The role of diffusion weighted MR imaging in the differentiation of malignant and benign urinary bladder lesions

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In recent years, a number of different magnetic resonance imaging (MRI) methods together with the conventional ones have been utilized as part of a routine radiodiagnostic application. Diffusion weighted MRI (DWI) is considered to be an imaging utility, evaluated within the context of functional MRI and based on the measurement of the accelerated or decelerated microscopic diffusion movements in the protons of the tissues' water molecules. Images can be obtained in short period snapshots and require no substance to be used as contrast (1-4).

The use of DWI had previously been limited to brain examinations due to the fact that it is sensitive to cardiac, respiratory and peristatic movements; however, it has been adopted for a much broader use, i.e., for the other parts of the body with the development of fast MRI sequences like echoplanar imaging (EPI). In the previous studies, the diffusion weighted images and the apparent diffusion coefficient (ADC) of tissues and lesions have been measured, and the different values obtained were shown to be useful in differential diagnosis. In later studies, it has been reported that ADC values were related with the cellular intensity of a tumour and significant reduction in ADC pointed malign tumours (1-4).

In DWI studies conducted on cases with head and neck lesions, the mean ADC level was significantly lower in malign lymphomas, moderately low in cases with carcinomas, moderately high in benign solid masses and remarkably higher in benign cystic lesions (5).

In recent years, DWI has been adopted in a wide-spread use for abdominal examinations. In DWI studies conducted on liver masses in metastatic and HCC lesions, ADC levels were found to be significantly lower, moderately higher in cavernous hemangiomas and remarkably higher in cysts (6).

There are also studies reporting benign renal tumors to have much higher ADC values than malignant tumours and that cystic renal lesions have much higher ADC values than benign solid renal tumours (7).

Various researchers in different studies have pointed out that DWI can be an important diagnostic tool in the detection and characterization of tumors in different regions like breast, prostate, bladder, cervix, colon, ovary, pancreas and liver. In these studies, it was also indicated that malign tumors showed much more diffusion restriction and much lower ADC levels than benign tumours due to the cellularity (8, 9).
Although DWI studies conducted on bladder masses have not been reported on a broader scale, there is an increased tendency to conduct such studies recently. In these studies, the mean ADC levels in bladder tumours have been compared with the surrounding soft tissues and statistically significant results have been obtained. ADC levels in bladder carcinomas were found to be significantly lower than the surrounding soft tissues. DWI was also found to have a high sensitivity and specificity in the detection of bladder tumours (10, 11).

In this study, the mean ADC values obtained from malignant and benign urinary bladder wall pathologies in patients referred to our clinic with a prediagnosis of bladder tumor were compared with the mean ADC values of bladder wall in the normal control group. In our study, also the ADC levels of the histopathologic sub-groups of urinary bladder carcinomas were compared among each other. It is aimed to investigate whether DWI could be used in the differentiation of malignant and benign urinary bladder lesions, and whether ADC values found in malignancies could give any information about the nature of malignant masses, and thus to research the diagnostic contribution of DWI in standard treatment protocols.
Methods and Materials

This prospective study was carried out between January 2008 and July 2009 in Yuzuncu Yil University School of Medicine, Department of Radiology. A total of 88 individuals were recruited for evaluation. However, 5 of them were excluded from the study due to the fact that their general condition were too bad, no respiratory cooperation could be maintained and that they were not proper for MRI. Therefore 83 individuals were included in the study. Sixty-three patients (53 males, 10 females) detected to have bladder wall pathology (mass, wall thickening) on conventional MRI constituted the case group; the mean age being 62.84±11.23 years. Cystoscopic biopsy was performed in all of the patients of the case group. For the control group, 20 healthy individuals (13 males, 7 females), who had no bladder pathology, were chosen, the mean age being 42±18.17 years.

In order to conduct this study, ethics committee approval had been obtained. The patients were informed before the procedure and the consent form was signed. During the MRI examination, due communications were made with patients through earphone system. In order to have a much more adequate evaluation of the bladder wall, bladder distension was encouraged before the procedure.

Imaging

Pelvic examinations were maintained by a 1.5 Tesla (T) MRI system (Siemens Magnetom Symphony, Erlangen, Germany), with phase array body coil. The gradient power of the superconductive (Niobium-Titanium) magnet was 30 mT/m, and FOV width was 350 cm.

Before the DWI examination was performed with SS-EPI, T2 weighted True FISP sequence with chemical shift fat suppression technique in axial and coronal planes (TR: 4.3 sec; TE: 2.15 sec; Average 1; Flip Angle 75°; Matrix 256x256; slice number: 23; slice thickness: 5 mm; FOV: 350 cm; slice gap: 15%) was applied. The protocol used for echoplanar diffusion in our clinic was defined as 0 mm²/sec-500 mm²/sec-1000 mm²/sec-ADC or it was shortly named as ‘trace diffusion’.

