

# The influence of TURBT on staging of bladder cancer

## Abstract

**Introduction:** Bladder cancer is common, expensive and the number of cases rising with increased survival in the elderly population. Most centres do CT scan at the point of investigation and some will carry this out along with MRI scan to have better local staging once the diagnosis of invasive cancer is made. Any surgical procedure would have a likelihood of influencing local staging and this is a common belief without any evidence.

**Methods:** We have retrospectively analyzed our data to see where the truth lies. We have compared the final pathology of 236 radical cystectomy patients to the staging reports of 241 CT scans and 65 MRI scans.

**Results:** We have ascertained accuracy, sensitivity and specificity and whether they were influenced by the timing of the TURBT. There was no significant difference between CT and MRI and the timing of the TURBT.

**Conclusion:** This is the first report in the literature outlining the non-influence of TURBT. We accept the limitation due to the retrospective nature, small sample size and variability of the biology of bladder cancer.

**Keywords:** bladder cancer, staging, MRI, CT, TURBT

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## Introduction

Bladder cancer is a common worldwide problem.<sup>1-3</sup> It is expensive and fraught with problems regarding optimal staging and management. The vast majority are transitional cell cancers and 70% present as superficial disease with a very low chance of metastasis and 30% present as muscle invasive with a high risk of death from distant metastasis.<sup>4</sup> Metastases develop in 25% of muscle invasive tumors and 50% of tumors invading the perivesical fat. Neo adjuvant and adjuvant chemotherapy regimens may improve the outcome for muscle invasive disease and metastatic disease. So, accurate staging is crucial, especially to avoid radical surgery in incurable patients.<sup>5</sup> Prognosis has not improved<sup>3,5,6</sup> for muscle invasive bladder cancer<sup>7,8</sup> implying that it should be treated earlier in the cancer pathway.<sup>8</sup> It is one of the most expensive cancers due to surveillance requirement of non muscle invasive bladder cancer and the high recurrence rate.<sup>9,10</sup> The patient has a lifelong increased risk of cancer along the whole of the urothelial tract.<sup>11</sup> The current accepted pathway for bladder cancer patients is to have a flexible cystoscopy, then a TURBT as a first intervention to diagnose grade and stage. This is the treatment for superficial NMIBC. But, because it cannot assess the depth of wall invasion or whether tumour extends beyond the wall, the role of TURBT is controversial as it has been proposed that timing of this can affect accuracy of staging.<sup>4,11,12</sup> Imaging is then needed for local and distant staging for muscle invasive bladder cancer patients will then need surgery or radiotherapy. For MIBC the best cross sectional imaging modality remains to be determined in order to establish the subsequent management.<sup>4,13</sup> It was originally held that CT and MRI were of equal but of limited use.<sup>14,15</sup> Imaging can be inaccurate causing inappropriate treatment and/or delays. Few studies have investigated this. CT does not allow the confident diagnosis of flat lesions, lesions at bladder base or recurrence from vesical inflammation after both intravesical chemotherapy and post TURBT scarring.<sup>15</sup> CT is not very accurate at T staging as it cannot depict the individual layers of the wall<sup>16</sup> although some have yielded better results<sup>17</sup> but it is good for detection with hematuria.<sup>11,15,18,19</sup> Although CT is probably not so definitive for localized disease PET CT is useful for metastatic

disease.<sup>4</sup> However, the consensus is that MRI is superior to CT for T staging.<sup>20,21</sup> MRI imaging is considered superior to CT for T staging because of its intrinsic high soft tissue contrast, sub millimeter spatial resolution and direct multi planar imaging capabilities.<sup>11,20,21</sup> to determine depth of invasion.<sup>22</sup> However, there is a chemical shift artifact from differences in the resonance frequencies of protons in water and fat causing black and bright bands along interfaces with bladder wall and this can impair the identification of cancer.<sup>22</sup>

