

Diffusion Weighted MRI as a Predictor of Muscle Invasive Bladder Carcinoma: Review Article

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ABSTRACT

Background: Bladder cancer is a common genitourinary tumor in Egypt. Muscle invasive bladder cancer can be treated by bladder preservation protocol (BPP), which include maximum TURBT, radiotherapy and chemotherapy. Eventually bladder preservation treatment could fail.

Objective: To use Diffusion weighted MRI as a non-invasive test to predict response of tumor to BPP before the patient is exposed to the hazard of this therapy.

Methods: We searched Science Direct, Google Scholar as well as PubMed for relevant articles on Muscle invasive, Bladder carcinoma and Diffusion weighted MRI. Only the most recent or thorough study was taken into account between 2004 and 2020. The authors also evaluated the value of resources culled from other works in the same genre. Documents written in languages other than English have been ignored due to lack of translation funds. Unpublished works, oral presentations, conference abstracts, and dissertations were generally agreed upon not to qualify as scientific research.

Conclusion: Apparent diffusion coefficient (ADC) as an imaging biomarker is not recommended for routine clinical use due to a lack of standardisation and validation according to (EAU) guidelines, our small group study may be in need of extension on larger group of patients and the ADC values narrow band could be a curbed point of our work.

Keywords: DWI, Muscle Invasive, Bladder Carcinoma.

INTRODUCTION

Since the introduction of "-omics" technologies a few years ago, It has been suggested to use molecular subclassifications of bladder cancer to accurately assess the biologic features of specific cases. Geneomics, proteomics, and metabolomics are a few examples of extensive methods for analyzing biologic data ⁽¹⁾.

Furthermore, a number of taxonomic classifications based on immunohistochemical profiling have been proposed, utilizing indicators of the cell cycle and tumor growth for clinical use. However, tissue collection is required for this classification based on histology, and the information is acquired after surgery. Thus, preoperative quantitative non-invasive testing is preferable ⁽²⁾.

According to research by **Fliedner and colleagues** ⁽³⁾, interactions with various barriers, including membranes, fibers, and macromolecules influence molecular diffusion in tissues rather than it being free. Diffusion patterns of water molecules might thus provide microscopic information on the architecture of tissue, whether it is healthy or diseased.

Diffusion imaging, according to Chen and colleagues, is an MRI technique that generates in vivo magnetic resonance pictures of biological tissues sensitive to the specific characteristics of molecular transport locally, usually involving water (but MR spectroscopic methods can also be used to explore other moieties). It is possible to make MRI sensitive to molecular motion. The behaviour of protons in water is

used in routine MRI capture to create contrast between a subject's clinically significant characteristics ⁽⁴⁾.

Fliedner et al. ⁽³⁾ also showed that the ability of MRI to produce contrast associated with microscopic tissue structure accounts for its versatile nature. An applied strong magnetic field excites the molecules of water in the sample. As a result, several protons in water molecules precess concurrently, resulting in signals in magnetic resonance imaging.

The measurement of the water protons' lack of synchronization or coherence yields contrast. Relaxation usually takes longer when water is in an atmosphere where it can tumble freely. This may result in contrast between a pathological area and the surrounding healthy tissue in specific clinical scenarios, such as cancer distinction between benign and malignant ⁽⁵⁾.

In clinical practice, contrast-enhanced CT and MRI are used for the locoregional staging of bladder cancer. A functional MRI technique called DWI is being used more and more in the treatment of bladder cancer. The degree of diffusivity of water molecules is reflected in the DWI signal, which is a unique signal that offers non-invasive information on physiologic tissue properties ⁽⁶⁾.

DWI can be used as an imaging biomarker to help characterize the pathophysiology of different kinds of cancers, according to mounting data. The potential use of DWI as an imaging biomarker to tailor treatment

strategies for bladder cancer is the main topic of this chapter ⁽⁶⁾.

DWI: Biophysical basis and clinical application:

The non-invasive functional imaging method known as DWI was first created by Stejskal and Tanner. The variation in the brownian of the contrast in the image is caused by the movement of the water molecules at DWI. The organization, density, and membrane integrity of cells are inversely correlated with this diffusion of water molecules. A lesion that obstructs water molecule diffusion typically exhibits a strong signal at DWI ⁽²⁾.

The majority of DWI cases have been used to diagnose intracranial cancers and acute cerebral infarction ⁽⁷⁾. DWI has been frequently used in malignant disorders because malignant tumors often have less extracellular space, increased cellularity, and tissue disarray—all of which limit water diffusion ⁽⁶⁾.

