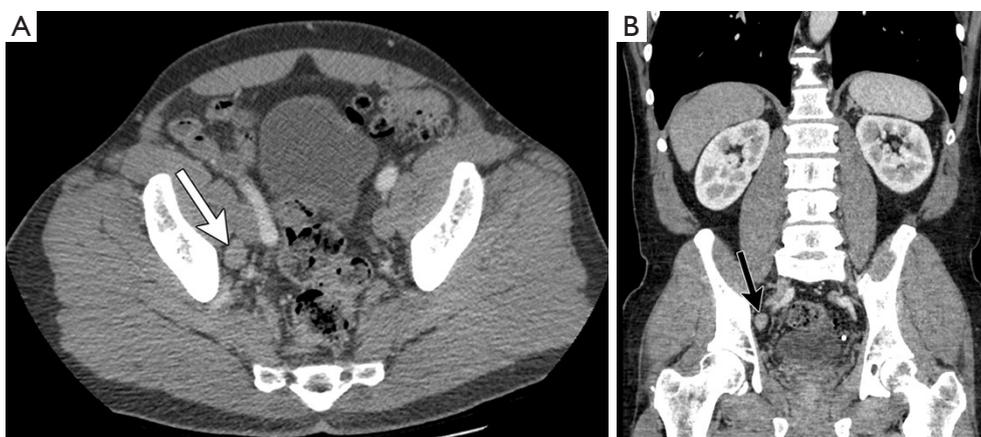
Figure 5 Contrast enhanced CT abdomen/pelvis—positive right external iliac lymph node. A 65-year-old man presented with gross hematuria and was found to have T1 disease on TURBT, treated initially with BCG. Follow-up imaging revealed multiple enlarged lymph nodes: including a right external iliac lymph node (arrows) seen on post-contrast CT in axial (A) and coronal (B) planes. The patient underwent radical cystoprostatectomy and was histologically staged as T4 N2 Mx. TURBT, transurethral resection of bladder tumor; BCG, Bacillus Calmette-Guerin.

approved for routine clinical use within the United States at this time and may require logistic hurdles due to the potential need for multiple separate episodes of scanning (7).

Lymph node evaluation on positron emission tomography-CT (PET/CT)

PET/CT is a potentially helpful modality for improving sensitivity in the detection of metastatic lymph nodes in

bladder cancer patients. The ACR appropriateness criteria lists PET/CT in the category of "may be appropriate" for bladder cancer staging (18). Due to physiologic excretion of radiotracer into the urinary tract, however, 18-Fluoro-deoxyglucose (FDG) PET/CT is of limited utility in local staging (4,7,18,22).

Metastatic lymph nodes have increased metabolic activity and, therefore, demonstrate increased radiotracer uptake on PET/CT (*Figures 10,11*) (4). Unfortunately,

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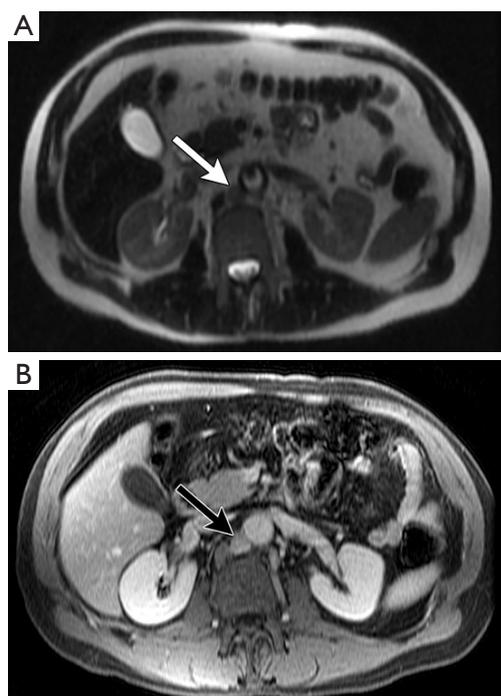
Figure 6 Contrast enhanced abdomen/pelvic MRI—new right aortocaval lymph node. A 67-year-old man was initially diagnosed with T1 bladder cancer and treated with mitomycin and BCG. One year later, new round lymph nodes were found on surveillance MR. A mildly enlarged round aortocaval lymph node (arrows) is isointense to the spleen on T2-weighted imaging (A), without a discernable fatty hilum and shows heterogeneous enhancement following intravenous gadolinium-contrast administration on T1 fat saturation post-contrast images (B). BCG, Bacillus Calmette-Guerin.

due to limitations in spatial resolution of PET, PET/CT has decreased accuracy in the detection of disease in non-enlarged but metastatic lymph nodes (<5 mm) (12). Furthermore, increased radiotracer uptake can be seen in lymph nodes that do not harbor metastatic disease (i.e., reactive or inflammatory lymph nodes). Thus, there are many opportunities for both false negative and false positive PET/CT results in bladder cancer patients.

