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Original research article

Role of dynamic contrast-enhanced magnetic resonance imaging in staging of bladder cancer

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Abstract

Background: Bladder cancer is one of the most prevalent malignancies of the genitourinary system, comprising 4% of all malignancies. Urinary bladder cancer is considered one of the most common malignancies worldwide with an incidence of 18.5 per 100,000 males and 5.7 per 100,000 females .Approximately 25% of newly diagnosed bladder carcinoma patients present with aggressive muscle-invasive disease.

Objectives and Aim: To elaborate the role of dynamic contrast-enhanced Magnetic Resonance Imaging in staging of bladder cancer.

Materials and Methods: Our study taken place in the Department of Radio diagnosis, Azeezia Institute of Medical Sciences, Meeyannoor, PO, Kollam, Kerala, India. A total number of 62 cases of histopathology proved urinary bladder cancer were referred for MRI scanning, aiming for T-staging of bladder cancer. Both T1 and T2-weighted turbo spin echo images were obtained, followed by non-contrast enhanced T1-spoiled gradient weighted image, and then fast dynamic gadolinium enhanced T1-spoiled gradient weighted imaging. Contrast enhanced studies were performed with intravenous administration of gadopentetate dimeglumine (Gd-DTPA) (Magnevist) (0.1mmol/kg) followed immediately by 20 ml of IV saline flush injection. Enhanced images were initiated 10 seconds after the start of contrast injection and images were repeatedly acquired four times each 16 seconds at the same sections.

Observations and Results: The final pathologic staging revealed 25 patients with stage T1, 8 patients with stage T2, 19 patients with stage T3, and 10 patients with stage T4. The MRI dynamic contrast enhanced study shows correct results in 52 cases of 62 patients 83.1%, over-staged in 7 cases of 62 patients 11.8%, under-staged were 3 cases of 62 patients 5.1% . Sensitivity, specificity, PPV, NPV and accuracy were 81.46%, 94.53%, 79.59%, 94.25% and 91.53%, respectively.

Conclusion: In this study, despite small differences between the results of the MRI and pathology, DCE-MRI was found to be an accurate modality for assessment of T staging, and its routine use in bladder cancer staging gives significant improvement of diagnostic accuracy of the staging and in treatment planning , thereby improving the prognosis of patients and their survival rates. Furthermore, the use of MRI systems with higher magnetic field and imaging techniques standardized with higher resolution could further enhance the accuracy of the method. Fast dynamic gadolinium enhanced MRI images appear to provide useful information for evaluating T-stage in patients with bladder cancer with 91.53% staging accuracy for fast dynamic gadolinium enhanced T1WI. It is particularly useful for differentiating T1-stage or lower tumors from T2-stage or higher tumors. So, contrast enhanced MRI images could be a useful adjunct to preoperative evaluation.

Keywords: Diagnostic modality, DCE-MRI, staging, bladder cancer, carcinoma, urinary bladder, MRI, enhanced MRI

Introduction

Bladder cancer is one of the most prevalent malignancies of the genitourinary system, which comprises 4% of all malignancies [1]. Bladder cancer comprises approximately 2-3% of malignancies in women and is the ninth leading cause of death due to cancer in men [2].

Urinary bladder cancer is considered one of the most common malignancies worldwide with an incidence of 18.5 per 100,000 males and 5.7 per 100,000 females and approximately 25% of newly diagnosed bladder carcinoma patients present with aggressive muscle-invasive disease [3]. In India bladder cancer has increased exponentially during the past 50 years, representing 16.2% of male cancers, due to the etiological relationship to endemic urinary schistosomiasis. In Indian population, it is one of the progressive cancer after lung cancer, non-Hodgkin lymphoma, ovarian cancer, leukemia and colorectal cancer, with its frequency being 4.0%, by far exceeded by breast cancer (37.6% of female malignancies.