The intrinsic tissue contrast provides the DWI signal. This imaging modality can be used on individuals with renal insufficiency or allergy to contrast agents without the need to administer contrast material. Moreover, the majority of modern MRI scanners can incorporate DWI into a standard MRI protocol with just a few extra minutes of processing time ⁽⁸⁾.

DWI of the body is now technically feasible high amplitudes, multichannel coils, and the invention of the single-shot echo-planar sequence using a parallel imaging technique that enable quick data collecting and enhanced picture quality. However, because to the effects of breathing, pulse, and bowel motion, It was once believed to be challenging to apply DWI to abdominal organs ⁽⁹⁾.

Nonetheless, body DWI in free-breathing conditions has demonstrated the ability to consistently produce superior DW pictures that are scalable to any plane. This technique combines robust (short inversion time inversion recovery STIR-based) fat suppression with the use of multiple signal averaging to acquire thin-slice pictures. DWI has evolved into a sophisticated technique for imaging the abdominal and pelvic organs as a result of these conceptual and technological advancements ⁽⁸⁾.

DWI as an imaging biomarker:

A biomarker was defined by the National Institutes of Health Biomarkers Definitions Working Group as “a trait that can be used to monitor and assess scientifically what biological processes are normal, pathogenic, or how the body is responding to a medication” ⁽¹⁰⁾. A quantifiable indicator of a biologic state or disease is called a biomarker. Biomarkers include some radiographic features as well as histologic, physiologic, or molecular results. DWI may be a helpful biomarker for the characterisation of lesions since it offers a distinct signal that reflects biophysical information ⁽¹⁰⁾.

For quantitative reasons, DWI should be carried out with a minimum of two b-values, the latter of which ought to be proportionate to the duration between the paired gradients ⁽⁶⁾, the gradient amplitude, and the duration of the applied gradient. A quantitative assessment of the degree of diffusion in tissue can be attained by doing a pixel-by-pixel apparent diffusion coefficient (ADC) map calculation using mathematics. On the majority of contemporary MRI systems, software packages that are easily accessible may perform this automatically. Alternatively, it can be visually performed by comparing the signal intensities of DW pictures obtained with various b-values. It has been shown that tumor ADC values correlate with tumor T stage, histologic grade, and proliferative state for a variety of cancers ⁽¹⁰⁾.

Clinical application of DWI in bladder cancer:

✚ Detection of Bladder Cancer:

An increasing number of research works have documented its use when managing bladder cancer, with consistently good tumor detection diagnostic performance. Bladder tumors typically exhibit a homogenous hyperintense signal at DWI with high b values of 800-1000 s/mm², which is indicative of homogeneous tissue composition ⁽¹¹⁾.

While, using a high b value produces a signal contrast that is easily visible between the typical tissue around the bladder cancer and the malignancy, it also causes the normal surrounding tissues to lose signal. Thus, concurrent morphologic imaging data is necessary in order to precisely pinpoint the aberrant DWI signal. Combined with conventional morphologic imaging, DWI integration is comparable to reading PET/CT studies (e.g., T2-weighted imaging) may be very helpful in this picture interpretation process ⁽¹¹⁾.

✚ Local staging of bladder cancer:

Both quantitative ADC value analysis and visual picture interpretation are used to evaluate the DWI signal. Due to the functional nature of DW images and their intrinsic spatial resolution limitation (voxels typically measure 4 × 3.5 × 3.5 mm³), local staging is carried out based on the signal intensity difference between the surrounding tissue and bladder cancer. The signal intensity is moderate and low in the submucosal and muscle layers at high b-values, respectively ⁽¹²⁾.

In order to diagnose bladder cancer that is not muscle-invasive, **Takeuchi et al.** ⁽¹²⁾ established staging criteria based on a weak submucosal signal is present. Moreover, the tumor stalk of the pedunculated tumor is made up of a combination of capillaries, fibrous tissue, and edematous submucosa. One of the hallmarks of bladder cancer that is not

muscle-invasive is this tumor stalk, which is represented by a low signal intensity.

Known as the "inchworm sign," A C-shaped high-signal-intensity area paired with a thicker submucosa or a low-signal-intensity submucosal stalk characterizes typical pedunculated papillary bladder tumors. **Takeuchi et al.** ⁽¹²⁾ further said that the diagnosis accuracy for differentiating between muscle-invasive and non-muscle-invasive bladder cancer rose when DWI was added to T2-weighted imaging from 79% to 96% ⁽¹²⁾. DWI is still not as good as conventional morphologic MRI for distinguishing soft tissues.

