DWI as an Imaging Biomarker for Bladder Cancer

OBJECTIVE. DWI has been increasingly applied in the management of bladder cancer. In this article, we discuss the role of DWI as an imaging biomarker for bladder cancer.

CONCLUSION. The DWI signal is derived from the motion of water molecules, which represents the physiologic characteristics of the tissue of interest. The emerging evidence highlights the utility of DWI for bladder cancer detection and characterization. DWI is a potentially useful tool to individualize treatment strategies.

Bladder cancer is the second most common genitourinary cancer among men and the ninth most common among women in the United States, and 76,960 new cases and 16,390 deaths from bladder cancer are estimated to have occurred in 2016 [1]. At initial presentation, two-thirds of all cases are diagnosed as non-muscle-invasive bladder cancer (stage T1 or less), which can be conservatively managed using transurethral resection of the bladder (TURB) and intravesical instillation therapy [2]. However, during follow-up evaluation, one-third of high-grade T1 bladder cancers have progressed, with muscle invasion or incurable metastatic disease [2]. In muscle-invasive bladder cancer, more extensive treatment, including radical cystectomy, is needed [3]. The clinical course of bladder cancer differs significantly among patients, and accurate prediction of its biologic behavior is needed.

In the last few years, with the advent of “-omics” technologies, which is a large-scale approach to analyze biologic data such as genomics, proteomics, or metabolomics, molecular subclassifications of bladder cancer have been proposed for the accurate assessment of biologic characteristics of individual cancers [4, 5]. In addition, several immunohistochemically derived profiling-based taxonomic classifications have been proposed, using markers of cell cycle and tumor proliferation for clinical application [4, 5]. However, this histology-based classification requires tissue sampling, and the information is obtained postsurgically. Preoperative noninvasive quantitative tests are hence desirable.

In recent clinical practice, for locoregional staging of bladder cancer, contrast-enhanced CT and MRI are applied [3]. DWI is a functional MRI technique that is increasingly applied in the management of bladder cancer [6, 7]. The DWI signal reflects the degree of diffusivity of water molecules, and this unique signal provides information on physiologic tissue characteristics in a noninvasive manner [8, 9]. Recently, growing evidence has shown that DWI can serve as an imaging biomarker that is useful for characterizing the pathophysiology of various types of malignancies [9, 10]. This review focuses on the potential role of DWI as an imaging biomarker useful for customizing therapeutic approaches to bladder cancer.

DWI: Biophysical Basis and Clinical Application

DWI is a noninvasive functional imaging technique that was initially developed by Stejskal and Tanner in 1965 [11]. The image contrast at DWI is derived from differences in the Brownian motion of water molecules [8, 9]. This diffusion of water molecules inversely correlates with cell density, organization, and membrane integrity. A lesion in which the diffusion of water molecules is impeded generally shows high signal intensity at DWI. Since Le Bihan et al. [12] reported the application of DWI to neurogenic disorders in 1986, the technique has mainly been used for the diagnosis of acute cerebral infarction and intracranial tumors. Because malignant tumors typically have higher cellularity, tissue disorganization, and de-
creased extracellular space, all of which impede water diffusion, DWI has been widely applied to malignant diseases [8, 9].

The signal of DWI is derived from the inherent tissue contrast. This imaging technique requires no contrast medium administration and can be applied to patients with allergies to contrast agents or those with renal insufficiency. Furthermore, the addition of DWI to a routine MRI protocol can be performed by most current MRI scanners, requiring only a few additional minutes. Thanks to the advent of the single-shot echo-planar sequence with a parallel imaging technique, high amplitudes, and multichannel coils that allow rapid data acquisition and improved image quality, DWI of the body has become technically possible [8, 13]. Nevertheless, the application of DWI to abdominal organs was initially still considered challenging because of the effects of respiratory movements, pulsation, and bowel motion. However, body DWI under free-breathing conditions, which was introduced by Takahara et al. [14] and which involves the acquisition of thin-slice images with multiple signal averaging combined with robust (STIR-based) fat suppression, has proven to reproducibly provide high-quality DW images that can be reformatted in any plane. Because of these technical and concept developments, DWI has developed into a mature method for abdominal and pelvic organ imaging.

