Conventional and diffusion-weighted MRI features in diagnosis of metastatic lymphadenopathy in bladder cancer

Daniel A. Wollin, MD,[1] Fang-Ming Deng, MD,[2] William C. Huang, MD,[1] James S. Babb, PhD,[3] Andrew B. Rosenkrantz, MD[3]

[1]Department of Urology, NYU Langone Medical Center, New York, New York, USA

[2]Department of Pathology, NYU Langone Medical Center, New York, New York, USA

[3]Department of Radiology, NYU Langone Medical Center, New York, New York, USA

WOLLIN DA, DENG F-M, HUANG WC, BABB JS, ROSENKRANTZ AB. Conventional and diffusion-weighted MRI features in diagnosis of metastatic lymphadenopathy in bladder cancer. *Can J Urol* 2014; 21(5):7454-7459.

Introduction: *To compare qualitative and quantitative imaging features from conventional and diffusion-weighted (DW) magnetic resonance imaging (MRI) in detection of metastatic pelvic lymph nodes in bladder cancer patients undergoing cystectomy.*

Materials and methods: *Thirty-six patients who had undergone cystectomy for bladder cancer with preoperative MRI with DWI sequence prior to surgery were included. Imaging features on conventional and DW-MRI were compared with histopathology at cystectomy.*

Results: *Nodal features associated with metastatic lymphadenopathy were short axis (AUC = 0.85, p < 0.001; when SA > 5 mm: sensitivity = 88%, specificity = 75%), long axis (AUC = 0.80, p < 0.001; when LA > 6 mm: sensitivity = 88%, specificity = 71%), apparent diffusion coefficient (ADC) on DWI, normalized to muscle (AUC = 0.66, p = 0.113; when nADC < 1.35: sensitivity = 75%, specificity = 68%), and absence of fatty hilum on conventional imaging (AUC = 0.73, p = 0.012; when fatty hilum absent, sensitivity = 75%, specificity = 71%).*

ADC without normalization was not associated with metastasis (p = 0.303).

Conclusions: *Imaging findings from conventional MRI and DWI achieved reasonable accuracy for detecting metastatic lymph nodes in bladder cancer, although sensitivity was higher than specificity.*

A short axis greater than 5 mm on conventional MRI had the highest accuracy of any individual finding.

When using DWI, normalization of ADC values to muscle ADC may improve diagnostic performance.

Key Words: bladder cancer, cystectomy, diffusion-weighted MRI, imaging, lymph node metastasis

Introduction

Bladder cancer is the second most common genitourinary malignancy, with over 74,690 new cases diagnosed in 2014.[1] The management of bladder cancer is dependent on tumor grade and stage, specifically the depth of invasion into and through the bladder wall. Approximately 20%-40% of patients present with or ultimately develop muscle invasive disease (invasion of the muscularis propria of the bladder wall).[2] In such cases, there is a substantially increased rate of metastasis and death. Therefore, in the United States, the standard treatment for muscle invasive disease is radical cystectomy and consideration of neoadjuvant chemotherapy.

The decision to proceed with radical cystectomy is based on many factors, including the results of preoperative assessment for metastatic disease and lymphadenopathy. Nonetheless, pelvic lymph node metastases are identified histologically in 14%-32% of patients at the time of cystectomy despite normal preoperative imaging.[3] Unfortunately, the presence and number of positive lymph nodes identified histologically after radical surgical treatment are

Accepted for publication September 2014

Address correspondence to Dr. Daniel Wollin, Department of Urology, NYU Langone Medical Center, 150 E. 32nd Street, New York, NY 10016 USA

associated with worsened post-cystectomy survival.[4] Thus, improved preoperative evaluation of the nodal environment associated with invasive bladder cancer may assist in both treatment selection and prognosis. A number of non-invasive imaging methods have been explored for this purpose including computed tomography (CT), magnetic resonance imaging (MRI), and position emission tomography (PET). However, each of these approaches has had moderate performance in past studies.[5-9]

The emergence of diffusion-weighted imaging (DWI) as an additional MRI sequence has led to improved radiologic diagnosis and staging in multiple cancers, including detection of metastatic lymph nodes.[10] By probing the motion of water molecules, DWI allows for assessment of the cellularity of a region through calculation of the apparent diffusion coefficient (ADC). A lower ADC reflects a higher cellularity, which in turn is associated with malignancy. It is possible that findings from DWI and associated ADC maps may assist in differentiating malignant from benign nodes in bladder cancer, however DWI has not been extensively evaluated in this setting. Therefore, in this study, our aim is to compare qualitative and quantitative imaging features from conventional MRI and DWI in detection of metastatic pelvic lymph nodes, using pathologic findings from radical cystectomy as the reference standard.

