ejpmr, 2023,10(10), 95-100

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

DIAGNOSTIC ACCURACY OF DIFFUSION WEIGHTED MAGNETIC RESONANCE IMAGING IN DIAGNOSING MUSCLE INVASION IN URINARY BLADDER CANCER, TAKING HISTOPATHOLOGY AS GOLD STANDARD

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Article Received on 13/08/2023 **Article Revised on 03/09/2023** **Article Accepted on 23/09/2023**

ABSTRACT

Introduction: Diffusion-weighted magnetic resonance imaging (DW-MRI) and determination of the apparent diffusion coefficient values (ADC) are modern functional MR-imaging techniques. The ADC value describes the ability of water molecules to diffuse in tissue, which is impaired by increased cellular density as is the case in tumors. **Objectives:** To determine the diagnostic accuracy of diffusion weighted magnetic resonance imaging in diagnosing muscle invasion in urinary bladder cancer, taking histopathology as gold standard. **Materials & Methods:** A total of 105 patients patients presented with hematuria >100 RBCs on high power microfield and irregular soft tissue structure projecting into bladder lumen from a fixed mural site on ultrasonography and age 25-65 years of either gender were included. Patients with h/o radiotherapy, CRF, recurrent tumour, biopsy proven muscle invasive urinary bladder cancer and any contraindication to MRI were excluded. All the patients were then underwent DW-MRI of the pelvis. DW-MRI findings were interpreted for presence or absence of muscle invasion in urinary bladder cancer and compared with DW-MRI findings. **Results:** In DW-MRI positive patients, 64 (True Positive) had muscle invasion and 03 (False Positive) had no muscle invasion on histopathology. Among 38, DW-MRI negative patients, 03 (False Negative) had muscle invasion on histopathology whereas 35 (True Negative) had no muscle invasion on histopathology (p=0.0001). Overall sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of diffusion weighted magnetic resonance imaging in diagnosing muscle invasion in urinary bladder cancer was 95.52%, 92.11%, 95.52%, 92.11% and 94.29% respectively. **Conclusion:** This study concluded that DW-MRI is a highly sensitive and accurate non-invasive modality for diagnosing muscle invasion in urinary bladder cancer.

KEYWORDS: Urinary bladder cancer, Muscle invasion, Diffusion weighted imaging.

INTRODUCTION

Bladder cancer is any of several types of cancer arising from the epithelial lining (i.e., the urothelium) of the urinary bladder. Rarely the bladder is involved by non-epithelial cancers, such as lymphoma or sarcoma, but these are not ordinarily included in the colloquial term "bladder cancer." It is a disease in which abnormal cells multiply without control in the bladder.[1] The most common type of bladder cancer recapitulates the normal histology of the urothelium and is known as transitional cell carcinoma or more properly urothelial cell carcinoma.[2] Five-year survival rates are around 77%.[3]

Bladder cancer is the second most common genitourinary cancer in the United States and some 55600 new cases and 15100 deaths from bladder cancer are estimated to have occurred in 2012.4 Ceylan K et al[5] in his study has shown the prevalence of urinary bladder cancer as 67.79% patients. At the initial diagnosis, a third of all cases are diagnosed as muscle-invasive bladder cancer (MIBC), and radical cystectomy has long been the treatment of choice for the treatment of localized MIBC. However, concern for patients' quality of life has strengthened the trend toward bladder-sparing approaches with various treatment modalities.[6] The initial evaluation of a patient who presents with hematuria is not uniform: Some institutions perform

computed tomographic (CT) urography for triage prior to cystoscopy, whereas others use cystoscopy as the first line of investigation. Nevertheless, cystoscopy and CT are complementary and have a definite management role in patients who present with hematuria.[7,8]

Today, ultrasonography (US), Contrast-enhanced CT and conventional MRI are the standard techniques that have been used for the radiological evaluation of urinary system tumors. While CT is generally used to screen for metastasis, MRI plays a pivotal role in the staging of bladder cancer because of its superior soft tissue delineation, especially in the context of muscle-invasion.8 Magnetic resonance (MR) imaging of the pelvis is usually performed for T (tumor) staging once bladder cancer has been diagnosed, although its use is not widespread.[9]