**DWI as an Imaging Biomarker**

As a measurable indicator of a biologic state or condition, the National Institutes of Health Biomarkers Definitions Working Group defined a biomarker as “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention” [15]. Some radiographic characteristics are included in biomarkers, as are molecular, histologic, or physiologic findings [16]. Because DWI

![Image](fig1.png)

**Fig. 1**—67-year-old man with non-muscle-invasive bladder cancer (urothelial cancer, stage pT1, grade 2). 
A, T2-weighted MR image shows hypointense tumor around left ureteral orifice. 
B, DW image with b value of 1000 s/mm² shows C-shaped high-signal tumor with low-signal-intensity stalk, or inchworm sign.

![Image](fig2.png)

**Fig. 2**—70-year-old man with muscle-invasive bladder cancer (urothelial cancer, stage cT3, grade 3). 
A, T2-weighted MR image shows solid hypointense tumor at trigone. 
B, DW image with b value of 1000 s/mm² shows tumor as homogeneous high-signal mass. Extension into perivesical fat with irregular margin indicates stage T3.
TABLE 1: Sensitivity and Specificity of DWI in Detecting Bladder Cancer

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of Patients</th>
<th>b Values (s/mm²)</th>
<th>Inclusion Criteria</th>
<th>No. of Control Subjects</th>
<th>Histologic Profile (%)</th>
<th>ADC Value (x 10⁻³ mm²/s), Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Bladder Cancer</td>
</tr>
<tr>
<td>Matsuki et al. [17]</td>
<td>17</td>
<td>0, 800</td>
<td>Known bladder cancer</td>
<td></td>
<td>UC, 90.7; SCC, 9.3</td>
<td>1.18 ± 0.19</td>
</tr>
<tr>
<td>El-Assmy et al. [21]</td>
<td>123</td>
<td>0, 800</td>
<td>Known bladder cancer</td>
<td></td>
<td>UC, 94.3, SCC, 5.7</td>
<td>1.40 ± 0.51</td>
</tr>
<tr>
<td>Kılıçkesmez et al. [24]</td>
<td>14</td>
<td>0, 500, 1000</td>
<td>Known bladder cancer</td>
<td></td>
<td>UC, 100</td>
<td>0.94 ± 0.18</td>
</tr>
<tr>
<td>Avcu et al. [19]</td>
<td>46</td>
<td>0, 500, 1000</td>
<td>Known bladder cancer</td>
<td></td>
<td>UC, 94.2</td>
<td>1.07 ± 0.26</td>
</tr>
<tr>
<td>Dağgülü et al. [22]</td>
<td>35</td>
<td>100, 600, 1000</td>
<td>Hematuria</td>
<td></td>
<td>UC, 94; UC + SCC, 5; AC, 1</td>
<td>0.86 (0.39–2.07)</td>
</tr>
<tr>
<td>El-Assmy et al. [23]</td>
<td>47</td>
<td>0, 800</td>
<td>Follow-up of bladder cancer</td>
<td></td>
<td>UC, 100</td>
<td>1.6 ± 0.57</td>
</tr>
</tbody>
</table>

Note—UC = urothelial carcinoma, SCC = squamous cell carcinoma, AC = adenocarcinoma, U/C = urinary cytology.

*Data are shown as median (range).

Clinical Application of DWI in Bladder Cancer

Detection of Bladder Cancer

Since Matsuki et al. [17] first reported the utility of DWI in detecting bladder cancer, the technique has been widely used in various settings. The sensitivity and specificity of DWI in detecting bladder cancer have been reported as 91–100%, 77–91%, and 81–96% for studies using b values of 800–1000, respectively [17–25] (Table 1). The high sensitivity and specificity of DWI in detecting bladder cancer are due to the high contrast between tumor and normal bladder wall, as well as the high sensitivity of DWI in detecting small lesions.

Apparent Diffusion Coefficient Value in Characterizing Bladder Cancer

The utility of the ADC value as an imaging biomarker in managing bladder cancer has been reported by several studies [17, 26–28] (Table 2). The ADC value is a quantitative measure of tumor diffusion, which reflects homogeneous tissue properties. A lower ADC value indicates a more heterogeneous tissue, which is associated with a higher likelihood of malignancy. The ADC value has been shown to be a valuable tool for characterizing lesions and evaluating tumor grade and stage [8, 9].

Local Staging of Bladder Cancer

The ADC value has also been used for local staging of bladder cancer. Yoshida et al. [29] reported that the ADC value is a useful tool for distinguishing non-muscle-invasive bladder cancer from muscle-invasive bladder cancer. The ADC value has also been shown to be a useful tool for identifying high-risk lesions, which are more likely to progress to muscle invasion [29].

Applying a high b value provides a unique signal reflecting biological information, which is essential for accurately localizing abnormal DWI. However, concomitant morphologic imaging is still necessary to accurately interpret the DWI signal.