Materials and methods

Patients

This retrospective study was Health Insurance Portability and Accountability Act (HIPAA) compliant and was approved by our institutional review board with a waiver of the requirement for written informed consent. We searched databases from our institution from 2006 to 2013 to identify patients who underwent cystectomy for bladder cancer and had preoperative MRI including DWI. The mean delay between MRI and pathologic assessment was 54 days ± 62 days. Patients were excluded if they underwent interval treatment between imaging and surgery (n = 3) or if DWI was non-diagnostic due to severe artifact (n = 3). The final cohort consisted of 36 patients (30 men, 6 women; mean age 71 years ± 9 years; range 48 years-88 years). Pathologic diagnosis was determined through cystectomy, all of which were performed by one of two surgeons at our institution. All surgeries were performed as open procedures that included associated pelvic lymph node dissection with the following borders: aortic bifurcation, genitofemoral nerve, bladder wall, inguinal ligment, and hypogastric vessels. Nodal specimens were sent to pathology labeled by anatomic station.

MRI technique

Imaging was performed at 1.5T (n = 31) or 3T (n = 5) using a pelvic phased-array coil. Sequences included multiplanar 2D turbo spin echo T2-weighted imaging of the bladder, dynamic pre- and post-contrast 3D fat-suppressed T1-weighted gradient-echo imaging using intravenous injection of 0.1 mmol/kg of gadolinium-based contrast agent, and axial single-shot echo-planar DWI of the bladder using b-values of 0, 400, and 800 s/mm^2 and inline reconstruction of the ADC map.

Image analysis

A single fellowship-trained radiologist with expertise in urologic MRI interpretation reviewed all cases while blinded to the final pathologic diagnosis. Cases were reviewed in random order in two different sessions, separated by 3 weeks to minimize recall bias. In the first session, the radiologist reviewed all conventional MRI sequences and identified all pelvic lymph nodes. Multiple imaging features were recorded for each identified node including location, long axis size (LA), short axis size (SA), ratio of SA to LA sizes (SA/LA), loss of fatty hilum, and irregularity of lymph node margins (assessed qualitatively). In the second session, the radiologist identified all pelvic lymph nodes on DWI and recorded, the node's location, LA, SA, SA/LA, and mean ADC. In addition, mean ADC was recorded centrally within the right obturator internus muscle, and a normalized ADC value to muscle (hereafter referred to as normalized ADC, or nADC) was then calculated for each node as the ratio between the ADC of the node and that of muscle. Tiny nodes measuring up to 3 mm were not recorded during either session.

Reference

The pathologic reference standard was obtained from the previously reported cystectomy specimens, all of which had been interpreted by pathologists trained in urologic pathology. Lymph nodes were identified as positive or negative for malignancy and documented in the nodal station from which they were removed during surgery.

Statistical analysis

Generalized estimating equations (GEE) based on multivariable binary logistic regression was initially applied to model the likelihood of correctly identifying individual nodes as metastatic or benign as a function of the imaging measures, based on a node-by-node

TABLE 1. **Patient demographics**

Patients	36
Male	30
Female	6
Age (years)	71, (range 44-88)
Nodes surgically removed	633
Pathologically metastatic nodes (%)	32 (5%)
Patients with metastatic nodes (%)	8 (22%)
Patients with no residual urothelial cancer on cystectomy specimen, T0 (%)	2 (5%)

comparison between MRI and pathology. Stepwise variable selection was used to identify sets of imaging measures representing independent predictors of pathology. The features most strongly associated with nodal metastatic disease from the multivariate analysis were then further evaluated in a patient-level analysis. For this purpose, subjects were characterized as reference standard positive for metastasis if pathology detected at least one metastatic node and as reference standard negative otherwise. Receiver operating characteristic (ROC) analysis was performed to assess the utility of imaging features, alone and in combination, to correctly classify a patient as metastasis positive, also determining the sensitivity and specificity of these classifications. All statistical tests were conducted at the two-sided 5% significance level using SAS 9.3 (SAS Institute, Cary, NC, USA).