Apparent diffusion coefficient (ADC) value in characterizing bladder cancer:

Numerous studies have documented the usefulness of the ADC value as an imaging biomarker for bladder cancer treatment. The majority of earlier research determined the ROI's mean ADC value after it was inserted into the tumor. On the ADC map, the intra-tumoral distribution of ADC values is typically homogeneous due to the uniform diffusion environments found within bladder malignancies, and in 83% of bladder cancers, the histogram displaying there was only one notable peak in the tumor's ADC distribution for every pixel ⁽¹³⁾.

The ROI's size and location are not standardized, yet the ADC readings' measurement variance might be rather small. Numerous studies have found a correlation between bladder cancer histologic grade and ADC readings. Compared to low-grade bladder cancer, high-grade bladder cancer's ADC values were consistently substantially lower cancer in these investigations. It has been suggested that microstructural alterations in the malignant tissue, such as greater cellularity and larger cell size, are the fundamental cause of the association between the ADC value and histologic features ⁽¹¹⁾.

The accuracy of local staging was further enhanced by the inclusion of ADC data in the visual DWI assessment. By employing the inchworm sign, the understaging rate of muscle-invasive bladder cancer was reduced from 27–25% to 4.5–4.0% by adding high ADC values to the sign (with a cut-off of $0.80 \times 10^{-3} \text{ mm}^2/\text{s}$) ⁽¹¹⁾.

The ADC value, in prospective research involving 132 patients with bladder cancer, can be employed as an imaging biomarker revealing the tumor's state of proliferation, as established by Ki-67. ADC value is correlated with p53, p21, and Ki-67 cell cycle regulators. Research has demonstrated a relationship between the ADC value and the state of tumor proliferation in cases of meningioma, hepatocellular carcinoma, and breast cancer ⁽¹⁴⁾.

Aggressive bladder tumors with highly proliferating cells have lower extracellular space and higher cellularity, which lowers ADC values. The bladder cancer's microstructural alteration and biologic features are both reflected in the ADC score. One potentially helpful quantitative diagnostic for evaluating the properties of cancer cells is the ADC value ⁽⁶⁾.

The ADC value is, however, intrinsically limited by the field strength, vendors, imager, and coil system; hence, the applied ADC threshold and the measured ADC value differed throughout the investigations. Standardization of the ADC value assessment process is required in order to use the value as a clinically useful biomarker that can be applied across centers with varying MRI techniques ⁽⁶⁾.

Apparent diffusion coefficient value in predicting the clinical course of bladder cancer:

The ADC value may be used as a biomarker to forecast how bladder cancer would behave clinically following treatment since it represents both the biologic aspects and the microstructure of the disease. Our team has demonstrated that the ADC value can be used to predict the therapeutic response to chemoradiation therapy (CRT), which consists of either a partial or radical cystectomy after two cycles of radiotherapy to the small pelvis and cisplatin (20 mg/day for five days) (40 Gy) ⁽¹³⁾.

Role of DWI in post-treatment follow-up:

Accurate treatment response assessment is a crucial component of managing bladder cancer. TURB is utilized as a first step in the care of bladder cancer, both for surgical therapy and histologic diagnosis and staging process. Initial TURB understaging of muscle-invasive bladder cancer and incomplete resection of non-muscle-invasive bladder cancer are concerns; all patients with T1 or grade 3 cancers should undergo a second TURB soon after the first, despite its disadvantages (high cost and invasiveness) ⁽¹⁵⁾.

For muscle-invasive bladder cancer, TURB and CRT combined have been used as a bladder-preservation regimen. Transurethral biopsy is typically used in this multimodal therapy method to evaluate therapeutic response following TURB and CRT ⁽¹⁶⁾.

Volume changes come before these DWI changes as a result of the effective treatment. Studies on a variety of cancers, such as brain gliomas, liver cancer, and soft-tissue sarcoma, have highlighted the importance of DWI in monitoring therapy responses and showed how the DWI signal changes based on the therapeutic effect ⁽¹⁷⁾. It's important to note that The DWI signal is not limited to cancer cells, it can also be strongly signalled by granulomas and inflammatory changes, which mimic malignant tissue. It is important to use caution when

assessing post-therapeutic changes as they may result in a false-positive diagnosis ⁽¹⁸⁾.

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