Assessment of the accuracy of PET/CT in the detection of nodal disease in bladder cancer has been an area of growing interest and investigation. As with CT and MRI, many studies have shown that PET/CT has limited sensitivity, but much better specificity in detecting and excluding lymph node metastases. A meta-analysis performed by Soubra *et al*. showed FDG PET demonstrated sensitivities
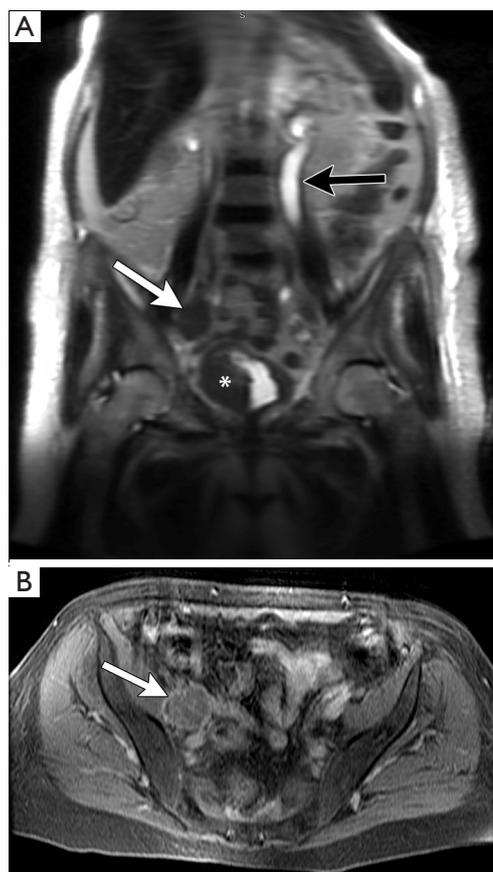
Figure 7 Contrast enhanced abdomen/pelvic MRI—positive right external iliac lymph node. A 71-year-old woman presented with gross hematuria, leading to a TURBT which showed T2NxMx papillary urothelial carcinoma. Unfortunately, the patient progressed on neoadjuvant chemotherapy. A pelvic MR showed a 3 cm right external iliac lymph node (white arrows) which is hypointense on coronal T2-weighted images (A) and peripherally-enhancing on axial post-contrast T1-weighted imaging with fat saturation (B). The primary bladder mass (asterisk) and post-obstructive left hydroureter (black arrow) are present on the coronal T2-weighted image (A). TURBT, transurethral resection of bladder tumor.

in detecting bladder cancer lymph node metastases of 33–78% and specificities of 86.7–100% (32). A prospective study and meta-analysis performed by Jeong *et al*. showed pooled sensitivities of 47% to 70% and specificities of 87% to 100% (33). A study of 233 patients by Goodfellow showed PET/CT had an improved sensitivity compared to conventional CT (69% *vs*. 45%), but resulted in a slight decrease in specificity (95% *vs*. 98%) (34).
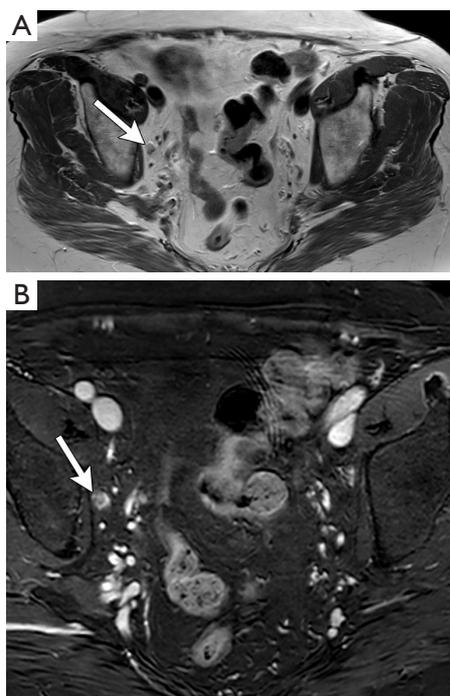
Figure 8 Contrast enhanced abdomen/pelvic MRI—positive right obturator lymph node. A 73-year-old woman presented with urinary retention and pelvic pressure. Cystoscopy and subsequent biopsy revealed high-grade T2 bladder carcinoma with urethral involvement. T2-weighted MR of the pelvis without fat saturation (A) shows a 7 mm right obturator lymph node (arrows) which enhances heterogeneously following gadolinium administration on T1 fat saturation post-contrast images (B). Although not enlarged, the lobulated margins and interval development since a CT performed 3 weeks previously make this highly suspicious for malignancy. Surgical pathology following cystectomy and lymph node dissection confirmed multiple positive right pelvic lymph nodes.

C11-Choline PET has been studied as a potential alternative tracer to be used in bladder cancer imaging due its limited urinary excretion (35). Kim *et al.* performed a meta-analysis of 10 studies on the diagnostic accuracy of C11-choline PET in the detection of nodal metastases from bladder cancer and found a pooled sensitivity of only 66% and a pooled specificity of 89% (35).