Image Analysis

The images were transferred to a work station (Leonardo Syngo 2002B Siemens Medical Solutions, Berlin, Germany) in order to process the data and ADC maps in DWI. Measurements were conducted through circular region of interest (ROI) on lesions. ADC levels were measured by using ROI from the most hypointense region of the mass lesions on the bladder wall or the pathologic wall thickening, where the ROI areas were recorded in a range of 15-180 mm². In the control group, measurements were made from the region limited to 3-5 pixel (6-9 mm²) from the normal bladder wall with freehand ROI. The signal
intensity changes in the lesions were visually determined according to $b=1000$ value diffusion-weighted trace images and the signal intensities on ADC images. In our study, the diagnostic relevance in patients diagnosed with DWI technique were compared with the histopathologic results of the cystoscopic biopsy.

Statistical Analysis

The definitive statistics in terms of the properties emphasized were expressed within the context of mean and standard deviation. One-way variance analysis (one-way ANOVA) was made in order to determine whether there existed any difference between patient and control groups in terms of ADC levels. The significance level in the measurements was taken as 5% and the measurements were carried out in SPSS statistic packet programme. In our study, sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of DWI were obtained for detecting bladder carcinomas.
Results

Of the 63 patients in the case group, 46 (37 males, 9 females; mean age: 61.54±12.29 years) revealed urethelial carcinoma and 17 of them (1 female, 16 males; mean age: 66.35±10.04 years) manifested benign wall pathology. Twenty-seven of the 46 cases with malignant mass were high grade, and 19 of them low grade carcinoma. In 17 patients with benign lesion, 12 of them were benign wall thickening secondary to BPH, 3 of them were eosinophilic cystitis, and 2 of them were polypoid cystitis (uroepithelial papilloma).

The histopathology of 46 cases were consistent with carcinoma, and restriction in diffusion (hyperintense appearance on DWI) was observed in all of the malignant masses. Of the 17 cases in benign group, 4 (2 of them were eosinophilic cystitis, and 2 of them were polypoid cystitis) revealed slight restriction in diffusion. In the remaining 13 benign cases (12 wall thickening secondary to BPH, and 1 eosinophilic cystitis), no restriction in diffusion was observed. Two of the 3 eosinophilic cystitis cases, and both 2 of the polypoid cystitis (uroepithelial papilloma) cases manifested diffusion restriction. In the detection of malignant lesions based on diffusion restriction, the sensitivity of DWI was 100%, specificity 76.5%, positive predictive value 92%, negative predictive value 100%, and accuracy rate was 93.65% (Table 1).

In malignant masses, lower ADC levels and diffusion restriction were observed. Definitive statistics and comparison results according to patient and control groups in terms of ADC values are given in Table 2.

The mean ADC in malignant group (1.068±0.26x10⁻³ mm²/sec) was significantly lower than those taken from benign wall pathologies (1.803±0.19x10⁻³ mm²/sec). It was also remarkably lower than those of the bladder wall in control group (2.010±0.11x10⁻³ mm²/sec). The difference was statistically significant (p<0.001). According to histopathological sub-groups, the mean ADC of high grade malignant masses (0.918 ±0.20x10⁻³ mm²/sec) was found to be significantly lower than those of low grade malignant masses (1.28±0.18 x 10⁻³ mm²/sec), which was shown in table 3 and scaled as p<0.01.

The cut-off value in ROC (Receiver Operator Characteristics) curve for differentiating malignant and benign bladder wall pathologies according to ADC values was found to be 1.545x10⁻³ mm²/sec. Based on this value, the sensitivity was 94.1% and specificity was 95.7%. In addition, the cut-off value in ROC curve for differentiating high and low grade malignant masses according to ADC levels was found to be 1.135x10⁻³ mm²/sec. Based on this value, the sensitivity was 78.9% and specificity 85.2%.
**Table 1.** Statistical results of diffusion-weighted imaging in the detection of malignant bladder lesions

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>46 / 46 = 100%</td>
</tr>
<tr>
<td>Specificity</td>
<td>13 / 17 = 76,5%</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>13 / 13 = 100%</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>46 / 50 = 92%</td>
</tr>
<tr>
<td>Accuracy</td>
<td>(13 + 46) / 63 = 93,65%</td>
</tr>
</tbody>
</table>