Results

Thirty-four of 36 patients had urothelial carcinoma in the bladder specimen; the other 2 patients were T0 at time of cystectomy. A total of 633 nodes were removed from the 36 patients. Of these, 32 (5%) nodes in 8/36 (22%) patients were metastatic. Two patients had documented extracapsular extension of the lymph node metastasis. The remainder of the patients [28/36 (78%)] had no metastatic lymphadenopathy, Table 1. Additionally, two patients received neoadjuvant chemotherapy prior to imaging; neither of these patients had nodal disease on pathologic examination.

Conventional MRI identified a total of 42 nodes in 16 patients. In these nodes, the mean LA was 11 mm (range 5 mm-18 mm), mean SA was 8 mm (range 4 mm-14 mm), and mean SA/LA ratio was 0.740 (range 0.333-1.000). Of the 42 nodes, 38 had an absence of a fatty hilum and 12 had irregular borders.

DWI detected 38 nodes in 16 patients. Morphologic characteristics of these nodes, as determined on DWI, were as follows: LA (mean 12 mm, range 7 mm-21mm), SA (mean 9 mm, range 6 mm-12 mm), and SA/LA ratio (mean 0.754, range 0.421-1.000). The nodes had a mean ADC of 1.20 x 10^{-3} mm^2/s (range 0.64-1.79 x 10^{-3} mm^2/s). nADC had a mean of 1.08 (range 0.59-2.04). A representative case is shown in Figure 1.

For conventional MRI, at initial node-by-node comparison between MRI and pathology, only SA showed a significant association with metastasis ($p = 0.002$), while LA ($p = 0.103$) and absence of fatty hilum ($p = 0.055$) showed non-significant associations. For DWI, at initial node-by-node comparison, no feature showed a statistically significant association with metastasis, although nADC ($p = 0.081$) showed a non-significant association. No other feature during either session, including the directly measured ADC, approached significance ($p \geq 0.165$).

TABLE 2. **Sensitivity and specificity with confidence intervals (CI) of various imaging features to detect nodal metastatic disease at the patient level**

Test criterion	Sensitivity (95% CI)	Specificity (95% CI)
Short axis > 5 mm	87.5% (47.3%-99.7%)	75.0% (55.1%-89.3%)
Long axis > 6 mm	87.5% (47.3%-99.7%)	71.4% (51.3%-86.8%)
ADC (normalized to muscle) < 1.35	75.0% (34.9%-96.8%)	67.9% (47.6%-84.1%)
Fatty hilum absent	75.0% (34.9%-96.8%)	71.4% (51.3%-86.8%)