Conclusions

Understanding changes in nodal staging guidelines is important for radiologists and urologists engaged in imaging review, in order to understand the staging implications based on the location and number of abnormal lymph nodes. Lymph node metastases from bladder cancer are also an important marker of disease prognosis. While, radiologists historically have relied on size, a combination of lymph node size, shape and internal architecture is most effective in identifying potentially metastatic lymph nodes. Conventional CT remains the mainstay of imaging for patients with known or suspected bladder cancer, likely due to its speed and easy availability, and can be viewed as more specific than sensitive for the detection of lymph node metastases. MRI and PET/CT have demonstrated better sensitivity than CT; however, the sensitivity of these studies in detecting lymph node metastases is still limited. Additional research is still necessary to demonstrate the potential impact these imaging modalities may have on patient management. Further investigation is needed to improve diagnostic accuracy and to balance any potential improvements with imaging costs and patient preferences.
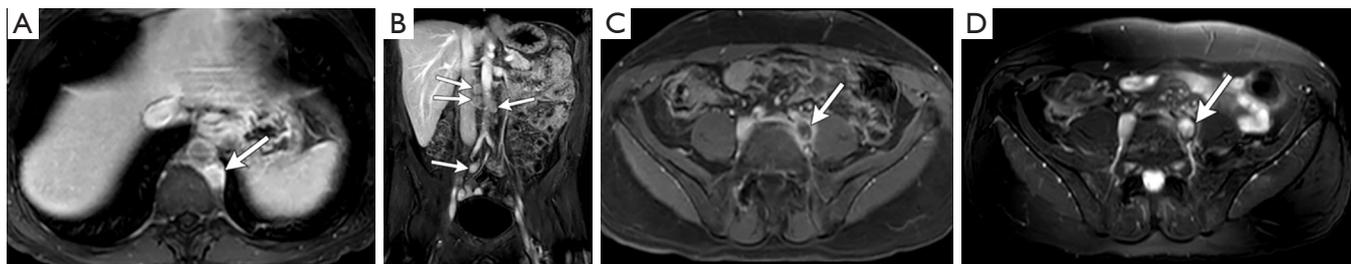
Figure 9 Contrast enhanced abdomen/pelvic MRI—new enlarged and necrotic lymph nodes. A 68-year-old man had gross hematuria for a month, and was found on cystoscopy to have high-grade urothelial bladder carcinoma. Axial post-contrast T1 fat saturation image (A) reveals an enlarged enhancing left retrocrural lymph node (arrow). Coronal post-contrast T1 fat saturation image (B) reveals additional enlarged and heterogeneously enhancing periaortic and right external iliac lymph nodes (arrows). Axial T1 fat saturation post-contrast (C) and axial T2 fat saturation (D) images reveal a peripherally enhancing (C, arrow) and a centrally T2-hyperintense (D, arrow) necrotic left common iliac lymph node.
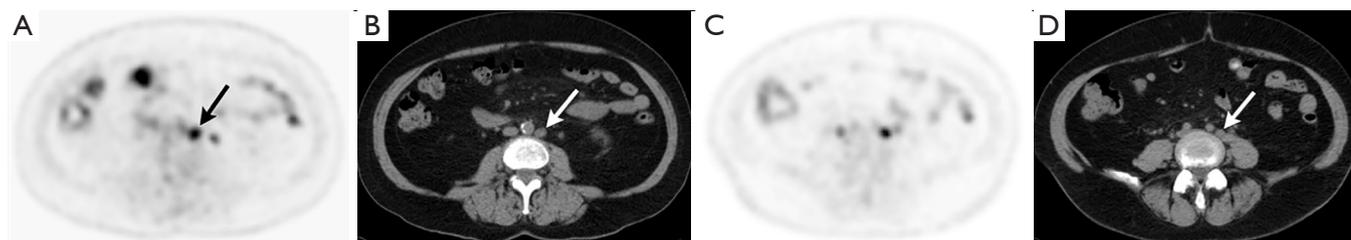
Figure 10 ^{18}F-FDG PET/CT—FDG-avid, morphologically benign appearing lymph nodes. A 73-year-old woman presented with hematuria and was found to have invasive high-grade papillary urothelial carcinoma on cystoscopy. One year following cystectomy and local lymph node dissection, a PET-CT was performed and demonstrated foci of increased radiotracer uptake at multiple locations including the left periaortic (A, black arrow) and left common iliac (C) stations, corresponding to morphologically normal lymph nodes on the associated non-contrast CT (B,D; white arrows). Percutaneous biopsy confirmed sites of metastatic urothelial carcinoma.

Figure 11 ^{18}F-FDG PET/CT—FDG-avid positive right inguinal lymph node. A 71-year-old male presented with rectal pain, leading to a colonoscopy which showed a large pelvic mass. He then developed a rectovesical fistula and was found to have high-grade urothelial cancer with sarcomatoid differentiation, treated with pelvic exenteration. The subsequent FDG PET-CT shows a metabolically active (A, black arrow), enlarged right inguinal lymph node (B, white arrow) which was percutaneously biopsied and which was confirmed as a urothelial cancer lymph node metastasis.

Acknowledgements

Footnote

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