ROLE OF DYNAMIC CONTRAST ENHANCED MAGNETIC RESONANCE IMAGING IN DIFFERENTIATION OF SUPERFICIAL AND INVASIVE URINARY BLADDER CANCER

By
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ABSTRACT

Background: Worldwide, bladder cancer is the ninth most common cancer, more common in men than women with high incidence in Egypt. In Egypt, bladder cancer has been the most common male cancer during the past 50 years and the 6th most common cancer in female after breast cancer, non- Hodgkin lymphoma, ovarian cancer, leukemia and colorectal cancer. Accurate preoperative staging of bladder carcinoma is the most important factor in determining the appropriate management, because the therapeutic method chosen and prognosis depend on the distinguishing between superficial and invasive tumors.

Objective: to evaluate the overall accuracy of dynamic gadolinium enhanced MRI in local staging of bladder cancer on a stage-by-stage basis and to determine the usefulness of MRI in determining superficial versus invasive disease, which is the main object of imaging of bladder cancer patients.

Patients and methods: The study was conducted at MRI unit of radiology department, Al- Hussein University Hospital at the period from July 2019 to April 2021. During the study period a total number of 59 cases of histopathology proved urinary bladder cancer were referred from urology department of Al- Hussein University Hospital, for dynamic MRI scanning aiming for T-staging of bladder cancer.

Results: 59 patients of included in this study, 54 males (91.5%) and 5 females (8.5%) with their age ranged from 43 to 76 years old. We evaluate the ability MRI to distinguish between the superficial (≤T1) and invasive (≥ T2a) tumors. On T2WI, 50 tumor were staged correctly, 5 were overstage, 4 were understage, sensitivity were 78.26%, specificity 88.89%, PPV were 86.49% and accuracy were 84.75%. On dynamic gadolinium enhanced T1WI, 53 tumor were staged correctly (89.83%), 3 were overstaged (5.08%), 3 were understaged (5.08%), yielding an overall sensitivity were 78.26%, specificity 88.89%, PPV were 86.49% , NPPV were 89.83% and accuracy were 89.83%.The overall accuracy of MRI to distinguish between the superficial (≤T1) and invasive (≥ T2a) tumors was 87.29 %.

Conclusion: Dynamic contrast-enhanced MRI scanning is helpful in the differentiation between the superficial (≤T1) and invasive (≥ T2a) tumors of bladder .

Keywords: dynamic MRI, bladder cancer.

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INTRODUCTION

Worldwide, bladder cancer is the ninth most common cancer. It is more common in men than women and its incidence rates are highest in Europe, United States, and Egypt (Ferlay et al 2013).

In Egypt, bladder cancer has been the most common male cancer during the past 50 years, representing 16.2% of male cancers, due to the etiological relationship to endemic urinary schistosomiasis. In Egyptian females, it is the 6th most common cancer after breast cancer, non-Hodgkin lymphoma, ovarian cancer, leukemia and colorectal cancer, with its frequency was 4.0%, by far exceeded by breast cancer (37.6% of female malignancies. 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 (El-Mawla et al, 2001).

PATIENTS AND METHODS

The study was conducted at MRI unit of radiology department, Al- Hussein University Hospital at the period from July 2019 to April 2021. During the study period a total number of 59 cases of histopathology proved urinary bladder cancer were referred from urology department of Al- Hussein University Hospital, for MRI scanning aiming for T-staging of bladder cancer.

All patients underwent the followings

History taking:
- Personal history and urinary tract symptomatology.
- Contraindication for MRI study: history about metallic implant lodged in patient body, like cardiac pacemaker, implanted hearing devices, metallic aneurysm clips or known metallic intraocular foreign body.

Laboratory investigations:
Including data on the serum creatinine level, to identify patients with a glomurular filtration rate (GFR) of less than 30 mL/min, for them gadolinium-based contrast agents administration carry the risk of developing nephrogenic systemic fibrosis. GFR can be calculated from the following formula described by and Cockcroft and Gault (1976):

For men: \[ \text{GFR} = \frac{(140 - \text{age}) \times \text{weight}}{(\text{Pcr} \times 72)} \]

For women: \[ \text{GFR} = \frac{(140 - \text{age}) \times \text{weight}}{(\text{Pcr} \times 85)} \]

GFR is expressed as milliliters per minute, age as years, weight as kilograms, and \( \text{Pcr} \): plasma creatinine as milligrams per deciliter.

Cystoscopy and biopsy:
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.

MRI Examination:
All MRI scans were performed at 1.5 T superconducting imager (Achieva, Philips health care, Japan) using a 16 channel pelvic phased-array coil.

-Patient care and preparation:
Metallic objects worn by the patient should be removed as well as personal effects like watches, mobiles or credit cards. The patient is reassured and the study is explained to him in brief. Optimal bladder distension was achieved by asking the patient to void two hours just before the examination and then withhold voiding desire until the end of the MRI
examination. The patient is instructed to avoid unnecessary voluntary movements within the bore of the scanner during the study to reduce motion related image artifacts.

