ORIGINAL ARTICLE

The Influence of Transurethral Resection of Bladder Tumor on Staging of Bladder Cancer

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ABSTRACT

Introduction: Bladder cancer is common, expensive, and the number of cases rising with increased survival in the elderly population. Most centers do computed tomography (CT) scan at the point of investigation, and some will carry this out along with magnetic resonance imaging (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 transurethral resection of bladder tumor (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 influence of TURBT. We accept the limitation due to the retrospective nature, small sample size, and variability of the biology of bladder cancer.

Key words: Bladder cancer, computed tomography, magnetic resonance imaging, staging, transurethral resection of bladder tumor

INTRODUCTION

Bladder cancer is a common worldwide problem.[1-3] It is expensive and fraught with problems regarding optimal staging and management. The vast majority are transitional cell cancers and 70% present as a superficial disease with a very low chance of metastasis and 30% present as muscle invasive with a high risk of death from distant metastasis.[4] Metastases develop in 25% of muscle invasive tumors and 50% of tumors invading the perivesical fat. Neoadjuvant and adjuvant chemotherapy regimens may improve the outcome of muscle invasive disease and metastatic disease. Hence, accurate staging is crucial, especially to avoid radical surgery in incurable patients.[5] Prognosis has not improved[3,5,6] for muscle-invasive bladder cancer (MIBC)[7,8] implying that it should be treated earlier in the cancer pathway.[8]

It is one of the most expensive cancers due to surveillance requirement of non-MIBC (NMIBC) and the high recurrence rate.[9,10] The patient has a lifelong increased risk of cancer along the whole of the urothelial tract.[11] The current accepted pathway for bladder cancer patients is to have a flexible cystoscopy, then a transurethral resection of bladder tumor (TURBT) as a first intervention to diagnose grade and stage. This is the treatment for superficial NMIBC. However, because it cannot assess the depth of wall invasion or whether a tumor extends beyond the

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wall, the role of TURBT is controversial as it has been proposed that timing of this can affect the accuracy of staging.[4,11,12] Imaging is then needed for local and distant staging for MIBC patients will then need surgery or radiotherapy.

For MIBC the best cross-sectional imaging modality remains to be determined to establish the subsequent management.[4,13] It was originally held that computed tomography (CT) and magnetic resonance imaging (MRI) were of equal but of limited use.[14,15] 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 or post-TURBT scarring.[15] CT is not very accurate at T staging as it cannot depict the individual layers of the wall[16] although some have yielded better results[17] it is good for detection with haematuria.[11,15,18,19] Although CT is probably not so definitive for localized disease positron emission tomography, CT is useful for metastatic disease.[4] However, the consensus is that MRI is superior to CT for T staging.[20,21] MRI imaging is considered superior to CT for T staging because of its intrinsic high soft tissue contrast, submillimeter spatial resolution, and direct multiplanar imaging capabilities[11,20,21] to determine the depth of invasion.[22] 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[22] DWI is better than conventional MRI[23,24] for T staging particularly differentiating T1 from T2 and higher.[25] Apparent diffusion coefficient (ADC) can also predict grade[25] this is still evolving.[15] The greatest problem for all methods is overstaging and dynamic MRI is no exception.[26] However, the potential superiority of MPI is further strengthened as DWI differentiates metastatic nodes from noninvolved nodes[27] and has good reproducibility amongst radiologist.[26] Tumor size and ADC can determine both stage and grade[28] DCE can distinguish between residual tumor and neoadjuvant chemotherapy effects.[29]

However, despite apparent advantages, there remains the problem of overstaging being the most frequent and longstanding error.[14] This is due to a partial volume effect at the tumor-wall interface, a thin bladder makes differentiation of muscle layers intrinsically difficult and can also due to overdistension.[30] Further, perivesical inflammation in part due to intravesical medication and TURBT[11,22,24] and reactive nodes[20,29,32-34] radiation and surgery may cause prolonged nonspecific thickening of the bladder and are difficult to distinguish from a tumor on imaging.[11] Intraluminal clot and stones can also cause false positives.[4] In addition, staging mistakes occur as MRI can understage as we see that 30% of MIBC are initially diagnosed as NMIBC.[35,36] This is due to chemical shift artifact and microscopic invasion into muscle or fat or adjacent organs.[30] TURBT is problematic as it can seed tumor cells.[37] Further, it delays radical treatment in MIBC.[35,37-39]

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 [Table 1].[12]

METHODS

We retrospectively assessed 236 sequential radical cystectomy patients at a single center (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 IQutopia 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 hematoxylin-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 intravesical 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, and positive and negative predictive values were done to gauge the approximate accuracy and clinical trends in imaging along with Cohen's Kappa test which measures interobserver (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.

Kappa score [Table 2]

Table 1: TNM stage classification of bladder cancer

Tx	Primary tumor cannot be assessed; information not known
T0	No evidence of primary tumor
Ta	Noninvasive papillary carcinoma
Tis	Noninvasive 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 tumor 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 tumor is in the inner half of the muscle layer
T2b	The tumor is in the outer half of the muscle layer
T3	Tumor 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
N categories	
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)

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 and 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 overstaging.

DISCUSSION

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

Overstaging

The values of sensitivity, specificity, NPV, and PPV were summated and divided by 2 to give the mean value.

Overstaging is a considerably greater problem than understaging. This is, in fact, the principal error with imaging of 40–67%.[23,25,27] Our images on MRI used T2 weighting. This reveals a high signal intensity for urine. Bladder wall has a low signal intensity, but cancer has an intermediate value.[22]

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 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.

Understaging

Imaging that states the tumor to be superficial when pathology reveals it to be muscle invasive generates false negatives. This lessens the sensitivity and negative predictive values.

Table 2: The detection of muscle-invasive (T2,3,4) from superficial (T1, a) 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 (understaged)	13	3	False negative (understaged)	18	0
Sensitivity	0.803	0.875	Sensitivity	0.836	1.0
True negative	9	3	True negative	12	1
False positive (overstaged)	16	6	False positive (overstaged)	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	0.50	NPV	0.4	1.0
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 versus after investigation	0.88	0.77
Accuracy (%)	68	73	Accuracy (%)	69	78

TURBT: Transurethral resection of bladder tumor, CT: Computed tomography, MRI: Magnetic resonance imaging

Table 3: MRI before and after TURBT

MRI	Before	After	Fishers *P* value
Sensitivity	0.875	1.0	0.23
Specificity	0.33	0.125	0.57
PPV	0.77	0.77	1.0
NPV	0.5	1.0	1.0

TURBT: Transurethral resection of bladder tumor, MRI: Magnetic resonance imaging

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	1.0
NPV	0.41	0.4	1.0

TURBT: Transurethral resection of bladder tumor, CT: Computed tomography

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 favorably with the literature of 30%.[30,36]

Overall, accuracy has been reported to be 52%–93%[20,27,29] or as low as 39%.[24] This can reach 98% if DW images are used as well,[25] but 64% was the best accuracy reported by others using DWI.[24,26]

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 favorably 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 recognize that this is a selected population representing patients with high-grade, initially superficial, cancers that have relapsed. We note that they have had variable intravesical chemotherapy regimens and systemic neoadjuvant treatments. Further, we appreciate the MRI numbers are low.

The department made a decision to do MRI in a select group of patients whose tumors 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 (multiparametric 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 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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