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For both sexes together, the frequency of bladder cancer was 10.1%, nearly the same as non-Hodgkin lymphoma (10.5%) and next in frequency to breast cancer [4]. The decision for the optimal treatment strategy is mainly based on results of imaging. Therefore accurate pre-treatment staging of these patients is of major importance [5]. Standard treatment for muscle invasive bladder carcinoma is radical cystectomy with pelvic lymph node dissection [6]. In patients treated with curative-intended radical cystectomy and pelvic lymph node dissection there is a 40% difference in three year cancer specific survival (91.4 ± 1.7% versus 50.9 ± 3.5%) between those with organ-confined bladder carcinoma and those with a cancer infiltrating perivesical fatty tissue or metastatic lymph nodes [7]. Especially in cases of locally advanced disease or high risk disease for development of metastases platinum-based neo adjuvant chemotherapy regimens have been shown to improve patient cure rates while palliative treatment is advocated for metastatic disease [8, 9]. MRI is the most promising imaging for staging of cancer bladder. It offers several advantages such as multiplanar imaging with better detection of tumors, better tissue characterization, superiority in evaluation of prostatic and seminal vesicles invasion, in addition to better differentiation post biopsy tissue changes and tumor itself [10].

Material and Methods: This prospective study was conducted in the department of Radio diagnosis, Azeezia Institute of Medical Sciences, Meeyannoor, PO, Kollam, Kerala, India. During the study period a total number of 62 cases of histopathology proven urinary bladder cancer were referred from urology department of the hospital, for MRI scanning aiming for T-staging of bladder cancer. In all patients of the study ,the diagnosis and initial staging of bladder cancers were made by cystoscopy and transurethral resection of the tumor with deep muscle biopsy performed at the base of the tumor. All patients with invasive cancer underwent radical cystectomy and pelvic lymphadenectomy, the extent of bladder tumor was assessed by pathological evaluation of resected bladder and peri-vesical tissues as well as assess of the infiltration of adjacent peri-vesical organ in relation to the tumor and pelvic lymph nodes.

MRI Examination: All MRI scans were performed at 1.5 Tesla, superconducting magnet,Toshiba vantage elan . All patients included in the study are found to be free of distant metastasis before they were referred for MRI. Their workup for distant metastasis included chest X-rays, abdominal sonogram, CT abdomen and bone scanning if required.

MRI technique: The patient lies supine, feet first on the scanner table, with the median sagittal plane perpendicular to the center of the table. Using the scanner alignment light ,the external reference point is obtained at the level of the anterior superior iliac spines. From this position the patient is moved to the isocenter of the magnet. Body coil was used in all patients. An initial midline sagittal localizer is performed to include the lower abdomen and pelvis. Using this image a series of variable oriented different MRI pulse sequences are obtained. Both T1 and T2-wieghted turbo spin echo images are obtained, followed by non-contrast enhanced T1- spoiled gradient weighted image, then fast dynamic gadolinium enhanced T1- spoiled gradient weighted image ; according to the parameters reported in table (1). T2-weighted MR Imaging was performed in axial, sagittal, and coronal planes. An axial T1-weighted image was performed in all cases with additional sagittal or coronal images performed according to the tumor orientation, reviewed on T2-wieghted images. Contrast enhanced studies were performed with intravenous administration of gadopentetate dimeglumine (Gd-DTPA) (Magnevist) (0.1mmol/kg) followed immediately by 20 ml of IV saline flush injection. Enhanced images were initiated 10 seconds after the start of contrast injection and images were repeatedly acquired four times each 16 seconds at the same sections. The total imaging time for the dynamic sequences is about 64 seconds. Late gadolinium enhanced T1-Weighted imaging was performed 5 minutes after the dynamic imaging with the same parameters of the previously used conventional T1-Weighted sequence.

