Lymph Node Assessment by Diffusion-Weighted Magnetic Resonance Imaging in Prostate, Bladder and Kidney Cancer

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Abstract

Knowledge of lymph node metastases in patients with urologic tumors is important for clinical management and may help the urologic surgeon in choosing the best treatment for these patients. Accurate nodal staging helps to predict prognosis. Conventional magnetic resonance imaging (MRI) often fails to differentiate between benign and malignant changes in lymph nodes because this technique is reliant on nonspecific features such as size and morphologic criteria. Therefore, there is a need for more accurate non-invasive diagnostic technique to improve nodal assessment.

Diffusion–weighted magnetic resonance imaging (DW-MRI) is a non-invasive functional imaging technique that provides unique information related to tumor cellularity and the integrity of the cellular membrane. DW imaging has the potential to differentiate malignant from benign lymph nodes based on the mean ADC value. Metastatic nodes show, as most primary malignant tumors, lower ADC values due to their impeded diffusion caused by high cellularity. Improved diagnostic of lymph node metastases might guide the surgeon to remove positive nodes only. Although initial results are promising, larger-scale studies will be needed to improve detection and localization of lymph node metastases. Standardizing the technical parameters and improving the image analysis represent major challenges to the widespread adoption of DW imaging.

Keywords: diffusion-weighted magnetic resonance imaging, lymph nodes, cancer, kidney, prostate, bladder.

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Introduction

Lymphatic metastasis is an important prognostic factor in patients with urologic tumors. Prostate, bladder and kidney cancers are classified according to the TNM staging system and recognition of nodal hyperplasia on preoperative imaging can considerable change the therapeutic approach.

The role of lymphadenectomy in the treatment of patients with renal cell carcinoma (RCC) is still a subject of debate. A landmark randomized study of 772 patients with preoperatively staged N0M0 renal tumors showed no survival advantage of a complete lymph node dissection in conjunction with a radical nephrectomy because the incidence of unsuspected lymph node metastases was found to be low (4%) [1]. Another study contradicts these results showing that a regional lymphadenectomy in patients requiring a radical nephrectomy for advanced RCC is beneficial for several reasons: morbidity is minimal, staging is more accurate and there is the possibility to remove the lymph nodes containing microscopic metastases [2].

For patients with prostate or bladder cancer, the presence of regional lymphadenopathy is an indication of systemic chemotherapy. Patients with a Gleason score ≥ 7 have a higher incidence of positive lymph nodes (25%) compared with those with a Gleason score < 6 (3%) [3]. For patients with bladder cancer the survival is significantly better in the absence of lymph node involvement.

In this report are reviewed the value and limitations of diffusion–weighted magnetic resonance imaging in detection and characterization of lymph node involvement for the three most frequent urologic tumors in an attempt to improve the diagnostic accuracy of MRI in the assessment of lymph node metastases for these patients.

Conventional MRI criteria for metastatic lymph nodes

The detection of nodal metastases with conventional MRI is reliant on lymph node size and morphologic characteristics such as homogeneity, margins and shape. Usually, the most common diagnostic criteria for determining lymph node metastases is the size criteria, an increase of nodal short-axis diameter more than 10 mm being considered pathological. MRI studies take into consideration the upper limits of 8 mm for round nodes and 10 mm for oval nodes in minimum short-axis diameter [4-7]. However, micrometastases can also be present in normal-sized lymph nodes.

Several studies showed that the use of these morphological criteria provide limited ability of conventional MRI to differentiate between benign and metastatic lymph nodes in patients with urogenital cancers. Sensitivities range from 24% to 75% for MRI based on size criteria only. Grubnic et al. recommended smaller values of maximum short-axis diameter: 6 mm for pelvic nodes and 5 mm for retroperitoneum nodes [8].

MRI with its excellent soft tissue contrast in the pelvic region and potential for 3D data acquisition is useful for evaluation lymph node metastases from bladder and prostate cancers since the regional nodes from these tumors are usually limited within the pelvic region [9]. About 25% of patients with these malignancies and with normal size lymph nodes on preoperative imaging studies have micrometastases according to histopathological findings [10-12].