**MRI pulse sequences:**
Both T1 and T2-weighted turbo spin echo images are obtained, followed by non contrast enhanced T1- spoiled gradient weighted image, then dynamic gadolinium enhanced T1- spoiled gradient weighted imaging according to the parameters reported in table (1).

### Table (1): Study standard MR Pulse sequences parameters.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>T1WI</th>
<th>T2WI</th>
<th>Dynamic T1WI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repetition time (TR)</td>
<td>800 msec</td>
<td>4000 msec</td>
<td>142 msec</td>
</tr>
<tr>
<td>Echo time (TE)</td>
<td>14 msec</td>
<td>120 msec</td>
<td>12 msec</td>
</tr>
<tr>
<td>Matrix</td>
<td>256x192</td>
<td>256x192</td>
<td>256x192</td>
</tr>
<tr>
<td>Field of view (FOV)</td>
<td>375 mm</td>
<td>200 mm</td>
<td>375 mm</td>
</tr>
<tr>
<td>Slice thickness</td>
<td>5 mm</td>
<td>3 mm</td>
<td>5 mm</td>
</tr>
<tr>
<td>Inter-slice gap</td>
<td>1 mm</td>
<td>1 mm</td>
<td>1 mm</td>
</tr>
<tr>
<td>Acquisition time (minutes: seconds)</td>
<td>3:50</td>
<td>3</td>
<td>0.16</td>
</tr>
<tr>
<td>Flip angle</td>
<td>-</td>
<td>-</td>
<td>70</td>
</tr>
</tbody>
</table>

T2-weighted MR Imaging was performed in axial, sagittal, and coronal planes. Axial T1-weighted images was performed in all cases with additional sagittal or coronal images performed according to the tumor orientation, reviewed on T2-weighted 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-Wighted imaging was performed 5 minutes after the dynamic imaging with the same parameters of the previously used conventional T1-Weighted sequence.

**MRI diagnostic criteria:**
The MRI images were evaluated based mainly on T2-weighed images and dynamic contrast enhanced T1-weighed images criteria described in deferent previous studies like Tanimoto et al, 1992, Hayashi et al, 2000 and Tekes et al, 2005 as follow.

**T1-stage:**

**T1-weighted images:** The contour of urinary bladder wall at the base of the tumor appears regular and surrounded by clear peri-vesical fat (this finding is not specific for T1-stage but also seen in T2.a and T2.b stages, where the depth of tumor infiltration into the bladder muscle coat cannot be assessed).

**T2-weighted images:** show a mass lesion surrounded by normal outer bladder muscle wall, seen as unbroken regular low signal intensity band.

**Dynamic contrast enhanced MRI:** shows enhanced tumor and adjacent mucosa surrounded by unbroken regular hypo-intense muscular layer.

**T2.a-stage:**

**T1-weighted images:** like T1-stge tumor, the contour of urinary bladder wall at the base of the tumor appears regular and surrounded by clear peri-vesical fat.

**T2-weighted images:** show a mass lesion surrounded by irregular inner contour of unbroken hypo-intense muscular layer with regular outer contour.

**Dynamic contrast enhanced MRI:** shows enhanced tumor and adjacent mucosa surrounded by unbroken hypo-intense muscular wall with irregular inner contour of muscle coat.
**T2.b stage:**
- **T1-weighted images:** like T1-stge and T2.a-stage tumors, the contour of urinary bladder wall at the base of the tumor appears regular and surrounded by clear peri-vesical fat.
- **T2-weighted images:** show a mass lesion surrounded by disrupted hypo-intense muscular layer without gross peri-vesical fat infiltration, denoted by regular interface between bladder wall and peri-vesical fat.
- **Dynamic contrast enhanced MRI:** show a mass lesion surrounded by disrupted hypo-intense muscular layer with smooth regular outer contour and clear peri-vesical fat.

**T3.b stage:**
- **T1-weighted images:** the contour of urinary bladder wall at the base of the tumor appears irregular, shaggy with streaky areas of the same signal intensity as the bladder wall muscle extending to the peri-vesical fat.
- **T2-weighted images:** shows a mass lesion disrupting the surrounding hypo-intense muscular layer, showing irregular shaggy outer border or streaky areas of the same signal intensity extending to the peri-vesical fat.
- **Dynamic contrast enhanced MRI:** shows enhanced tumor extending into peri-vesical fat.