In this image interpretation process, it is important to consider the local staging of bladder cancer. The ADC value is a useful tool for distinguishing non-muscle-invasive bladder cancer from muscle-invasive bladder cancer, and it can also be used to identify high-risk lesions. However, the utility of the ADC value is limited to a voxel size of around 4 × 3.5 × 3.5 mm³, local staging is performed using at least two b values with different durations of the applied gradient. Although the degree of diffusion in tissue can be visually assessed by comparing signal intensities, it is necessary to perform this assessment quantitatively by measuring the ADC value.
Most previous studies calculated the mean ADC value of an ROI that was placed in the tumor. Because of the homogeneous diffusion environments within bladder cancer, intratumoral distribution of ADC values tends to be homogeneous on the ADC map, and the histogram for the distribution of the ADC of each pixel within the tumor showed a single prominent peak in 83% of bladder cancers [29] (Fig. 4). Although the position and the size of the ROI are not standardized, measurement deviation of ADC values can be relatively small, as shown in upper urinary tract urothelial cancer by Sufana Iancu et al. [30]. An association between ADC values and histologic grade of bladder cancer has been reported by several studies [19, 25, 26, 31]. These studies consistently showed significantly lower ADC values of high-grade bladder cancer compared with low-grade cancer (Table 2). The underlying mechanism for the correlation of ADC value and histologic characteristics is proposed to be microstructural changes within the malignant tissue, including increased cellularity and larger cell size. Our group reported that the addition of ADC measurements to visual DWI assessment further improved the local staging accuracy. The understaging rate of the inchworm sign for muscle-invasive bladder cancer improved from 27–25% to 4.5–4.0% by incorporating high ADC values (using a cutoff of $0.80 \times 10^{-3} \text{mm}^2/\text{s}$) to the inchworm sign [25].

Recently, our group first described a potential use of ADC value as an imaging biomarker reflecting proliferation status of bladder cancer, as measured by Ki-67, in a prospective study including 132 patients with bladder cancer [32]. Sevcenco et al. [33] showed the association of ADC value with cell cycle regulators of p53, p21, and Ki-67. The correlation of ADC value with the tumor proliferation status has been shown in breast and hepatocellular carcinoma and meningioma [34–37]. Highly proliferating cells of aggressive bladder cancers lead to an increased cellularity and decreased extracellular space, which results in low ADC values. ADC value reflects biologic characteristics, as well as the microstructural change in the bladder cancer. The ADC value is a potentially useful quantitative biomarker for assessing cancer cells’ characteristics. However, as an intrinsic limitation, the ADC value depends on the coil system, imager, vendors, and field strength, and measured ADC value and applied ADC threshold varied among the studies [9]. To use ADC value as a clinically applicable biomarker across centers using different MRI protocols, standardization of the assessment of the ADC value is needed.

**Apparent Diffusion Coefficient Value in Predicting the Clinical Course of Bladder Cancer**

Because the ADC value reflects the biologic characteristics as well as the microstruc-

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**Fig. 3**—71-year-old man with bladder cancer (urothelial cancer).

A, On T2-weighted MR image obtained 5 weeks after initial transurethral resection of bladder, two bladder tumors are seen, signals of which are almost identical. Transurethral resection of these two tumors was performed. Dorsal tumor (white arrowhead) was pathologically diagnosed as residual bladder cancer (pT2, grade 3), whereas ventral tumor (black arrowhead) was proven to represent nonmalignant postoperative changes.

B, On DW image with b value of 1000 s/mm², residual bladder cancer shows high signal intensity (white arrowhead), whereas ventrally located nonmalignant postoperative changes do not (black arrowhead).