Table 1: Study standard MR Pulse sequences parameters

Pulse sequences			
Parameters	**T1W1**	**T2W1**	**Dynamic T1W1**
Repetition time (TR)	800 msec	4000 msec	142 msec
Echo time (TE)	14 msec	120 msec	12 msec
Matrix	256x192	256x192	256 x192
Field of view (FOV	375 mm	200 mm	375 mm
Slice thickness	5mm	3 mm	5 mm
Inter-slice gap	1 mm	1mm	1 mm
Acquisition time	3:50	3	0.16
Flip angle	-	-	70

Diagnostic MRI Criteria

MR images were interpreted without prior knowledge of the final staging obtained at transurethral resection, or cystectomy. The MRI images were evaluated based mainly on T2-weighted images and

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dynamic contrast enhanced T1-weighted images criteria described in different previous studies like (11, 12 and 13). T1-weighted images were used to help in differentiate between organ confined and non-organ confined tumors. On T2-weighted images, the normal bladder wall was identified as a hypointense line outlining the bladder lumen [14, 15]. On dynamic contrast-enhanced MR images, bladder tumors, mucosa, and submucosa (lamina propria) enhanced early, but the muscle layer maintained its hypointensity [16]. An intact, hypointense line (muscle layer) at the base of the tumor was classified as stage T1; an irregular inner margin of hypointense line, stage T2a. A disrupted hypointense line without perivesical fat infiltration, stage T2b . A lesion with an irregular, shaggy outer border and streaky areas of the same signal intensity of the tumor in perivesical fat, stage T3b; and a lesion extending into an adjacent organ or abdominal and pelvic side walls with the same signal intensity of the primary tumor, stage T4a or T4b, respectively [17]. Lymph nodes were considered abnormal if the long axis was 10 mm or more. All patients included in the study are found to be free of distant metastasis before they were referred for MRI. Their work up for distant metastasis included chest X-rays, abdominal sonogram, CT abdomen and bone scanning if required. Pathologic staging confirmed to the updated TNM system of the International Union against Cancer (table 2).

Statistical analysis

The collected data were organized, tabulated and statistically analyzed, using Statistical Package for Social Science (SPSS) version 19 (SPSS Inc, Chicago, USA), running on IBM compatible computer with Microsoft ® Windows 7 Operating System. Mean, frequency and percentage were used as descriptive predictors. Sensitivity, specificity, positive predictive value, negative predictive value and accuracy were used as measurements of validity for MRI tumor staging regarding the histopathological results.

Table 2: TNM staging of bladder carcinoma

		Primary tumor (T)
CIS		**CIS Carcinoma in situ.**
Ta		Ta Noninvasive papillary tumor.
T1		T1 Tumor invades the lamina propria, but not beyond.
T2	T2a	T2 T2a Tumor invades deep muscle (inner half).
	T2b	T2b Tumor invade superficial muscle (outer half)
T3	T3a	T3 T3a Tumors extend microscopically into perivesical fat
	T3b	T3b Tumors extend macroscopically into perivesical fat.
T4	T4a	T4 T4a Tumor invades prostate, vagina or uterus.
	T4b	T4b Tumor invades pelvis side wall or abdominal wall.
Regional lymph nodes		
NX		Regional lymph nodes status is unknown.
N0		No regional lymph nodes metastasis.
N1		Metastasis in a single lymph node 2 cm or less in greatest dimension.
N2		Metastasis in a single lymph node more than 2 cm but less than or equal 5 cm in greatest dimension, or multiple lymph node, none more than 5 cm in greatest dimension.
N3		Metastasis in a lymph nodes more than 5 cm.
Distant metastases (M)		
MX		Distant metastases cannot be assessed.
M0		No distant metastases.
M1		Distant metastases.

Results and Observations

Patient's sex and age: 62 patients were included in this study, 57 males (91.5%) and 5 females (8.5%) with their age ranged from 43 to 76 years old. The commonest age group encountered in the study was the age group (51-60) years (37.3%). As in figure 1.

MRI findings: Non enhanced T1WI

In all patients, the urinary bladder tumor appears either as focal mural thickening or mural based endoluminal mass, which has intermediate signal intensity equal to that of muscle, so that the depth of tumor infiltration into the bladder wall cannot be assessed. The interface between the bladder wall and peri-vesical fat was observed for assessment of tumors infiltration into the peri-vesical fat or adjacent organs. On non-enhanced T1-weighted images the tumor was classified into organ confined (T2-stage or less) and non-organ confined (T3-stage or more). **T2WI**: On T2-weighted images, the tumor has intermediate signal intensity, higher than bladder wall, and the depth of tumor infiltration into the bladder wall can be assessed. On T2WI the study has revealed 24 patients with stage T1, 10 patients with stage T2, 21 patients with stage T3, and 7 patients with stage T4.