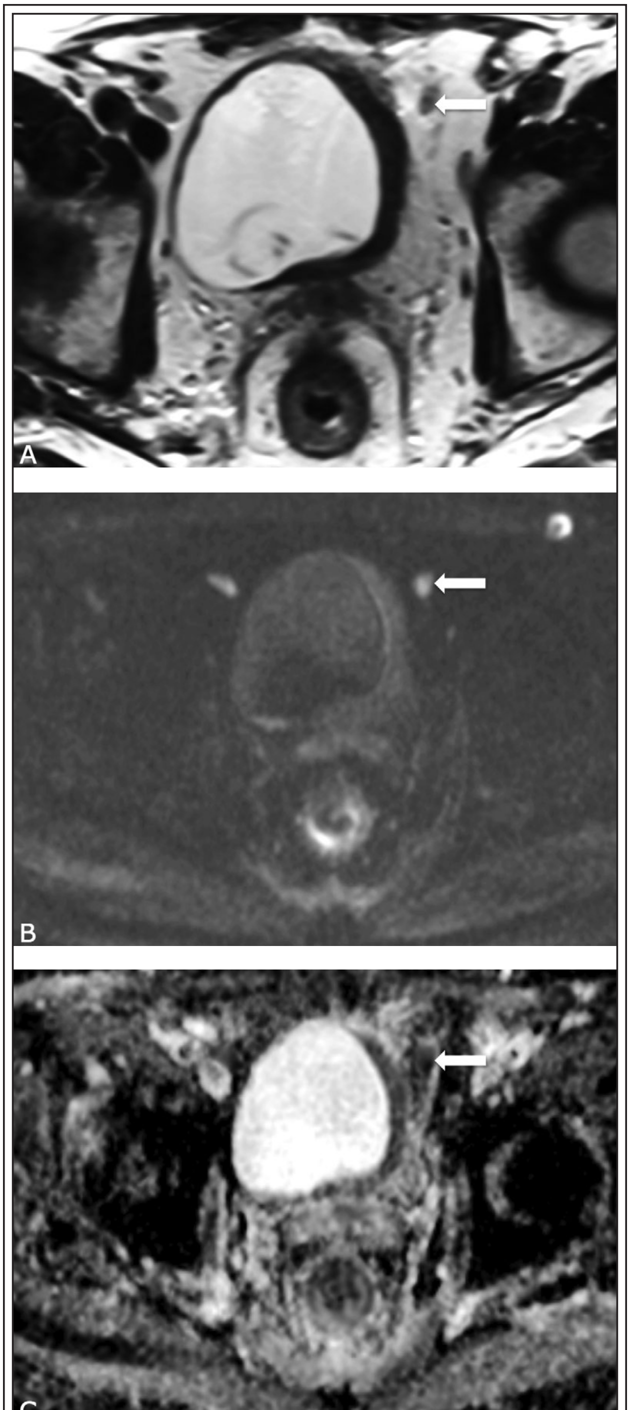

Figure 1. An 88-year-old man with bladder cancer. **(a)** Axial T2-weighted image shows an enlarged 8 mm x 6 mm lymph node (arrow) in the left perivesical region **(b)** DWI shows hyperintensity of this node (arrow) **(c)** ADC map shows hypointensity of this node (arrow) (ADC = 1.04 x 10-3 mm^2/s, nADC = 0.91). This node was found to harbor metastatic urothelial carcinoma at radical cystectomy.

Given the results of the node-level comparisons, for each patient the maximum SA and LA of any node at conventional MRI, presence of any node without a fatty hilum at conventional MRI, as well as minimum nADC of any node at DWI, were selected for further evaluation to identify metastatic lymphadenopathy at the patient level. ROC analysis yielded optimal criteria for identification of nodal metastases as follows: SA > 5 mm (AUC = 0.85, $p < 0.001$; sensitivity = 87.5%, specificity = 75.0%), LA > 6 mm (AUC = 0.80, $p < 0.001$; sensitivity = 87.5%, specificity = 71.4%), and nADC < 1.35 (AUC = 0.66, p = 0.113; sensitivity = 75.0%, specificity = 67.9%), presence of node without a fatty hilum (AUC = 0.73, p = 0.012; sensitivity = 75.0%, specificity = 71.4%). Table 2 shows these data assessing optimal imaging features at the patient level.

At multivariate assessment, no set of two or more imaging measures were identified that served as significant independent predictors of metastasis, either at the node-level or the patient-level.

Discussion

MR imaging is increasingly used to assess the stage and aggressiveness of cancers, urologic and otherwise. The addition of functional sequences such as DWI has contributed to improved accuracy in non-invasively characterizing pathologic features. In bladder cancer specifically, DWI has been shown to assist in T staging of primary tumors and also to correlate with tumor grade and presence of metastases.[11-15] Furthermore, DWI improves evaluation of lymphadenopathy in non-urologic cancers compared with standard anatomic imaging, particularly given that morphologic features are less useful at small sizes (i.e., < 10 mm). For instance, lymphadenopathy has been accurately characterized using DWI in head and neck, ovarian, rectal, and breast cancer.[16-19]

An earlier preliminary examination of DWI in evaluation of metastatic lymphadenopathy in bladder cancer reported a sensitivity of 76% and specificity of 89%.[20] This study suffered from small sample size and looked solely at ADC values, not taking into account other imaging features on conventional MRI or DWI. Still, this initial study suggested that ADC values could be useful for differentiating metastatic and benign lymphadenopathy at the nodal level in bladder cancer.