Diffusion-weighted magnetic resonance imaging (DW-MRI) and determination of the apparent diffusion coefficient values (ADC) are modern functional MR-imaging techniques. The ADC value describes the ability of water molecules to diffuse in tissue, which is impaired by increased cellular density as is the case in tumors.[10,11] In a meta-analysis, the prevalence of muscle invasive urinary bladder cancer was found to be 33.46% and sensitivity and specificity of DW-MRI in differentiating muscle invasive from non-muscle invasive urinary bladder cancer as 85.0% and 90.0% respectively.[12] In another study, the sensitivity, specificity and diagnostic accuracy of DW-MRI for differentiating muscle invasive from non-muscle invasive urinary bladder cancer were 88.0%, 85.0% and 87.0%, respectively.[13]

Although previously many studies are available on this topic but I have found no local study on this topic, so I had decided to conduct this study to determine the diagnostic accuracy of diffusion weighted magnetic resonance imaging in diagnosing muscle invasion in urinary bladder cancer, taking histopathology as gold standard. My study will not only provide the local statistics but will also be a useful addition in the existing literature. And if it's diagnostic accuracy will be found high then this technique can be opted routinely in our practice for pre-operative assessment of urinary bladder cancer for taking proper surgical management in order to reduce the morbidity and mortality of these particular patients.

MATERIALS AND METHODS

Approval from ethical review committee was taken. Informed consent was taken from patients. This cross-sectional validation study included 105 patients of both genders (Male and Female) with age 25-65 years. Sample size of 105 cases has been calculated with 95% confidence level, the prevalence of muscle invasive urinary bladder cancer as 33.46% and 10% desired precision for sensitivity and 10% for specificity of DW-MRI in diagnosing muscle invasive urinary bladder cancer as 85.0% and 85.0% respectively. Non-probability, consecutive sampling was used. Patients presented with hematuria >100 RBCs on high power microfield and irregular soft tissue structure projecting into bladder lumen from a fixed mural site on ultrasonography were included. Study was conducted at Shahida Islam Teaching Hospital in Lodhran and Bahawal Victoria Hospital, Bahawalpur, from July 2021 to June 2022. The study excluded patients with history of radiotherapy, renal disease, already biopsy proven muscle invasive urinary bladder cancer, contraindication to MRI i.e. claustrophobia and cardiac pacemakers and pregnant females.

Then in all patients, diffusion weighted imaging (DWI) MR sequences with b=0, b=500 and b=1000, followed by apparent diffusion coefficient (ADC) mapping was done. DW-MRI findings were interpreted by consultant radiologist (at least 3 years of post-fellowship experience) for presence or absence of muscle invasion in urinary bladder cancer. Biopsy was done in the concerning ward and histopathology report was compared with DW-MRI findings.

Collected data was analyzed through computer software SPSS 20.0. Mean and standard deviation were calculated for quantitative variables. Frequency and percentage were calculated for qualitative variables. 2×2 contingency table was used to calculate the sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of DW-MRI in diagnosing muscle invasion in urinary bladder cancer, taking histopathology as gold standard.

Muscle invasion in urinary bladder cancer on DW-MRI		**Muscle invasion in urinary bladder cancer on Histopathology**	
		Yes	No
	Yes	True Positive (a)	False Positive (b)
	No	False Negative (c)	True negative (d)

Sensitivity: a / a+c x 100
Specificity: d / b+d x 100
Positive predictive value: a / a+b x 100
Negative predictive value: d / c+d x 100
Diagnostic accuracy: a+d / a+b+c+d x 100

RESULTS

Age range in this study was from 25-65 years with mean age of 51.50 ± 9.29 years. Majority of the patients 73 (69.52%) were between 45 to 65 years of age. Out of these 105 patients, 70 (66.67%) were male and 35 (33.33%) were females with male to female ratio of 2:1.