**Table 2.** Mean ADC values in malignant group, benign group, and control group.

<table>
<thead>
<tr>
<th>ADC</th>
<th>n</th>
<th>Mean ADC x10^{-3} mm^2/sec</th>
<th>St. Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary bladder carcinoma</td>
<td>46</td>
<td>1.0684</td>
<td>0.26</td>
</tr>
<tr>
<td>Benign pathology</td>
<td>17</td>
<td>1.8030</td>
<td>0.19</td>
</tr>
<tr>
<td>Control group</td>
<td>20</td>
<td>2.0105</td>
<td>0.11</td>
</tr>
</tbody>
</table>

ADC: Apparent Diffusion Coefficient

**Table 3.** ADC values based on histopathological subgroups of malignant lesions.

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Mean ADC x10^{-3} mm^2/sec</th>
<th>St. Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>High grade carcinoma</td>
<td>27</td>
<td>0.9185</td>
<td>0.20</td>
</tr>
<tr>
<td>Low grade carcinoma</td>
<td>19</td>
<td>1.2815</td>
<td>0.18</td>
</tr>
</tbody>
</table>

ADC: Apparent Diffusion Coefficient
Fig. 0: Axial T2-weighted MR image depicting polypoid solid mass with a lobulated contour on the left lateral wall of the bladder.

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Fig. 0: On b:1000 diffusion-weighted image, the mass lesion on the left lateral bladder wall (the same lesion with Figure 1) shows hyperintense signal corresponding to restriction in diffusion.

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Fig. 0: ADC map of the same lesion with Figure 2. The ADC value of the lesion was measured as $1.27 \times 10^{-3}$ mm$^2$/sec. Histopathologically the lesion was reported as low-grade non-invasive urethelial carcinoma.

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Fig. 0: Axial T2-weighted MR image depicting huge polypoid solid mass with a lobulated contour on the left wall of the bladder.

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**Fig. 0:** On b:1000 diffusion-weighted image, the mass lesion on the left bladder wall (the same lesion with Figure 4) shows hyperintense signal corresponding to restriction in diffusion.

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**Fig. 0:** ADC map of the same lesion with Figure 5. The ADC value of the lesion was measured as $0.73 \times 10^{-3}$ mm$^2$/sec. Histopathologically the lesion was reported as high-grade invasive urethelial carcinoma.
**Fig. 0:** Axial T2-weighted MR image depicting small polypoid solid mass with a lobulated contour on the left posterior wall of the bladder.

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Fig. 0: On b:1000 diffusion-weighted image, the mass lesion on the left bladder wall (the same lesion with Figure 7) does not show restriction in diffusion. The ADC value of the lesion was measured as 2,01x10-3 mm²/sec. Histopathologic result was polypoid cystitis.

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**Fig. 0:** Axial T2-weighted MR image shows diffuse thickening of the bladder wall.
**Fig. 0:** On b:1000 diffusion-weighted image, the thickened bladder wall (the same patient with Figure 9) does not show restriction in diffusion.

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The ADC value of the thickened bladder wall (the same patient with Figure 10) was measured as $1.64 \times 10^{-3}$ mm$^2$/sec. Histopathologic result was benign wall thickening.

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Conclusion

In patients who refer to the hospital with hematuria complaint but reveal normal upper urinary system examinations, bladder tumour is considered among the foremost possible diagnoses. More than half of the urinary system tumours are located in the bladder. More than 90% of bladder tumours, 80-90% of which are macroscopically of polypoid origin, are considered to be carcinomas with mutating epithelial cells.

Cystoscopy is accepted as the most reliable and gold standard examination method in the detection of bladder tumours. However, radiologic examinations are also needed in order to find out tumours both in follow-up process and the staging of the disease. There is no accepted algorithm for radiological imaging of the bladder tumours. Imaging techniques, such as intravenous pyelography (IVP), ultrasonography (US), computerized tomography (CT), and MRI are used either alone or together (12). DWI has recently been used in clinical applications as a new functional imaging method. DWI, which was formerly used in neuroradiology, has recently been preferred in abdominal examinations with the development of ultra fast sequences such as EPI. Although a few DWI studies conducted on bladder masses are present, a spate of new research is making its presence felt. Most of the investigations conducted about abdomen diffusion have been carried out with SSEPI sequence.

With SSEPI technique, images can be taken in less than a second of period of time and physiological movements are frozen (13). With the addition of breath-holding to EPI technique, respiratory artefacts are removed and ADC measurement in the abdomen can be made (14). Whereas the previous studies with DWI were conducted involving breath-holding, Theony et al carried out a study during normal respiration and observed no remarkable movement artefact (15).

