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Clinical-Bladder Cancer

Value of multiparametric magnetic resonance imaging for local staging of invasive urinary bladder tumours.

Eline H. Huele[a], Paul W. Veenboer[a], Frank J. Wessels[b], Trudy N. Jonges[c], Richard P. Meijer[a,*]

[a] *Department Oncological Urology, University Medical Center Utrecht, The Netherlands*
[b] *Department Radiology, University Medical Center Utrecht, The Netherlands*
[c] *Department Pathology, University Medical Center Utrecht, The Netherlands*

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Abstract

Background: Initial tumour staging in bladder cancer mainly relies on the histo-pathological outcome of the transurethral bladder tumour resection (TURBT) and imaging by means of a CT-scan (CT-intravenous urography; CT-IVU). The reported risk of understaging varies from 24-50%. To further improve the the evaluation of depth of invasion of the bladder tumour the application of magnetic resonance imaging (MRI) may be useful. To substantiate the additional value of this imaging modality the present observational study was designed.

Study design: This is a prospective observational study to analyse bladder tumour staging with multiparametric magnetic resonance imaging (mpMRI) in patients with a known bladder tumour, who are planned for radical cystectomy.

Study population: Patients with an invasive bladder cancer who are planned for radical cystectomy.

Intervention: Patients were accrued during their visit to the outpatient department of urology. They underwent routine cystoscopy, laboratory tests (including serum Creatinin) and CT-IVU investigations and subsequently a mpMRI.

Main study parameters/endpoints: To demonstrate the value of mpMRI in the initial staging of bladder tumours using radiological bladder tumour stage (T-stage) based on mpMRI and pathological bladder tumour stage based on 'whole-mount' histo-pathology after radical cystectomy.

Results: Thirty-seven participants with known bladder tumours underwent mpMRI and subsequent cystectomy. After mpMRI 10 participants were diagnosed with non-muscle-invasive bladder cancer (NMIBC) and 27 participants with muscle-invasive bladder cancer (MIBC). In the 'whole-mount' pathology results 12 participants had NMIBC and 25 participants had MIBC. We found a sensitivity and specificity of 0.88 en 0.58 respectively, for the evaluation of MIBC. The positive and negative predictive value were 81% and 70% respectively. The diagnostic accuracy of mpMRI to differentiate between NMIBC and MIBC was 78%.

Conclusions: We found a sensitivity of 88% and a specificity of 58% for mpMRI to discriminate NMIBC from MIBC.

Keywords: Bladder cancer; Tumour staging; Multiparametric MRI; Whole-mount pathology

1. Introduction

Bladder cancer is the tenth most common cancer worldwide [1]. 7556 cases of bladder cancer were reported by The Dutch Cancer registry in the Netherlands in 2021 [2]. Bladder cancer is subdivided into two main groups; non-muscle-invasive bladder carcinoma (NMIBC), which is confined to the urothelium and/or lamina propria of the bladder, and muscle-invasive bladder cancer (MIBC), which by definition invades the detrusor muscle [3]. It is important to differentiate between these two stage groups, as the treatment options and prognosis differ significantly [4,5]. At diagnosis about 25% of all bladder cancer patients present with muscle-invasive disease [6].

After initial diagnosis, usually by cystoscopy, transurethral resection of the bladder tumour (TURBT) should be performed as both a diagnostic and therapeutic procedure. This tumour resection should include detrusor muscle to

*Corresponding authors.
E-mail address: rmeijer6@umcutrecht.nl (R.P. Meijer).

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determine if the tumour is muscle-invasive and if the entire lesion has been removed [6,7]. Initial tumour staging in bladder cancer mainly relies on the histopathological outcome of the TURBT and imaging by means of a CT-intravenous urography (CT-IVU). Clinical staging is of great importance in the diagnostic work up of bladder cancer because of the difference in treatment and prognosis between NMIBC and MIBC. Nevertheless a discrepancy between initial clinical stage and final pathological stage after cystectomy often occurs, the reported risk of understaging varies from 24-50% [8–11]. This underlines the need for a more accurate tool for initial local staging of bladder tumours.