Mean duration of disease was 5.05 ± 1.87 months. The mean size of lesion was 3.90 ± 1.21 cm. Mean BMI was 29.14 ± 2.44 kg/m2.

All the patients were subjected to Diffusion weighted magnetic resonance imaging (DW-MRI). DW-MRI supported the diagnosis of muscle invasion in urinary bladder cancer in 67 (63.81%) patients and non-muscle invasion in 38 (36.19%) patients. Histopathology findings confirmed muscle invasion in urinary bladder cancer in 67 (63.81%) patients and non-muscle invasion in 38 (36.19%) patients. In DW-MRI positive patients, 64 (True Positive) had muscle invasion and 03 (False Positive) had no muscle invasion on histopathology. Among 38, DW-MRI negative patients, 03 (False Negative) had muscle invasion on histopathology whereas 35 (True Negative) had no muscle invasion on histopathology (p=0.0001) as shown in Table I. Overall sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of diffusion weighted magnetic resonance imaging in diagnosing muscle invasion in urinary bladder cancer was 95.52%, 92.11%, 95.52%, 92.11% and 94.29% respectively.

Table I: Diagnostic accuracy of diffusion weighted magnetic resonance imaging in diagnosing muscle invasion in urinary bladder cancer, taking histopathology as gold standard.

	Positive result on histopathology	Negative result on histopathology	P-value
Positive on DW-MRI	64 (TP)*	03 (FP)***	0.0001
Negative on DW-MRI	03 (FN)**	35 (TN)****	

*-TP=True positive **-FP=False positive ***-FN=False negative ****-TN=True negative

Sensitivity: 95.52%
Specificity: 92.11%
Positive Predictive Value (PPV): 95.52%
Negative Predictive Value (NPV): 92.11%
Diagnostic Accuracy: 94.29%

DISCUSSION

The DW-MRI technique was initially devised by Stejskal and Tanner in 1965. Since 1985, DW-MRI has been mainly used for neuroimaging, especially for diagnosis of acute cerebral infarction and intracranial tumors. With the recent advent of echo planar imaging, high gradient amplitudes, multichannel coils, and parallel imaging, DW-MRI of the abdomen and pelvis has become possible, and a growing number of studies have demonstrated the usefulness of this imaging technique in the diagnosis of malignant tumors of the abdomen.[14] Because the signal of DW-MRI is derived from the inherent tissue contrast, this imaging technique requires no contrast agent and is applicable to patients with allergies to contrast agents or those with renal insufficiency. Furthermore, the addition of DW-MRI to a routine MRI examination requires only a few additional minutes and can be adopted for most current clinical MRI scanners.

Age range in my study was from 25-65 years with mean age of 51.50 ± 9.29 years. Majority of the patients 73 (69.52%) were between 45 to 65 years of age. Out of these 105 patients, 70 (66.67%) were male and 35 (33.33%) were females with male to female ratio of 2:1. DW-MRI supported the diagnosis of muscle invasion in urinary bladder cancer in 67 (63.81%) patients and non-muscle invasion in 38 (36.19%) patients. Histopathology findings confirmed muscle invasion in urinary bladder cancer in 67 (63.81%) patients and non-muscle invasion in 38 (36.19%) patients. In DW-MRI positive patients, 64 (True Positive) had muscle invasion and 03 (False Positive) had no muscle invasion on histopathology. Among 38, DW-MRI negative patients, 03 (False Negative) had muscle invasion on histopathology where as 35 (True Negative) had no muscle invasion on histopathology (p=0.0001). Overall sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of diffusion weighted magnetic resonance imaging in diagnosing muscle invasion in urinary bladder cancer was 95.52%, 92.11%, 95.52%, 92.11% and 94.29% respectively.