Gadolinium enhanced fast dynamic T1WI

On fast dynamic contrast enhanced MRI images, all tumors had increased enhancement compared with uninvolved bladder. The bladder tumor, mucosa and submucosa enhanced early but the muscle layer

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maintained its hypo-intensity. Gadolinium enhanced T1WI revealed 23 patients with stage T1, 8 patients with stage T2, 18 patients with stage T3, and 10 patients with stage T4.

The final pathologic result and staging: Urinary bladder carcinomas were pathologically proven in all patients of the study by deep muscle biopsy performed at the base of the tumor during cystoscopy and transurethral resection of the tumor. Noninvasive bladder cancer was proved in 23 patients, and invasive bladder cancer was proved in 36 patients. All patients with invasive cancer underwent radical cystectomy and the extent of bladder tumor was assessed by pathological evaluation of resected bladder and peri-vesical tissues, as well as assessment of the infiltration of adjacent peri-vesical organ and excised pelvic lymph nodes. Transitional cell carcinoma was encountered in 34 of 59 cases (57.63 %), squamous cell carcinoma was encountered in 21 patients (35.59 %), mixed transitional and squamous cell carcinoma was encountered in 3 cases (5.1%) and adenocarcinoma was encountered in one patient of 59 cases (1.69%). The final pathologic staging revealed 23 patients with stage T1, 10 patients with stage T2, 18 patients with stage T3, and 8 patients with stage T4. The tumor were staged correctly in 49 cases of 59 patients 83.1%, overstated in 7 cases of 59 patients 11.8%, under stage were 3 cases of 59 patients 5.1%, sensitivity, specificity, PPV, NPV and accuracy were 81.46%, 94.53%, 79.59%, 94.25% and 91.53%.

Table 3: Staging results of Gadolinium Enhanced MRI

MRI			**Histological stage**		
	T1	**T2**	**T3**	**T4**	**Total**
T1	22	3	0	0	25
T2	3	5	0	0	8
T3	0	2	17	0	19
T4	0	0	2	8	10
Total	25	10	19	8	62

Table 4: Sensitivity, Specificity, PPV, NPV and accuracy of Gadolinium Enhanced MRI

MRI	**Pathology stage**	**Positive**	**Negative**	**Total**	**Sens.**	**Spec.**	**PPV**	**NPV**	**Accuracy**
T1	Positive	21	3	24					
	Negative	3	35	38	86.96	92.31	86.96	91.67	89.83
	Total	24	38	62					
T2	Positive	5	3	8					
	Negative	5	49	54	50	94.23	62.5	90.20	86.44
	Total	10	52	62					
T3	Positive	17	2	19					
	Negative	2	41	43	88.89	95.35	88.89	95.12	93.22
	Total	19	43	62					
T4	Positive	8	2	10					
	Negative	0	52	52	100	96.23	80	100	96.61
	Total	8	54	62					

Superficial versus invasive tumors: Staging accuracy was evaluated by another way to reflect clinical utility. We evaluate the ability of MRI to distinguish between the superficial and invasive tumors. On gadolinium enhancement T1WI, 53 tumor were staged correctly(89.83%), 3 were overstated (5.08%), 3 were understated (5.08%), yielding an overall sensitivity were 78.26%, specificity 88.89%, PPV 81.82%, NPPV were 86.49% and accuracy were 89.83%.

Table 5: Accuracy of gadolinium enhanced MRI in differentiating superficial from invasive tumor Organ confined versus non-organ confined

MRI		**Histological stage**		
MRI Stage	**Superficial**	**Invasive**	**Total**	
Superficial	21	3	24	
Invasive	3	35	38	
Total	24	38	62	
Sens	Spec.	PPV	NPV	Accuracy
86.9	91.6	86.96	91.67	89.83

Non enhanced T1WI revealed 38 patients with organ confined and 24 patients with non-organ confined. T2WI revealed 34 patients with organ confined and 28 patients with non-organ confined. Gadolinium enhanced T1WI revealed 33 patients with organ confined and 29 patients with non-organ confined tumor. The final pathologic staging revealed 34 patients with organ confined and 28 patients with non-organ confined tumors.