**T4.a-stage:**
- **T1-weighted images:** shows a mass lesion contiguous with the contour of adjacent pelvic organ (this finding is not specific due to lack of signal differentiation between the tumor and invaded structure on T1-weighted images), that the tumor may be in contact with an adjacent organ without necessarily invading it.
- **T2-weighted images:** shows a mass lesion disrupting the surrounding hypo-intense muscular layer, extending to adjacent pelvic organ.
- **Dynamic contrast enhanced MRI:** shows enhanced tumor extending to adjacent pelvic organ.

**T4.b-stage:**
- **T1-weighted Images:** shows a mass lesion contiguous with the contour of abdominal wall or pelvic sidewall (this finding is also not specific due to lack of signal differentiation between the tumor and intermediate muscle signal on T1-weighted images).
- **T2- weighted images:** shows a mass lesion disrupting the surrounding hypo-intense muscular layer, extending to the abdominal or pelvic side walls.
- **Dynamic contrast enhanced MRI:** contrast enhanced tumor, extending to the abdominal or pelvic side walls.

**Lymph nodes:** were considered abnormal if the long axis was 10 mm or more.

**RESULTS**

59 patients were included in this study, 54 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%).

Gross painless hematuria was the most common clinical presentation, encountered in 54 patient (91%), followed by bladder irritability symptoms like frequency, urgency, dysuria and pyuria.

<table>
<thead>
<tr>
<th>T2WI</th>
<th>Histopathological stage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T1</td>
</tr>
<tr>
<td>T1</td>
<td>18</td>
</tr>
<tr>
<td>T2</td>
<td>5</td>
</tr>
<tr>
<td>T3</td>
<td>0</td>
</tr>
<tr>
<td>T4</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>23</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Correct stage</th>
<th>Under stage</th>
<th>Over stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>42</td>
<td>8</td>
</tr>
<tr>
<td>%</td>
<td>71.19</td>
<td>13.56</td>
</tr>
</tbody>
</table>
Table (2): Staging results of T2WI on stage by stage basis.

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 muscle, 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 all the tumors has intermediate signal intensity, higher than bladder wall, that the depth of tumor infiltration into the bladder wall can be assessed. On T2WI the study has revealed 22 patients with stage T1, 10 patients with stage T2, 20 patients with stage T3, and 7 patients with stage T4.

- **Gadolinium enhanced dynamic T1WI:**
  On 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 maintained its normal 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.

On T2WI tumor were staged correctly in 42 cases of 59 patients 71.19 %, overstaged in 9 cases of 59 patients 15.25 %, understage were 8 cases of 59 patients 13.56 %, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy were 66.02%, 91.11%, 67.06%, 82.55% and 85.60%.

The final pathologic result and staging
Urinary bladder carcinomas were pathologically proven in all patient 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 assesses of the infiltration of adjacent peri-vesical organ and excised pelvic lymph nodes.

Transitional cell carcinoma were encountered in 34 of 59 cases (57.63 %), squamous cell carcinoma were encountered in 21 patients (35.59 %), mixed transitional and squamous cell carcinoma were encountered in 3 cases (5.1%) and adenocarcinoma were 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.

On T2WI tumor were staged correctly in 42 cases of 59 patients 71.19 %, overstaged in 9 cases of 59 patients 15.25 %, understage were 8 cases of 59 patients 13.56 %, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy were 66.02%, 91.11%, 67.06%, 82.55% and 85.60%.

On dynamic gadolinium T1WI tumor were staged correctly in 49 cases of 59 patients 83.1%, overstaged 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%.

Superficial versus invasive tumors:
We evaluate the ability MRI to distinguish between the superficial (≤T1) and invasive (≥ T2a) tumors.

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Figure (2): 60 years old male patient presented with dysuria. MRI revealed urinary bladder anterior wall mass lesion. The mass shows T1WI signal isointense to muscle with regular outer contour and clear peri-vesical fat (Image A). The lesion displays heterogeneous increased T2WI signal (image B), and early marked T1 post-contrast enhancement (image C). The peripheral hypo-intense muscle coat at the base of the lesion appears attenuated but still intact, showing irregular inner contour and regular outer contour on both T2WI and T1-post contrast with no gross extra-vesicle extension. No pelvic lymphadenopathy. The distal right ureter appear dilated secondary to distal ureteric obstructive stone (not shown).

Histopathology results: Grad II TCC , infiltrating lamina propria and deep muscle layer. Correct MRI staging on both T2WI and post-contrast T1WI corresponding to (T2.a-stage).

1: Dilated right ureter.  2: Bladder mass.  3: Foley’s catheter

Figure (3): 55 years old male patient presented with haematuria. MRI revealed solid mass lesion at the urinary bladder dome. The lesion shows T1 signal isointense to muscle (Image A), heterogeneous intermediate T2WI signal (Image B) and marked heterogeneous T1WI post-contrast enhancement (Image C). No peripheral hypo-intense outer muscle layer could be seen at the base of the lesion neither on T2WI nor post-contrast T1WI. Exophytic extra-vesical extension of the lesion is seen at the bladder dome with irregular outer contour. No pelvic lymphadenopathy. No infiltration to surrounding pelvic structures. Histopathology results shows Grad II-III transitional cell carcinoma infiltrating the muscle layer and peri-vesical fat. Correct staging on both T2WI and post-contrast T1WI corresponding to (T3.b-stage). 1: Bladder mass 2: symphysis pubis 3: Prostate 4: Seminal vesicles 5: Rectum.