DWI is better than conventional MRI<sup>23,24</sup> for T staging particularly differentiating T1 from T2 and higher.<sup>25</sup> ADC can also predict grade.<sup>25</sup> this is still evolving.<sup>15</sup> The greatest problem for all methods is over staging and dynamic MRI is no exception.<sup>26</sup> However, the potential superiority of MPI is further strengthened as DWI differentiates metastatic nodes from non involved nodes.<sup>27</sup> and has good reproducibility amongst radiologist.<sup>26</sup> Tumor size and ADC can determine both stage and grade.<sup>28</sup> DCE can distinguish between residual tumor and neo adjuvant chemotherapy effects.<sup>29</sup> However, despite apparent advantages, there remains the problem of over staging being the most frequent and longstanding error.<sup>14</sup> This is due to a partial volume effect at tumor-wall interface, a thin bladder makes differentiation of muscle layers intrinsically difficult and can also due to overdistension.<sup>30</sup> Further, perivesical inflammation in part due to intra vesical medication and TURBT.<sup>11,22,24</sup> and reactive nodes,<sup>20,29,32-34</sup> radiation and surgery may cause prolonged nonspecific thickening of the bladder and are difficult to distinguish from tumor on imaging.<sup>11</sup> Intra luminal clot and stones can also cause false positives.<sup>4</sup>. In addition, staging mistakes occur as MRI can understate as we see that 30% of MIBC are initially diagnosed as NMIBC.<sup>35,36</sup> This is due to chemical shift artifact and microscopic invasion into muscle or fat or adjacent organs.<sup>30</sup> TURBT is problematic as it can seed tumor cells.<sup>37</sup> Further, it delays radical treatment in MIBC.<sup>35,37-39</sup> One would like to separate superficial from invasive tumors at diagnosis This could save time, costs and improve outcomes. We have tried to elucidate whether a TURBT before imaging is more accurate than imaging after a TURBT which is described as being confounded by staging errors<sup>12</sup> (Table 1).

**Table 1** TNM stage classification of bladder cancer

Tx	primary tumour cannot be assessed; information not known
T0	no evidence of primary tumour
Ta	Non invasive papillary carcinoma
Tis	Non invasive flat carcinoma, also called flat carcinoma in situ. This means that the disease is still localized, or contained within the urothelium layer of the bladder wall. Cancer cells have not invaded the deeper layers of bladder wall tissue.
T1	the tumour has grown from the layer of cells lining the bladder into the connective tissue below. It has not grown into the muscle layer of the bladder.
T2	tumor has grown into the muscle layer
T2a	the tumour is in the inner half of the muscle layer
T2b	the tumour is in the outer half of the muscle layer
T3	tumour has grown through the muscle layer and into the surrounding fatty tissue
T3a	this spread into the fatty tissue can only be seen with a microscope
T3b	this spread into the fatty tissue is large enough to be seen on imaging test or to be seen/felt by the surgeon
T4	tumor has spread into nearby organs or structures. It may be growing in the stroma (main tissue) of the prostate, the seminal vesicles, uterus, vagina, pelvic wall or abdominal wall
N categories for bladder cancer:	
Nx	nearby lymph nodes cannot be assessed; information not known
N0	the cancer has not spread to any nearby lymph nodes
N1	the cancer has spread to one lymph node in the true pelvis
N2	the cancer has spread to two or more lymph nodes in the true pelvis
N3	the cancer has spread to lymph nodes that lie along the common iliac artery
M categories	
M0	no distant spread
M1	the cancer has spread to distant sites outside the bladder region (for example, the lungs, liver or bones)

## Methods

We retrospectively assessed 236 sequential radical cystectomy patients at a single centre (Frimley Healthcare Foundation Trust) a district general hospital. The records of imaging, pathology and operations were all electronically stored on PACS, ICE and master lab, and IQtopia systems. The operations were done by a single surgeon (HM) over a 14 year period 1999-2014. We compared the final pathological stage (stained with haematoxylin-eosin by a pathologist) with the radiological stage for both CT and MRI. We were able to compare 241 CT scans and 65 MRI scans reported by an experienced radiologist. Imaging was then stratified by whether it was performed before or after TURBT. We then compared both modalities before and after TURBT with regard to staging accuracy. This was divided into superficial NMIBC pT1 and muscle invasive MIBC pT2

and higher. The NMIBC patients represent patients with primary NMIBC and failed intra vesical chemotherapy regimens and are thus a selected population. We documented the timing of the TURBT, before or after the scan. Statistics Medcalc software was used. Sensitivity, specificity, positive and negative predictive values were done to gauge the approximate accuracy and clinical trends in imaging along with Cohens Kappa test which measures inter observer (imaging modality) agreement. This accounts for the possibility of agreement by chance. Fisher's exact test was used to detect statistical significance.

## Results

There were 91 CT performed pre-TURBT and 150 post-TURBT: for MRI these figures were 33 and 32 respectively. 57 patients had both modalities (Tables 2–4).