Lymph node staging: MRI images revealed 7 patients of 62 patient with enlarged pelvic lymph nodes with their long axis diameter exceeding 10 mm and 55 patients who were free of lymph node

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enlargement. All patients with enlarged lymph nodes were of invasive cancer bladder (T2-T4-stage). Of these 7 patients of MRI detected enlarged lymph nodes, 6 patients proved to be neoplastic lymph nodes and 1 false positive case which revealed inflammatory changes on final pathologic staging. The final pathologic staging revealed 8 patients with neoplastic lymph node involvement. That neoplastic lymph nodes were correctly detected in 6 patients of 7 MRI detected enlarged lymph nodes compared to 8 patients with histopathology proved neoplastic lymph nodes with sensitivity, specificity, PPV, NPV and accuracy were 75%, 98%., 85%, 96% and 94.9%.

Table 6: MRI lymph node staging results

Lymph Node		**Histological stage**		
MRI Stage	**NO.**	**N1-N2**	**Total**	
No	53	2	55	
N1-N2	1	6	7	
Total	54	8	62	
Sens	Spec.	PPV	NPV	Accuracy
75	98	85.7	96	94.9

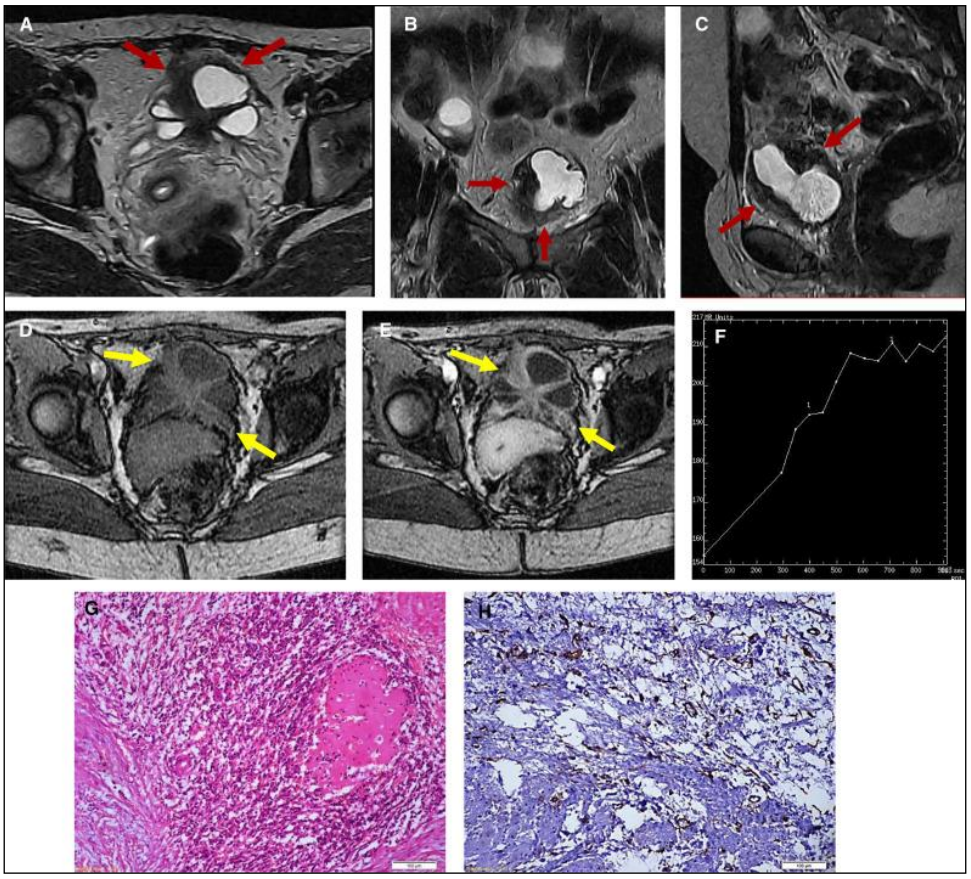

Fig 1: 44-years-old female patient, presented with irritative bladder symptoms and frequent attacks of hematuria Proved to be follicular cystitis. Magnetic resonance imaging T2 high resolution: axial (A), coronal (B), and sagittal (C) views revealed: reduced bladder capacity, irregular circumferential bladder wall thickening with sessile lesions at the bladder dome, anterior, and right lateral walls, displaying hypointense signal intensity with infiltration of the perivesical fat (red arrows). Dynamic contrast-enhanced magnetic resonance imaging, axial view. (D) Early post-contrast gradient T1 showed mild diffuse enhancing circumferential bladder thickening (yellow arrow). (E) Late post-contrast gradient T1: persistent and increasing enhancement (yellow arrow). (F) Time-signal intensity curve shows slow enhancement followed by slow increase with no washout. (G) Haematoxylin-eosin stained slide: follicular cystitis. (H) CD34 expression (×250). Mean of MVD = 84.

Discussion

Erroneous signals in the perivesical fat, adjacent to the tumour location as a result of vascular hyperaemia due to post operative and inflammatory processes can cause false overestimation leading to upstaging of the tumour. For example, tumours were reported as T3b in five patients in stage T2b. Vascular hyperaemia adjacent to the tumour or inflammatory process that occurred in the tissues around bladder following TUR biopsy of tumours could cause these abnormal signals. In addition, chemical shift artefact at the bladder-perivesical fat junction may obscure the bladder wall or be regarded as pathological. Urinary bladder cancer is a common disease worldwide with its incidence varying