On T2WI, 50 tumor were staged correctly, 5 were overstage, 4 were understage, sensitivity were 78.26%, specificity 88.89%, PPV 81.82% NPPV were 86.49% and accuracy were 84.75%.

On gadolinium enhancement T1WI, 53 tumor were staged correctly (89.83%), 3 were...
overstaged (5.08%), 3 were understaged (5.08%), yielding an overall sensitivity were 78.26%, specificity 88.89%, PPV 81.82%, NPV were 86.49% and accuracy were 89.83%.

The overall accuracy of MRI to distinguish between the superficial (≤T1) and invasive (≥ T2a) tumors was 87.29%.

**Lymph node staging:**

MRI images revealed 7 patients of 59 patient with enlarged pelvic lymph nodes with their diameter exceeding 10 mm and 52 patients who were free of lymph node 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 histopathologically proved neoplastic lymph nodes with sensitivity, specificity, PPV, NPV and accuracy were 75%, 98%, 85%, 96% and 94.9%.

**DISCUSSION**

The correct staging of bladder cancer at time of presentation is a 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 (Bostrom et al, 2010).

Imaging studies in bladder cancer are used in an attempt to improve diagnostic value by providing information regarding wall invasion, extra-vesical spread, ureteric obstruction and extension of the tumor to pelvic lymph nodes. There are frequent studies compare the accuracy of many clinical and radiological tools used for the assessment of bladder cancer. Various imaging methods including intravenous urography, ultrasonography, CT and MRI have been introduced to improve the staging accuracy of bladder cancer.

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 benefit of contrast enhanced images 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.

In our study T2WI tumor were staged correctly in 42 cases of 59 patients 71.19%,
overstaged in 9 cases of 59 patients 15.25 %, understage were 8 cases of 59 patients 13.56 %, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy were 66.02 %, 91.11 %, 67.06 %, 82.55 % and 85.60 %. The overall staging accuracy of T2WI was 85.6 %, which is higher than the results demonstrated by Tanimoto et al (1992), Barentsz et al (1999), Eldaiasty et al (2003) and Takeuchi et al (2009) which demonstrate 58 %, 67 %, 77.7 % and 67 % accuracy respectively.

Our staging accuracy for dynamic Gd-T1WI was 91.53 %, which is concurs with existing results in the literature by Scatoni et al (1996), who reported an accuracy of 92 % with contrast administration. Our staging accuracy for fast dynamic Gd-T1WI were higher than the results reported by Eldaiasty et al (2003), Tekes et al (2005) and Takeuchi et al (2009) which revealed accuracy 86 %, 62 % and 79 % respectively, but lower than that reported in the study by Fernandez et al (2001) 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, in Eldaiasty et al (2003) and Takeuchi et al (2009), 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 with overall accuracy of MRI in the study 87.29 %. This accuracy results are close to the results reported by Tekes et al (2005), 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 Scatoni et al (1996), 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 staging accuracy for T2WI in assessing superficial versus invasive disease is less than that reported by Rabie, et al (2016), who reports 97 % accuracy of MRI in differentiating of superficial tumours from invasive tumours.

Our study reported 15.25 % overstaging for T2WI and 11.8 % for contrast enhanced T1WI when evaluating T-stage. This is contrary to the findings of the study by Buy et al (1988), who 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. Tekes et al (2005) reported that, overstaging was the most common error in (32 %) of patients of the study when evaluating T stage.

In our study nodal assessment with MR imaging which relies on nodal size 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 Tekes et al (2005), which reported sensitivity, specificity and accuracy 78 %, 98 % and 96 %, respectively in detecting lymph node involvement. It is also close to the result demonstrated by Willem et al (2004), which reported sensitivity, specificity and accuracy 76 %, 99 % and 92 % respectively.

CONCLUSION

We conclude from this study that, dynamic gadolinium enhanced MRI images appear to provide useful information for evaluating T-stage in patients with bladder cancer with 85.6 % staging accuracy for non enhanced MRI images and 91.53 % for dynamic gadolinium enhanced T1WI. It is particularly useful for differentiating T1-stage or lower tumours from T2-
stage or higher tumors, with over stage error in 15.25% and under stage 13.56 for non-enhanced MRI images (T2WI), reduced to 11.8% and 5.1% respectively for contrast enhanced MRI images. So, contrast enhanced MRI images could be a useful adjunct to preoperative evaluation.

REFERENCES