**Table 2** The detection of muscle invasive (T2,3,4) from superficial (T1a) using CT and MRI before and after TURBT.

Investigation pre TURBT (n = 93)	CT (91)	MRI (33)	Investigation post TURBT (n = 143)	CT (150)	MRI (32)
True positive	53	21	True positive	92	24
False negative (under staged)	13	3	False negative (under staged)	18	0
Sensitivity	0.803	0.875	Sensitivity	0.836	1
True negative	9	3	True negative	12	1
False positive (over staged)	16	6	False positive (over staged)	28	7
Specificity	0.36	0.33	Specificity	0.3	0.125
Kappa	0.169	0.233	Kappa	0.148	0.176
PPV	0.77	0.77	PPV	0.76	0.77
NPV	0.41	0.5	NPV	0.4	1
Fishers P (MRI v CT)	0.66	0.66	Fishers P (MRI v CT)	0.39	0.39
Fishers P	0.88	0.77	Fishers P TURBT before v after investigation	0.88	0.77
Accuracy	68%	73%	accuracy	69%	78%

**Table 3** MRI before and after TURBT

MRI	Before	After	Fishers P value
Sensitivity	0.875	1	0.23
Specificity	0.33	0.125	0.57
PPV	0.77	0.77	1
NPV	0.5	1	1

**Table 4** CT before and after TURBT

CT	Before	After	Fishers P value
Sensitivity	0.803	0.836	0.68
Specificity	0.36	0.3	0.78
PPV	0.77	0.76	1
NPV	0.41	0.4	1

Kappa score (Table 2) this looks at any significant intra-observer variability (between CT and MRI). Looking at staging for MIBC or NMIBC there is no significant difference between CT or MRI using a kappa score. Table 3 (MRI) and Table 4 (CT) show data from table 2 for each modality for clarity. 6 Regression looking at time of scan after TURBT was not significant in over staging.

## Discussion

The timing of TURBT has been viewed as problematic due to both over and understating. CT cannot visualise flat lesions, it cannot differentiate the musculature, MRI has issues with chemical shift and both overstate due to partial volume effect, thin bladder walls, perivesical inflammatory changes, previous radiation, surgery, stones and clot.<sup>4,11,13,15,16,22,27,29,30</sup> Using the two principal imaging modalities available to us, we have attempted to determine if imaging is more accurate before or after the TURBT.

### Overstating

The values of sensitivity, specificity, NPV and PPV were summated and divided by 2 to give the mean value. Overstating is a considerably greater problem than understating. This is, in fact, the principal error with imaging of 40-67%.<sup>23,25,27</sup> Our images on MRI used T2 weighting. This reveals high signal intensity for urine. Bladder wall has low signal intensity but cancer has an intermediate value.<sup>22</sup> When imaging states that the cancer is muscle invasive, but histology reveals it to be superficial, this generates false positives that lessen both the specificity and the positive predictive values. Our false positive rate for MRI=77% with a specificity of 0.23 (P= 0.57) and positive predictive value of 0.77 (P= 1.0). CT yields a false positive rate of = 67% with a specificity of 0.33 (P=0.78) and positive predictive value of 0.765 (P=1.0). None of the values were significant.

### Understating

Imaging that states the tumour to be superficial when pathology reveals it to be muscle invasive generates false negatives. This lessens the sensitivity and negative predictive values. Our false negative rate for MRI = 6% with a sensitivity is 0.94 (P= 0.23) and negative predictive value of 0.75 (P= 1.0) on average pre and post TURBT. Our false negative rate for CT= 18% with a sensitivity of 0.82 (P= 0.68) and negative predictive value of 0.4 (P=1.0) on average pre and post TURBT. No values reached significance. This compares favourably with the literature of 30%.<sup>30,36</sup> Overall accuracy has been reported to be 52%-93%.<sup>20,27,29</sup> or as low as 39%.<sup>24</sup> This can reach 98% if DW

images are used as well<sup>25</sup> but 64% was the best accuracy reported by others using DWI.<sup>24</sup> We have accuracy for CT pre TURBT at 68%, post TURBT at 69%. For MRI pre TURBT accuracy is 73% and post TURBT at 78% which compares favourably for differentiating between NMIBC and MIBC. The timing of the TURBT had no detectable influence on staging accuracy using these two imaging modalities in our institution.

## Limitations

- We recognise that this is a selected population representing patients with high grade, initially superficial, cancers that have relapsed. We note that they have had variable intra vesical chemotherapy regimens and systemic neo-adjuvant treatments. Further, we appreciate the MRI numbers are low.
- The department made a decision to do MRI in a select group of patients whose tumours were larger and seemed to be invasive by the person doing the initial flexible cystoscopy.
- There were a number of different radiologists reporting the scans. Improvements will be probably be shown with dedicated radiologists and improved technology (multi parametric MRI).

## Conclusion

Our results, based on retrospective analysis, suggest that whether one uses imaging for staging pre or post TURBT, it does not influence eventual final staging. However, we accept the limitation of individual variation of reporting and the retrospective nature with a small sample size. The CT scan is now an integral part of initial imaging of hematuria investigation in the western world and newer advances in technology have improved its value and it is as good as MRI for local staging. Therefore the role of MRI is limited unless CT imaging is contraindicated.

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## Conflicts of interest

The authors declared there is no conflict of interest.

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