In recent years reports emerged suggesting that magnetic resonance imaging (MRI), could be a superior mode of imaging for local staging of bladder tumours. Especially multiparametric magnetic resonance imaging (mpMRI), which includes T1- and T2 weighted sequences and functional sequences, such as diffusion weighted and dynamic contrast-enhanced MRI, has been proposed to stage tumours more accurately as the specific components of the bladder wall are visualized in more detail [12–15]. Although the CT-IVU may give a reasonable impression of the tissue surrounding the bladder, the presence of hydronephrosis and potential lymphadenopathy, it is insufficient to adequately determine whether the primary bladder tumour has invaded the detrusor muscle [16]. In recent studies mpMRI appears to demonstrate high sensitivity and specificity in discriminating between NMIBC and MIBC [4,17]. The rise of mpMRI in clinical staging of bladder tumours led to the need to standardize the reporting. The Vescial Imaging Reporting and Data System (VI-RADS) make up a systematic approach to describe bladder mpMRI and the depth of tumour invasion in particular [12].

The aim of our study is to demonstrate the additional value of multiparametric 3T-MRI in the initial staging of bladder tumours. We conducted a prospective observational study to investigate bladder tumour staging with mpMRI in patients with a known bladder tumour, who were planned for radical cystectomy.

2. Material and methods

2.1. Data collection

Medical Ethical Committee approval was obtained (NL49868.041.16; METC-protocolnumber 17-847/D). Patients eligible for the study were identified between October 2018 and February 2021. Inclusion criteria were: 1) patients with an invasive bladder tumour who were scheduled for radical cystectomy at the University Medical Center Utrecht (UMCU), 2) renal function, determined by estimated creatinine clearance (CKD-EPI), had to be $\geq$ 30 mL/min. Patients were excluded from the study when they met exclusion criteria for MRI following the protocol of the radiology department of the UMCU, when they received prior radiation therapy on the pelvic region or when they were not able to sign a written informed consent.

In order to reject the null hypothesis that the accuracy is 75%, a sample size of 40 patients will be sufficient to obtain 79% power for an exact binomial test with two-sided significance level (alpha) of 0.10, if the true accuracy is 90%. Thus, it was decided that 40 patients would be included.

Before the MRI examination an intravenous cannula was placed and during the MRI 0.1mL/kg Gadovist® is administered once to perform a dynamic contrast-enhanced scan. An estimation of depth of invasion of the bladder tumour was made in three directions based on the 3TMRI-scan, including T2-weighted images, diffusion-weighted magnetic resonance imaging and dynamic contrast enhanced magnetic resonance imaging. The mpMRI-scans were evaluated by one of two dedicated radiologists with expertise in the field of pelvic MRI-scanning and over 5 years of experience at the start of the study. Tumour size, tumour location, invasion of the lamina propria, muscle-invasion, extravesical extension, whether it was a solitary or multiple lesion(s) and hydronephrosis were evaluated on mpMRI. On the T2 weighted images muscle-invasiveness is evaluated by looking for interruption of low signal intensity (SI) muscularis propria. In the dynamic contrast enhanced images the muscularis propria does not enhance as early as the inner layer consisting of urothelium and lamina propria, tumour enhances early in a similar fashion as this inner layer. Extension of early enhancing tumour in the low SI muscularis propria is assessed. On diffusion weighted images the tumour appears hyperintense while the muscularis propria appears as an intermediate signal intensity line. A disruption of this line by the hyperintense tumour is indicative of muscle-invasion. The technical parameters of MRI imaging are shown in Table 1.

A radical cystectomy with extended lymph node dissection was performed and 'whole-mount' histopathological evaluation was carried out on the cystectomy-specimen. The histopathological report was standardized to specify tumour location, multifocality, tumour grade, depth of tumour invasion and the presence of extravesical extension

Table 1
Technical parameters of multiparametric MRI.