In a meta-analysis, the prevalence of muscle invasive urinary bladder cancer was found to be 33.46% and sensitivity and specificity of DW-MRI in differentiating muscle invasive from non-muscle invasive urinary bladder cancer as 85.0% and 90.0% respectively.[12] In another study, the sensitivity, specificity and diagnostic accuracy of DW-MRI for differentiating muscle invasive from non-muscle invasive urinary bladder cancer were 88.0%, 85.0% and 87.0%, respectively.[13]

Since the first report by Matsuki et al[15] showing the utility of DW-MRI for detecting bladder cancer, a number of studies have shown the usefulness of DW-MRI for the diagnosis of bladder cancer.[15,16] On DW-MRI with a high b-value, bladder cancers generally show a hyperintense signal, while the signals of the surrounding tissues, including urine, are much less intense.[15] This good signal contrast is obtained between bladder cancer and the surrounding tissue. The sensitivity, specificity and accuracy for detecting bladder cancer were reported to be 90%-98%, 92%-93% and 91%-97%, respectively.[16] In several studies, quantitative analysis consistently showed restricted diffusion

and lower ADC values in bladder cancer compared with the surrounding structures.[15]

MIBC has the potential to metastasize to lymph nodes and distant organs, and detecting metastatic lesion is another problem in managing MIBC. At the time of surgery, 25% of the patients who undergo radical cystectomy have a lymph node metastasis. Lymph node staging has been generally performed by CT or conventional MRI based on size criteria and morphological appearance, and the accuracy for staging nodal disease ranges from 73% to 90%.[17] On DW-MRI, benign lymph nodes show high signal intensity due to their highly cellular structures composed of lymphoid elements. The utility of DW-MRI has been shown in lymph node staging in various cancers.[18,19] Papalia et al[20] showed that malignant lymph nodes have a significantly lower ADC value than benign lymph nodes with sensitivity of 76.4% and specificity of 89.4% in a study that included 36 patients with bladder cancer undergoing radical cystectomy. However, there is a substantial overlap in ADC values between malignant and benign lymph nodes, and discriminating malignant nodes from benign nodes on DW-MRI is still challenging.[21] Recently, Thoeny et al[22] reported an excellent diagnostic accuracy of 90% in detecting pelvic lymph nodal involvement by the combined use of ultra-small super paramagnetic iron oxide (USPIO) and DW-MRI. This agent is taken up by macrophages resulting signal loss in normal lymph nodes, while the signal of metastatic lymph nodes is not influenced.[22-24]

El-Assmy et al[25] reported the ability to discriminate MIBC from NMIBC with an accuracy of 63.6% in a study that included 106 patients. Takeuchi et al[26] reported that bladder cancer staging accuracy improved from 67 to 88% when DW-MRI was added to T2WI. Takeuchi et al[26] reported that the ADC value of grade 3 tumors was significantly lower than that of grade 1 and 2 tumors in a prospective study that included 40 patients. Avcu et al[27] also reported similar results showing an inverse correlation between the ADC value and the histological grade. The existence of a substantial overlap between the histological grades or stages poses a limit to qualitative analysis and the clinical application of this technique. However, these studies indicated that advanced and aggressive bladder cancers tend to have a low ADC values. Actually, Kobayashi et al[28] found that clinically aggressive tumors, including MIBC and high-grade T1 tumors, had a significantly lower ADC value than the other less aggressive tumors. A threshold ADC value differentiated these two entities with 87% accuracy in a series of 121 patients. The underlying mechanisms whereby the ADC value reflects these tumor characters are thought to be the tumor cell morphological characters such as dense cellularity and large cellular size.[29,30] Recent studies have shown an inverse correlation between ADC value and the Ki-67 labeling index, a marker of cell proliferation, in bladder cancer.[31,32]

CONCLUSION

This study concluded that DW-MRI is a highly sensitive and accurate non-invasive modality for diagnosing urinary bladder cancer, and has improved patient care by early screening, timely and proper treatment and avoiding unnecessary diagnostic biopsies, which consequently reduces patients' morbidity and mortality. So, we recommend that diffusion weighted MRI should be used routinely as a prime modality for pre-operative status of urinary bladder cancer for selecting proper treatment option and post-operative management plan for these particular patients which will result in reducing the morbidity and mortality of these patients.

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