C, Fusion image of T2-weighted MRI and DWI is useful to anatomically localize pathologic DWI signals of dorsal tumor (white arrowhead) and ventral tumor (black arrowhead).
<table>
<thead>
<tr>
<th>Reference</th>
<th>MRI Magnet Strength (T)</th>
<th>b Value (a/mm²)</th>
<th>No. of Bladder Cancers</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Accuracy (%)</th>
<th>Histologic Grade, ADC Value (x 10⁻³ mm²/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>El-Assmy et al. [21]</td>
<td>1.5</td>
<td>0, 800</td>
<td>123</td>
<td>63.6</td>
<td></td>
<td></td>
<td>Grade 1, 1.29 ± 0.27; grade 2, 1.13 ± 0.24; grade 3, 0.81 ± 0.11; grade 1 vs grade 3, p &lt; 0.01; grade 2 vs grade 3, p &lt; 0.01</td>
</tr>
<tr>
<td>Watanabe et al. [28]</td>
<td>1.5</td>
<td>0, 1000</td>
<td>19</td>
<td>79</td>
<td></td>
<td></td>
<td>High-grade, 0.92 ± 0.20; low-grade, 1.28 ± 0.18; p &lt; 0.01</td>
</tr>
<tr>
<td>Takeuchi et al. [26]</td>
<td>1.5</td>
<td>0, 1000</td>
<td>52</td>
<td>93</td>
<td></td>
<td></td>
<td>High-grade, 0.79 (0.69–0.88); low-grade, 0.99 (0.92–1.09); p &lt; 0.0001</td>
</tr>
<tr>
<td>Avcu et al. [19]</td>
<td>1.5</td>
<td>0, 500, 1000</td>
<td>46</td>
<td></td>
<td></td>
<td></td>
<td>High-grade, 0.79 (1.15–1.32); low-grade, 1.23 (0.70–0.89); p &lt; 0.01</td>
</tr>
<tr>
<td>Kobayashi et al. [25]</td>
<td>1.5</td>
<td>0, 500, 1000, 2000</td>
<td>121</td>
<td>83.3–90.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sevcenco et al. [31]</td>
<td>3.0</td>
<td>50, 400, 1000</td>
<td>43</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gupta et al. [27]</td>
<td>1.5</td>
<td>0, 1000</td>
<td>60</td>
<td>62.5</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note — ADC = apparent diffusion coefficient.

Data are shown as median (range).

Data are shown as mean (95% CI).
successful treatment precede volume changes. Several studies in many types of malignancies, including liver cancer, cerebral gliomas, and soft-tissue sarcoma, have shown changes in the DWI signal according to the therapeutic effect and have highlighted the utility of DWI in monitoring therapeutic responses [50–52].

Importantly, the DWI signal is not specific to cancer cells, and inflammatory changes and granulomas also show high signal intensity, mimicking malignant tissue [53–56]. Care should be taken when interpreting posttherapeutic changes, because these could give rise to a false-positive diagnosis.

El-Assmy et al. [23] and Wang et al. [57] have reported the sensitivity and specificity of DWI in detecting bladder cancer recurrence as 94–100% and 81–91%, respectively, during the yearly follow-up after TURB. Our group has reported the superiority of DWI in monitoring therapeutic responses to CRT, in comparison with T2-weighted imaging and DCE-MRI [46]. In detecting pathologic complete response after CRT, the specificity and accuracy of DWI were 92% and 80%, respectively, which were superior to those of T2-weighted imaging (45% and 44%, respectively) and DCE-MRI (18% and 33%, respectively), whereas the sensitivity of DWI (57%) was comparable to that of T2-weighted imaging (43%) and DCE-MRI (57%). These data suggest that posttherapeutic changes on DWI might have little or short-lived effects and that DWI is a useful adjunct in the assessment after TURB (Fig. 5). However, its diagnostic ability for detecting small residual lesions requires improvement, as with T2-weighted imaging and DCE-MRI, and it should still be used in combination with cystoscopy and biopsy findings.

Whole-Body DWI as an Imaging Biomarker

An estimated 12,500 deaths per year in the United States are attributable to metastatic bladder cancer [58]. Before any curative treatment, it is essential to evaluate for the presence of distant metastases [3]. CT and MRI are generally considered equivalent for diagnosing local disease and distant metastases in the abdomen, but CT is regarded as the method of choice for diagnosis of pulmonary metastases [3]. Surveillance after cystectomy, after multimodal treatment, or in patients with metastatic disease mainly focuses on identifying distant disease [60]. Most guidelines recommend imaging of the chest, abdomen, and pelvis every 3–6 months for 2 years and then at longer intervals [60]. FDG PET and PET/MRI are being investigated as potential staging alternatives [61–64], but their roles have not been clarified yet.

Whole-body DWI is another method that may be used as a completely noninvasive and radiation-free alternative for staging and follow-up.
Fig. 5—67-year-old man with bladder cancer (urothelial cancer, stage cT3, grade 3 with glandular differentiation).

A and B, MR images obtained before chemoradiation therapy. Solid tumor is seen on T2-weighted MRI (arrow, A). Tumor shows high signal intensity on DW image (arrow, B) with b value of 1000 s/mm².