Parameters setting at 3.0T	T2W	DWI	DCE
TR (ms)	2000-6000	8200	4.6
TE (ms)	110	77	4.6/1.4
Flip angle (degree)	90	90	10
FOV (cm)	33	32	42
Matrix	660 × 791	168 × 135	336 × 273
Slice thickness (mm)	3	4	1
Slice gap (mm)	0	0	0
B values		0-800 s/mm^2	

T2W = T2 weighted imaging, DWI = diffusion-weighted imaging, DCE = dynamic contrast-enhanced imaging, TR = repetition time, TE = echo time, FOV = field of view.

of the tumour. This 'whole-mount' evaluation of the cystectomy-specimens was done by a dedicated uro-pathologist.

We collected information on radiological bladder tumour stage on MRI (TNM classification) and pathological tumour staging based on 'whole-mount' histopathology after radical cystectomy.

2.2. Analysis

The extent of the bladder tumour defined by cT-stage based on MRI scan was compared with the pT-stage found at histopathologic examination, the 'gold standard'. Sensitivity and specificity, and negative and positive predictive values, were determined by two by two tables. To depict the study population, descriptive statistics will be used. Statistical Package for the Social Sciences (SPSS) 20.0 was used for statistical computation.

3. Results

Forty-four participants were included in this study. Seven participants were excluded for the various reasons described in Table 2.

Therefore, thirty-seven participants were included for analysis. After mpMRI 10 participants were diagnosed with NMIBC and 27 participants with MIBC. After 'whole-mount'-histopathological examination of the cystectomy specimens, 12 participants had NMIBC and 25 participants had MIBC as described in Table 3. For the evaluation of muscle-invasive disease, the sensitivity and specificity were 88% and 58%, respectively. The positive and negative predictive value were 81% and 70% respectively. T-stage divided by histopathological and radiological examination is shown in Table 4. In the distinction between NMIBC and MIBC multiparametric 3T-MRI showed a diagnostic accuracy of 78%. When the distinction was made by T-stage the overall accuracy was 43%. In the histopathological examination after cystectomy there was no (residual) tumour found in 4 participants. 7 MRI-scans were evaluated by the radiologist as 'no visible tumour'. However, there were only 2 participants who both in radiologic examination and histopathologic examination had no residual bladder tumour.

Nineteen of the 37 included patients underwent a form of neoadjuvant therapy, including chemotherapy and immunotherapy as described in Table 5. In addition, all 37 participants underwent TURBT before mpMRI. The mean time interval between TURBT and mpMRI was 87 days. The interval ranged between 20 and 251 days. In patients, who received neoadjuvant therapy, a range of 22 − 251 days was observed, for patients who received no prior treatment the interval was 20 − 172 days.

Table 2
Reasons for exclusion.

Reason for exclusion	Number of participants
Nephrostomy catheters on both sides making the MRI inconclusive due to an empty bladder	1
Prostate cancer instead of bladder tumour	1
No mpMRI prior to cystectomy	2
Not eligible for surgery due to metastatic disease	1
Patient decided to withdraw	1
Prior radiation therapy on the pelvic region	1

4. Discussion

This is a prospective study to evaluate the value of mpMRI for bladder tumours with 'whole-mount' pathology of cystectomy specimens. To our best knowledge this is the first study in which 'whole-mount' histology was used for evaluation of the diagnostic value of mpMRI in bladder cancer. We found a sensitivity of 88% and a specificity of 58% for mpMRI to discriminate NMIBC from MIBC. We focused on the distinction between NMIBC and MIBC on mpMRI, as this determines the possible treatment options and prognosis for patient with a bladder tumour and is consequently clinically most relevant [4,5].

Cornelissen et al. performed a systematic review to determine the value of mpMRI in the initial staging of bladder tumours. They included 20 articles with a total of 1724 patients and found a pooled sensitivity and specificity of 0.92 and 0.88 respectively, to differentiate between NMIBC and MIBC. This was a heterogeneous group of studies,

Table 3
NMIBC vs MIBC divided by histopathological and radiological examination.