Basic principles and technical aspects of DW-MRI

DW-MRI is a noninvasive imaging technique that measures microscopic mobility of water molecules in the tissues, by applying two equally size gradients separated by a 180° radiofrequency pulse. Static molecules are unaffected by gradients and measured signal intensity is not significant change. Moving water molecules acquire phase information from the first gradient but their signal is not entirely re-phased by second gradient due to their motion, which is visible as signal loss on the resulting image. The value of signal loss is dependent on the quantity and speed of the moving molecules and on the gradient amplitude, which is indicated by a parameter known as the “b value”.

DWI is performed using at least two different diffusion-weightings (b values), typically ranging between 0 and 1000 s/mm² and thus a quantitative analysis is possible. This analysis is represented by the calculation of the apparent diffusion coefficient (ADC) of water molecules. The effect of the movement of water molecules on the ADC value is inversely related to their speed. By using lower b-values (typically up to 100-150 s/mm²) the resulting ADC value is higher.

In general, at higher b values (e.g. > 800 s/mm²) most types of malignant tumors (increased cellular proliferation) will present greater impeded water diffusion compared with normal tissues being hyperintense (bright) on diffusion-weighted images and hypointense (dark) on the corresponding ADC map (low measured ADC value). However, edema or inflammation (increased cellular infiltration) can sometimes have similar appearance and manifest as high signal intensity on high b values images. The distinction between tumor and
inflammation or edema is performed by means of ADC measurements, where a high ADC is present in both edema and inflammation but not in tumors. A cystic or necrotic component of a heterogeneous tumor is dark on the high b-value images (greater signal attenuation) and bright on the ADC map, (water diffusion is less restricted) with higher ADC values than those of a normal parenchyma or a solid lesion [13-17].

DW-MRI examinations can be executed on most 1.5-T or 3.0-T MRI scanners. For urologic tumors, most DW images are acquired in the axial plane in “free breathing” or with respiratory triggering especially in patients with irregular breathing. Non-breath-hold spin-echo echo-planar DWI combined with fat suppression is a technique widely applied for several reasons: multiple slice excitation and signal averaging increase the signal-to-noise ratio, it is quick to perform (typically 3-6 minutes) and can be easily added to the conventional MRI sequences [18]. The image acquisition time using this technique provides flexibility in the use of multiple (>5) or of high b values. Application of more b values is usually recommended: the higher the number of b values used, the more precise is the ADC fit. In the clinical practice an acceptable ADC fit can normally be obtained with 3-4 b values [19]: one b value greater than 100 sec/mm², another b value greater than 500 sec/mm² (most often b = 1000 sec/mm²) and a b value of 0 sec/mm² for easy detection of blood vessel anomalies [20].

Example parameters for complete DW imaging of the urogenital tract

<table>
<thead>
<tr>
<th>Sequence type</th>
<th>Free breathing spin-echo echo-planar imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plane</td>
<td>Axial</td>
</tr>
<tr>
<td>Field of view (FOV)</td>
<td>360-400 mm</td>
</tr>
<tr>
<td>Matrix</td>
<td>104-112/256</td>
</tr>
<tr>
<td>Number of sections</td>
<td>40-46</td>
</tr>
<tr>
<td>Section thickness (mm)</td>
<td>5-6 mm</td>
</tr>
<tr>
<td>Intersection gap (mm)</td>
<td>0</td>
</tr>
<tr>
<td>Repetition time (msec)</td>
<td>5000-7000 ms</td>
</tr>
<tr>
<td>Echo time (msec)</td>
<td>65-68 ms</td>
</tr>
<tr>
<td>b Values (sec/mm²)</td>
<td>0,500,1000 sec/mm²</td>
</tr>
<tr>
<td>Parallel imaging factor</td>
<td>2</td>
</tr>
<tr>
<td>EPI factor</td>
<td>75-112</td>
</tr>
<tr>
<td>Bandwidth (Hz/pixel)</td>
<td>1800 Hz/pixel</td>
</tr>
<tr>
<td>No. of signals acquired</td>
<td>4-5</td>
</tr>
<tr>
<td>Acquisition time (min)</td>
<td>4 min</td>
</tr>
</tbody>
</table>

The radiologist should be aware of the susceptibility artefacts in the pelvis because of bowel motion, thus the administration of a spasmolytic drug is recommended in order to minimize these effects during the acquisition of DW images [21,22].