In our study, the initial multivariate evaluation of MRI features predicting metastatic nodal disease produced only a single significant feature: short axis on conventional MRI. However, long axis, absence of fatty hilum, and normalized ADC exhibited non-significant associations in a node-by-node comparison.

As this was a retrospective study, lymph nodes were not removed specifically based upon pre-operative MRI findings, and nodal stations were documented per the judgment of the individual surgeon at the time of cystectomy. For this reason, it may be problematic to attempt direct 1:1 nodal matching between imaging and pathologic standard. Partly for this reason, we performed a subsequent analysis applying the above features at the patient level, using the most concerning feature of any visualized nodes within each patient as the test criteria. These results more accurately defined the ability of MRI to detect the presence of metastatic lymphadenopathy in a given patient, which is paramount for clinical decision-making.

A key weakness of DWI is the variation in ADC values due to a host of biologic factors, such as tissue temperature and perfusion, as well as technical factors, such as choice of scanner and sequence.[21] Additionally, interobserver reproducibility of lymph node ADC values is not negligible.[22] For these reasons, it can be challenging to produce a standard threshold ADC below which metastasis is more likely. It is possible that this variability contributed to the lack of a significant association between ADC and metastatic disease. This variability was countered by normalizing nodal ADC values to the ADC of the right obturator internus muscle of each patient, producing more consistent measures. While other methods of normalization have also been used, including normalization of to primary tumor ADC, the optimal method of ADC correction has not been established and this step is not routinely performed by radiologists in clinical practice.[23] Nonetheless, our findings support a role for normalization to improve the accuracy of DWI-based diagnostics in routine practice. Despite this association between nADC and presence of metastatic lymph node disease, it is notable that size of lymph nodes on conventional MRI was the most accurate individual imaging feature for detecting nodal metastatic disease. While such comparisons between imaging findings warrant further evaluation in larger studies, our results regarding the performance of nADC remain encouraging.

There are several limitations to this study that warrant mention. First, this was a retrospective study with a small sample size. A prospective study would allow for standardized surgical planning and uniform nodal documentation during cystectomy. By improving the consistency of documentation between imaging and surgical pathology, more accurate node-by-node comparison is possible. In addition, the patients were imaged over the course of 8 years with several different MRI scanners and ongoing evolution in DWI technology, which may have influenced the ADC measurements. However, previous studies from our institution support good ADC reproducibility in bladder cancer.[14] Also, only a single radiologist's interpretation was evaluated in this pilot study; future studies may assess the inter-reader variability of these metrics. Finally, while the patient-level analysis of imaging features is useful for determining overall presence of metastatic lymph node disease for purpose of prognosis and treatment selection, a more detailed correlation of specific nodal stations may have potential to improve surgical planning.

Conclusion

In conclusion, our preliminary assessment showed that conventional MRI and DWI achieved reasonable accuracy for detecting metastatic lymph nodes in bladder cancer. Short axis, long axis, absence of fatty hilum, and normalized ADC values were useful features, although in general sensitivity was greater than specificity. Such normalization of ADC values has not been previously evaluated for bladder cancer lymph nodes and warrants continued investigation. Additional studies may further delineate the role of conventional MRI and DWI in the diagnosis, prognosis, and management of bladder cancer. ☐

References

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. *CA Cancer J Clin* 2014;64(1):9-29.
2. Stein JP, Lieskovsky G, Cote R et al. Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. *J Clin Oncol* 2001;19(3):666-675.
3. Abdel-Latif M, Abol-Enein H, El-Baz M, Ghoneim MA. Nodal involvement in bladder cancer cases treated with radical cystectomy: incidence and prognosis. *J Urol* 2004;172(1):85-89.
4. Bruins HM, Huang GJ, Cai J, Skinner DG, Stein JP, Penson DF. Clinical outcomes and recurrence predictors of lymph node positive urothelial cancer after cystectomy. *J Urol* 2009;182(5): 2182-2187.
5. Baltaci S, Resorlu B, Yagci C, Turkolmez K, Gogus C, Beduk Y. Computerized tomography for detecting perivesical infiltration and lymph node metastasis in invasive bladder carcinoma. *Urol Int* 2008;81(4):399-402.
6. Gofrit ON, Mishani E, Orevi M et al. Contribution of 11C-choline positron emission tomography/computerized tomography to preoperative staging of advanced transitional cell carcinoma. *J Urol* 2006;176(3):940-944; discussion 4.
7. Hafeez S, Huddart R. Advances in bladder cancer imaging. *BMC Med* 2013;11:104.
8. Powles T, Murray I, Brock C, Oliver T, Avril N. Molecular positron emission tomography and PET/CT imaging in urological malignancies. *Eur Urol* 2007;51(6):1511-1520; discussion 20-21.