Also in our study, SSEPI technique was used and breath-holding was not preferred during DWI. Thus, an appropriate examination could be made in patients who were not able to hold their breath for a long period of time. Also, since the bladder is located at the lower abdomen, respiration has little movement effect upon it. There are studies in previous literature reporting that DWI and mean ADC levels are useful tools in the differentiation of malignant versus benign lesions and characterization of solid renal tumours, liver lesions and gastric tumours. These studies also reported that there were statistically significant differences between ADC levels of lesions (9, 16-21).

DWI studies related with bladder masses have been more intensely conducted in recent years. In a study conducted by Matsuki et al. (22), 17 tumour masses in 15 cases with bladder cancer were examined and ADC levels in tumoral tissue were found to be
significantly lower compared with the surrounding tissue. Therefore, these researchers stressed that further studies should be carried out.

Kılıçkesmez et al. (23), in a study which included 14 bladder carcinomas and 9 prostate carcinomas, found that the mean ADC level of tumours were significantly lower than the control group.

Takeuchi et al. (24) investigated a total of 52 bladder tumours in 40 patients and found that DWI contributed to T staging, and ADC levels in the tumours of higher grade were found to be significantly lower than those in tumours of lower grade.

In a study carried out by Abou-El-Ghar et al (10), 130 (106 with bladder carcinoma) patients with gross hematuria went through T2-weighted MRI, DWI, and after 48 hours, cystoscopy. The sensitivity of DWI in detecting the tumoral mass by itself was found to be 98.5% and PPV 100%.

In a study by El-Assmy et al (25), a comparison of DWI and T2-weighted MRI on tumour staging was made in a total of 106 patients with 106 bladder tumours. DWI was found to have more supremacy over T2-weighted MRI on tumour staging by itself. In another study carried out by El-Assmy et al (11), conducted on 43 patients with bladder tumours, ADC was found to be significantly lower in bladder carcinomas than the surrounding tissues.

In our study, ADC levels of 63 patients who referred to our clinic with a prediagnosis of bladder tumour were measured. These levels were compared with bladder wall ADC levels of 20 healthy individuals in the control group. Of the 63 cases, 46 revealed carcinomas in their histopathology. In all of the 46 mass lesions in malignant group, diffusion restriction was observed. Of the 17 cases in benign group, 4 manifested diffusion restriction and their pathology showed accordance with cystitis (2 polypoid cystitis, 2 eosinophilic cystitis). In 13 benign cases (12 wall thickening secondary to BPH, 1 eosinophilic cystitis) diffusion restriction was not observed. In 2 of a total of cases with eosinophilic cystitis and 2 of cases with polypoid cystitis, diffusion restriction attracted our attention. Based on these results, in the detection of malignant lesions, the sensitivity of DWI was found to be 100%, specificity 76.5%, positive predictive value 92%, negative predictive value 100%, and accuracy rate 93.65% (Table 1).

In our study the mean ADC levels of 46 malignant cases (1.068±0.26×10⁻³ mm²/sec) were found to be significantly lower than those of normal bladder wall in the control group (2.010±0.11×10⁻³ mm²/sec) (p<0.001). These results supported the results of other studies in the literature. The mean ADC levels of 17 cases detected to have benign wall pathology were found to be 1.803±0.19×10⁻³ mm²/sec, which was significantly higher.
than the mean ADC levels of the malignant urinary bladder tumours (p<0.01). In terms of the subgroups, the mean ADC of high grade uroepithelial carcinoma cases (0.918 ±0.20x10^{-3} mm^{2}/sec) were found to be significantly lower than ADC of the low grade urothelial carcinoma cases (1.28±0.18x10^{-3} mm^{2}/sec), which was scaled as p<0.01.

The cut-off value in ROC curve for the differentiation of malignant and benign wall pathologies according to ADC levels was 1.545×10^{-3} mm^{2}/sec. Based on this value, the sensitivity was 94.1% and specificity 95.7%. In addition, the cut-off value in ROC curve for the differentiation of high and low grade malignant masses according to ADC levels was 1.135×10^{-3} mm^{2}/sec. According to these levels, the sensitivity was 78.96% and specificity 85.2%.

In our study, in the detection of malignant lesions based on diffusion restriction, the sensitivity of DWI was 100%, specificity 76.5%, positive predictive value 92%, negative predictive value 100% and the accuracy rate 93.65%.

In conclusion, before histopathologic sampling, more accurate predictions can be made about the malignancy potentials of the urinary bladder lesions by the aid of ADC quantification. Due to the fact that it is noninvasive, fast, free of contrast material administration and ionizing radiation, DWI is a beneficial and safe method for the differentiation of malignant and benign urinary bladder lesions and for providing a notion about the grade of urinary bladder carcinomas.
References