C and D, MR images obtained 2 weeks after debulking transurethral resection of bladder and chemoradiation therapy. Extravesical component of bladder tumor becomes larger on T2-weighted MRI (arrow, C). On DW image with b value of 1000 s/mm² (D), signal of extravesical component is negative (arrow, D). Deep resection of tumor revealed no remaining tumor cells, indicating that appearance on T2-weighted MRI was false-positive.

E, MR image obtained 3 weeks after restaging transurethral resection shows that deep resection of bladder wall was performed (arrow). Generally, posttherapeutic changes have greater influence on T2-weighted MRI. DWI generally provides better information than T2-weighted MRI on whether complete resection has been achieved.
of patients with or at risk of metastatic disease. Given the previously mentioned potential advantages and increasingly important role of DWI in the local assessment of bladder cancer, DWI may well be extended to the entire body. Whole-body DWI was developed in 2004 [14] and has matured into a robust technique that can be performed with most modern (1.5-T) MRI systems. When using the concept of whole-body DWI with background body signal suppression, which involves a STIR high-b-value free-breathing acquisition with thin slices and multiple signal averaging [14, 65, 66], high-quality whole-body DW images can be obtained with an acquisition time of around 20 minutes (for the neck, chest, abdomen, and pelvis). The first advantage of whole-body DWI is its high lesion-to-background contrast, which may facilitate the detection of metastatic lesions. STIR has another inherent advantage in that tissues with a long T1 value, which is another hallmark of cancer, will also produce a high signal intensity [67]. Of note, the most common sites of metastasis from bladder cancer are pelvic lymph nodes (with decreasing incidence of involvement of more distant lymph nodes), bones, lung, liver, and peritoneum [59]. DWI is recognized as an excellent method for lymph node detection and can classify enlarged lymph nodes as pathologic. However, characterization of normal-sized lymph nodes still remains an issue, although it has been reported that analysis of lymph nodes with impeded diffusion that also takes into account morphologic characteristics of malignancy may increase accuracy [68]. Combining whole-body DWI with ultrasmall superparamagnetic particles of iron oxide, in which metastatic lymph nodes will become relatively hypointense but normal lymph nodes will remain relatively hyperintense [69, 70], may further improve lymph node characterization in the future when these contrast agents become more

**Fig. 6**—78-year-old man with bladder cancer. A–G, PET/CT (A), whole-body DWI (B), and T2-weighted MRI (C) show liver metastasis from bladder cancer (arrowheads). Whole-body DW images (D and F) and T2-weighted MR images (E and G) were obtained after one course (D and E) and four courses (F and G) of chemotherapy. Whole-body DWI preceded T2-weighted MRI in showing treatment response.
widely available. DWI has been reported to be a useful method for the detection of bone [71], liver [72], and peritoneal [73] metastases, although additional MRI sequences may be helpful for lesion localization and improving specificity. DWI may fail to detect small lung metastases (i.e., < 0.7 cm [74], although this threshold is likely to decrease with future technologic developments), but DWI has been reported to be an accurate method for pulmonary nodule characterization with ADC measurements [75]. Future studies are still required to determine and compare the value of whole-body DWI to CT and FDG PET for metastasis detection in bladder cancer. The second potential advantage of whole-body DWI is the possibility to quantify tumor diffusion volumes and ADC in the entire body, which may serve as a prognostic and treatment response biomarker. DWI may allow a more timely evaluation of treatment response than structural imaging modalities such as CT, which rely on tumor size and morphologic features [10] (Fig. 6). Moreover, it can assess tumor response in anatomic sites that are considered not measurable according to the Response Evaluation Criteria in Solid Tumors guidelines [76], such as the bone marrow. The feasibility and clinical utility of measuring total tumor diffusion volume and median ADC value from whole-body DWI examinations has recently been shown in bone metastatic prostate cancer [77, 78]. The median survival of patients with metastatic bladder cancer is only 12 months [58], but several ongoing trials are investigating newer treatment strategies [60]. Because these treatment regimens are costly and have associated adverse effects, there is a timely need to evaluate their effectiveness. Future studies are required to investigate whether whole-body DWI can serve this purpose.

**Conclusion**

DWI enables assessment of physiologic characteristics of tissues in a noninvasive manner. This unique imaging technique provides qualitative and quantitative information on histologic and biologic characteristics of bladder cancer. The emerging evidence shows the utility of DWI in every step of the management of these patients, which highlights its potential to individualize treatment strategies against bladder cancer. Furthermore, the whole-body DWI technique has substantial promise for staging and follow-up of patients with or at risk of metastatic disease. However, the application of DWI as an imaging biomarker for bladder cancer is just emerging, and there are still major challenges to validate and standardize data acquisition and analysis.

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