	PA − NMIBC (pTa/pT1/CIS or no residual tumour)	PA- MIBC (pT2/pT3/pT4)	Total
MRI − NMIBC (cTa/cT1 or no visible tumour)	7	3	10
MRI − MIBC (cT2/cT3/cT4)	5	22	27
Total	12	25	37

PA = Whole mount histopathology; CIS = carcinoma in situ.

Table 4
T-stage divided by histopathological and radiological examination.

cT-stage MRI	pT-stage 'whole-mount' histopathologic examination					
	Ta/CIS	T1	T2	T3	T4	No (residual) tumour
T1	0	2	0	0	0	1
T2	0	3	6	0	0	1
T3	1	0	5	6	4	0
T4	0	0	0	1	0	0
No tumour	1	1	2	1	0	2

CIS = carcinoma in situ.

which included cystectomy, as well as TURBT or both as a reference standard. They conclude that mpMRI is effective for making the distinction between NMIBC and MIBC, but not for determining T-stage [17]. In addition, Woo et al. and Huang et al. performed a meta-analysis of ≥1.5T MRI for identifying MIBC and found similar sensitivity and specificity and concluded that 3T MRI devices showed higher specificity than 1.5T scanners [4,5].

In our cohort overstaging of the T-stage of the tumour on MRI was seen more often than understaging. In several cases it was difficult to discriminate a bladder tumour from inflammatory changes post-TURBT, this was also reported by Saksena and Kim and thought to be a cause of overstaging [13,18].

The implementation of mpMRI in the clinical staging of bladder tumours has led to the Vesical Imaging Reporting and Data System (VI-RADS), with the purpose to standardize radiology reports especially in discriminating a muscle-invasive tumour from a superficial one [12]. In a systematic review and meta-analysis which included 1770 patients across 6 studies a pooled sensitivity and specificity of 0.83 and 0.90 was seen for diagnosing MIBC using the VI-RADS reporting system. In addition, higher sensitivity was seen in studies using only 3T MRI scanners. When applying VIRADS, a 5 point score is generated. An important factor was the VIRADS-cutoff score to determine MIBC, with a cutoff score of ≥ 3 correlating with a sensitivity and specificity of 92% and 84%, while a cutoff score of ≥ 4 to 72% and 96%, respectively. Which is a difference inherent to a diagnostic test. In the included studies only transurethral resection or a combination of TURBT and cystectomy was used, this could have led to understaging [19]. Bichetti et al. included 139 patients with suspected bladder tumours who underwent TURBT within 6 weeks after mpMRI. MpMRI-scans were evaluated by one experienced and one less experienced radiologist. When a VIRADS-cutoff score ≥ 3 was used to determine muscle-invasion a sensitivity and specificity of 93% and 80% respectively was found for experienced readers and 95% and 73% respectively for the less experienced radiologist. When the VIRADS-cutoff was changed to ≥ 4 a sensitivity and specificity of 83% and 92% for experienced radiologist and 83% and 86% for less experienced readers was found [20]. Similarly, in 231 patients a sensitivity and specificity of 91.9% and 91.1% was seen when a VIRADS-cutoff value of ≥ 3 was used by Del Giudice et al [21]. A sensitivity and specificity of 84.1% and 92.3% respectively was seen in 331 patients who underwent mpMRI and TURBT within one week with a VIRADS-cutoff of ≥3. 90 of these patients underwent a re-TURBT because pathological outcome revealed a high grade Ta or T1 tumour. When these pathological results were used a sensitivity and specificity of 89.9% and 90.1% were found using a VIRADS-cutoff ≥ 2 [22].

Table 5
Number of patients who underwent neoadjuvant therapy.