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significantly between geographical regions and countries [18]. In India, bladder cancer has been the most common male cancer during the past 50 years, representing 16.2% of male cancers. In Indian females, it is the 6th most common cancer after breast cancer, non-Hodgkin lymphoma, ovarian cancer, leukemia and colorectal cancer (2). Approximately 90% of all bladder cancers are transitional cell carcinomas (TCC) in western countries, mainly related to smoking as a risk factor. India had at some places different histological pattern than other countries with high incidence of squamous cell carcinoma (SCC) related to endemic schistosomiasis [19]. There are multiple studies reporting significant changes in the histo-pathological profile of bladder cancer in India over the last few decades due to the effect of successful control measures against endemic schistosomiasis. In our study transitional cell carcinoma was encountered in 36 of 62 cases (57.63%), squamous cell carcinoma was encountered in 22 patients (35.59%), mixed transitional and squamous cell carcinoma were encountered in 3 cases (5.1%) and adenocarcinoma were encountered in one patient of 62 cases (1.69%). These results agree with previously mentioned multiple studies which reported the increase in frequency of TCC and decrease in frequency of SCC relative to previous early reports, which indicate a transition phase from the schistosomiasis associated bladder cancer to the western pattern of bladder cancer, which is mainly related to smoking as risk factor. The correct staging of bladder cancer at time of presentation is of significant prognostic value and essential in planning therapy. The treatment and prognosis of carcinoma of urinary bladder are largely determined by the depth of tumor infiltration and extent of metastases [20] Various imaging methods including, ultrasonography (US), CT and MRI have been introduced to improve the staging accuracy of bladder cancer. US is easily available, cost effective, non-ionizing and non-invasive technique, requiring no special preparation, providing images of both the upper and lower urinary tract [21]. Despite the remarkable improvements in the diagnostic accuracy, some of the pitfalls of US for evaluation of the bladder still remain. Smaller lesions (smaller than 0.5 cm) and lesions located in the dome or bladder neck are more difficult to visualize sonographically. Tumor configuration is also an important factor; plaque-like lesions are almost certainly harder to detect than polypoid ones. In addition, accuracy in the detection of lymph node metastases remains very low [23]. The current standard pre-operative imaging modality represents contrast-enhanced computed tomography (CT). However, in up to 40% of cases, CT underestimates the disease. It has been reported that CT can only marginally differentiate between tumor stages Ta to T3a and even in cases with macroscopic invasion of perivesical fatty tissue, accuracy rates rangefrom 55-92%. In addition, regenerative and inflammatory postoperative tissue alterations after previous transurethral resection of the bladder carcinoma further impair exact local T-staging. The sensitivity for detection of lymph node metastases (48-87%) is also disappointing. MRI imaging of the urinary bladder has been investigated by many studies and most of the published reports have concentrated on the ability of MR imaging to diagnose and stage primary urinary bladder carcinoma and the benefit of contrast enhanced imaging in improvement of staging accuracy. In this study the ability of MRI to differentiate local tumor stage on stage by stage basis was assessed and compared to the confirmed pathologic staging data obtained from TUR deep muscle biopsy performed at the base of the tumor and by pathologic evaluation of resected bladder and