9. Setty BN, Holalkere NS, Sahani DV, Uppot RN, Harisinghani M, Blake MA. State-of-the-art cross-sectional imaging in bladder cancer. *Curr Probl Diagn Radiol* 2007;36(2):83-96.
10. Koh DM, Collins DJ. Diffusion-weighted MRI in the body: applications and challenges in oncology. *AJR Am J Roentgenol* 2007;188(6):1622-1635.
11. Rosenkrantz AB, Haghighi M, Horn J et al. Utility of quantitative MRI metrics for assessment of stage and grade of urothelial carcinoma of the bladder: preliminary results. *AJR Am J Roentgenol* 2013;201(6):1254-1259.
12. Takeuchi M, Sasaki S, Ito M et al. Urinary bladder cancer: diffusion-weighted MR imaging--accuracy for diagnosing T stage and estimating histologic grade. *Radiology* 2009;251(1):112-121.
13. Wu LM, Chen XX, Xu JR et al. Clinical value of t2-weighted imaging combined with diffusion-weighted imaging in preoperative T staging of urinary bladder cancer: a large-scale, multiobserver prospective study on 3.0-T MRI. *Acad Radiol* 2013;20(8):939-946.
14. Rosenkrantz AB, Mussi TC, Spieler B, Melamed J, Taneja SS, Huang WC. High-grade bladder cancer: association of the apparent diffusion coefficient with metastatic disease: preliminary results. *J Magn Reson Imaging* 2012;35(6):1478-1483.
15. Lim KS, Tan CH. Diffusion-weighted MRI of adult male pelvic cancers. *Clin Radiol* 2012;67(9):899-908.
16. Cho EY, Kim SH, Yoon JH et al. Apparent diffusion coefficient for discriminating metastatic from non-metastatic lymph nodes in primary rectal cancer. *Eur J Radiol* 2013;82(11):e662-e668.
17. Chung J, Youk JH, Kim JA et al. Role of diffusion-weighted MRI: predicting axillary lymph node metastases in breast cancer. *Acta Radiol* 2014;55(8):909-916.
18. Lin G, Ho KC, Wang JJ et al. Detection of lymph node metastasis in cervical and uterine cancers by diffusion-weighted magnetic resonance imaging at 3T. *J Magn Reson Imaging* 2008;28(1):128-135.
19. Vandecaveye V, De Keyzer F, Vander Poorten V et al. Head and neck squamous cell carcinoma: value of diffusion-weighted MR imaging for nodal staging. *Radiology* 2009;251(1):134-146.
20. Papalia R, Simone G, Grasso R et al. Diffusion-weighted magnetic resonance imaging in patients selected for radical cystectomy: detection rate of pelvic lymph node metastases. *BJU Int* 2012;109(7): 1031-1036.
21. Kim JK, Kim KA, Park BW, Kim N, Cho KS. Feasibility of diffusion-weighted imaging in the differentiation of metastatic from nonmetastatic lymph nodes: early experience. *J Magn Reson Imaging* 2008;28(3):714-719.
22. Kwee TC, Takahara T, Luijten PR, Nievelstein RA. ADC measurements of lymph nodes: inter- and intra-observer reproducibility study and an overview of the literature. *Eur J Radiol* 2010;75(2):215-220.
23. Yasui O, Sato M, Kamada A. Diffusion-weighted imaging in the detection of lymph node metastasis in colorectal cancer. *Tohoku J Exp Med* 2009;218(3):177-183.