Neoadjuvant therapy	Number of patients
Chemotherapy	14
Immunotherapy	5

Furthermore, the timing of mpMRI after transurethral resection could also hamper adequate MRI-staging due to artefacts after transurethral biopsy that can appear as a bladder tumour. Nakamura et al. included 23 patients who underwent mpMRI after TURBT and compared the results to pathology findings after a second TURBT. The accuracy of differentiating residual bladder cancer after a second TURBT was 53% in T2-weighted MRI, 50% in dynamic contrast-enhanced MRI and 67% in diffusion-weighted MRI [23]. In our cohort al patients underwent mpMRI after transurethral biopsy. The aim was to examine the additional value of mpMRI in initial bladder tumour staging by comparing mpMRI results with 'whole-mount' pathology results. This required patients with known invasive bladder tumours which entailed histopathological evidence obtained by transurethral biopsy. In one patient the bladder tumour was scored as T2 after mpMRI, while the 'whole-mount' pathology showed no tumour, however on multiple sites bladder inflammation was described. In the systematic review, all included studies but one examined mpMRI before TURBT or cystectomy. They conclude that it cannot be determined if the findings can be generalized to patients who underwent mpMRI after TURBT [19]. Panebianco et al. advise MRI examination to take place before or at least two weeks after TURBT [12]. In our cohort the mean time interval between TURBT and MRI was 87 days. The shortest interval was 20 day, therefore al patients were

more than two weeks post-TURBT before undergoing mpMRI.

In addition, 19 of the 37 included patients underwent neoadjuvant therapy before mpMRI. 14 patients were treated with chemotherapy and 5 patients underwent immunotherapy previously. This could furthermore influence the diagnostic accuracy of mpMRI in differentiating NMIBC from MIBC, since chemotherapy and chemoradiation can provoke inflammatory and fibrotic changes to the bladder [24]. When participants in this cohort where divided by whether they underwent neoadjuvant therapy the numbers where too small to draw any conclusions. Further research is warranted.

Previous studies have concluded that clinical staging of bladder tumours is not always accurate, transurethral biopsy does not provide information about important aspects of staging such as metastasis and extravesical extension of tumour [25]. Ficarra et al. analyzed 156 patients retrospectively and found that 43% of patients clinically diagnosed with a T1 tumour to have ≥T2 tumour on pathological examination after radical cystectomy [26]. This was also the case for Dutta et al. who conducted research in 78 patients clinically diagnosed with NMIBC, who underwent cystectomy because of lack of response to intravesical therapy, high grade tumour, multifocal disease, suspicion of invasive disease based on radiologic finding or severe symptoms, where 40% of patients proved to be under staged. However this also included patients who did not have detrusor muscle in their pathology findings after TURBT [10]. Shariat et al. examined 778 patients with urothelial carcinoma, where the clinical stage was determined by transurethral biopsy and the pathology results after pelvic lymphadenectomy with 'en bloc' radical cystectomy. In 42.3% patients were upstaged after cystectomy, while 22.1% proved to have a lower T-stage in pathological findings after cystectomy [8].

These findings show the need for a more accurate tool to clinically stage bladder tumours. A possible benefit of mpMRI in clinical staging, when the diagnostic accuracy is proven adequate, is that it could render a transurethral resection of the tumour redundant, and cystectomy could be the primary choice. Which in addition would prevent the chance of tumour spill. Moreover, mpMRI may also be used to monitor treatment response after radiotherapy or chemotherapy [14].

4.1. Limitations

The limited number of participants prevents us from drawing definite conclusions on the added value of mpMRI in patients with a known bladder tumour. In comparison to earlier studies the relative low specificity found in this cohort might be attributed to the small number of participants with NMIBC on final pathological examination after cystectomy. To optimally evaluate the value of mpMRI in NMIBC, the current group of patients with NMIBC, who underwent mpMRI and subsequently cystectomy was too small.

5. Conclusion

In this prospective study to evaluate the value of mpMRI for bladder tumours with 'whole-mount' histopathology of cystectomy specimens, we found a sensitivity of 88% and a specificity of 58% for 3T-mpMRI to discriminate NMIBC from MIBC. However due to the limited number of patients and mpMRI in the post-TURBT and neoadjuvant treatment setting these results need to be interpreted cautiously.

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