Applications of DW imaging in the assessment of lymph node metastases in prostate, bladder and kidney cancer

DW imaging has the potential to differentiate malignant from benign lymph nodes based on the mean ADC value. Metastatic nodes show, as most primary malignant tumors, lower ADC values due to their impeded diffusion caused by high cellularity.

The literature on the potential of DW imaging for lymph node staging is still limited.

To the best of our knowledge, there is no study that used DW-MRI to differentiate between enlarged reactive nodes and metastatic lymph nodes in renal cell carcinoma.

In prostate and bladder cancer findings of recent studies showed the potential of DW imaging in detection and characterization of lymph nodes.

In a study of 29 patients with prostate cancer evaluated by DW-MRI at 1.5T significant differences were observed in the mean ADC for b values of 50, 300 and 600 s/mm² between malignant (1.07±0.23×10⁻³ mm²/s) and benign (1.54±0.25×10⁻³ mm²/s) lymph nodes. Compared to benign lymph nodes, malignant lymph nodes showed restricted diffusion resulting in a lower ADC-value. Sensitivity and specificity were 86% and 85%, respectively, using a cut-off value of 1.30 x 10⁻³ mm²/s. Also the analysis showed a good accuracy (85.6%) of DW imaging in the assessment of lymph node metastases. These results are superior to those of a size-based analysis at a cutoff of 8 mm: accuracy of 66.1%, sensitivity of 82.0% and specificity of 54.4% (P < 0.01) [23]. In 2011 the authors achieved similar results for DW imaging in a smaller group including 14 patients with prostate cancer evaluated with DW-MRI at 1.5 T and (11)C-choline-positron emission tomography (PET)/CT [24]. In the same year, Budiharto et al. reported disappointing results for DW-MRI in a group of 36 high-risk prostate cancer patients treated with radical prostatectomy and extended lymph node dissection and with no lymph node metastasis on conventional imaging. In a lymph node region-based analysis sensitivity was only 19% (specificity 98%) and increased to 43% (specificity 82%) in a per-patient analysis [25]. The sensitivity of DW imaging is particularly limited in small lymph nodes.
Another recent study conducted on a total of 120 patients with prostate and/or bladder cancer with no enlarged lymph nodes on preoperative cross-sectional images showed promising results. All patients were examined with a 3-T MRI unit, and examinations included conventional and DW-MR imaging of the pelvis. From the total of 4846 lymph nodes resected at 120 patients, 88 lymph nodes were found to be metastatic, with a short-axis diameter less than or equal to 3 mm in 68 lymph nodes, more than 3 mm to 5 mm in 13 nodes, more than 5 mm to 8 mm in 5 nodes and more than 8 mm in 2 nodes. Three independent radiologists who analyzed images reported specificities of 85%, 79% and 84%. According to hemipelvis, lymph node metastases were detected with histopathologic examination in 44 cases and the three readers correctly detected these on DW-MR images in 26, 19 and 28 of the 44 cases [26].

Conclusions
Conventional MRI plays a limited role in the assessment of lymph node metastases for the urologic tumors because this standard imaging technique is based on nonspecific features such as lymph node size and morphologic characteristics, criteria that provide limited diagnostic specificity. Accurate detection of lymph node metastases continues to rely on lymphadenectomy despite the fact that it is an invasive technique, which often underestimates the real extent of lymphatic metastasis.

DW–MRI performed with or without a lymphotropic contrast agent is a functional imaging technique that shows promising results in differentiating malignant lymph nodes from inflammatory nodes based on the ADC value. Metastatic nodes show, as most primary malignant tumors, lower ADC values due to their impeded diffusion caused by high cellularity.

Further evaluation in lymph node imaging is necessary. Although USPIO agents are clinically not available at the moment, preliminary results of USPIO-DW-MRI are encouraging and this technique may have important implications in the future.

Standardization of technical parameters and improvement in image analysis represents a major challenge to the widespread adoption of DW imaging.

Acknowledgement: This paper is supported by the Sectoral Operational Programme Human Resources Development (SOP HRD), financed from the European Social Fund and by the Romanian Government under the contract number POSDRU/159/1.5/S/137390.

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