peri-vesical tissues after total cystectomy. Our staging accuracy for fast dynamic Gd-T1WI was 91.53%, which is concurs with existing results in the literature by [24], who reported an accuracy of 92% with contrast administration. Our staging accuracy for fast dynamic Gd-T1WI were higher than the results reported by [25, 26, 27] which revealed accuracy 86%, 62% and 79% respectively, but lower than that reported in the study by [28] which revealed 95% accuracy. Our study is agreed with all previously mentioned studies in that; the overall accuracy in tumor staging improves after use of gadolinium enhanced MR imaging. For examples, the overall accuracy improved from 77.7% to 86% and from 67% to 79% respectively after use of gadolinium enhanced MR imaging. In our study overall accuracy improved from 85.6% to 91.53% after use of gadolinium enhanced MR imaging Our staging accuracy for T2WI in assessing superficial versus invasive disease was 84.75%, which increased to 89.83%after contrast administration. This accuracy results are close to the results reported by, who demonstrated overall staging accuracies of 85% for T2WI and Gd-T1WI in differentiating superficial from muscle invasive tumors and higher than that reported by, who reported that muscular infiltration is correctly staged in 54.5% by unenhanced MR imaging, the accuracy increase after use of dynamic enhanced imaging up to 59%. Our study reported 11.8% for contrast enhanced T1WI when evaluating T-stage. This is contrary to the findings of the study, which used a 0.5-T MR scanner without contrast administration and reported that, the most common staging error was underestimation in (33%) of the patients of the study. Lymph nodes in our study denoted nodal assessment with MR imaging which relies on nodal size and shows sensitivity, specificity and accuracy in detecting lymph node involvement were 75%, 98% and 94.9% respectively. These data is close to the result of, which reported sensitivity, specificity and accuracy 78%, 98% and 96%, respectively in detecting lymph node involvement. It is also close to the result demonstrated which reported sensitivity, specificity and accuracy 76%, 99% and 92% respectively. We conclude from this study that fast dynamic gadolinium enhanced MRI images appear to provide useful information for evaluating T-stage in patients with bladder cancer with 91.53% staging accuracy for fast dynamic gadolinium enhanced T1WI. It is particularly useful for differentiating T1-stage or lower tumors from T2-stage or higher tumors, with over

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stage error in 11.8% and under stage in 5.1% respectively for contrast enhanced MRI images. So, contrast enhanced MRI images could be a useful adjunct to preoperative evaluation.

Conclusion

In this study, despite small differences between the results of the MRI and pathology, DCE-MRI was found to be an accurate modality for assessment of T staging, and its routine use in bladder cancer staging causes significant improvement of diagnostic accuracy of the staging and treatment planning and hence improvement of the prognosis of patients and their survival rates. Furthermore, the use of MRI systems with higher magnetic field and imaging techniques standardized with higher resolution could further enhance the accuracy of the method. Fast dynamic gadolinium enhanced MRI images appear to provide useful information for evaluating T-stage in patients with bladder cancer with 91.53% staging accuracy for fast dynamic gadolinium enhanced T1WI. It is particularly useful for differentiating T1-stage or lower tumors from T2-stage or higher tumors. So, contrast enhanced MRI images could be a useful adjunct to preoperative evaluation.

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Conflict of interests: None.

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