The presence of detrusor muscle in the pathological specimen after transurethral resection of primary pT1 bladder tumors and its relationship to operator experience

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Introduction: *To assess the quality of transurethral resection of bladder tumors (TURBTs) performed by "senior" and "junior" urologists for pT1 tumors in terms of detrusor muscle (DM) presence and recurrence rate at 3 month first cystoscopy (RR-FC). Non-muscle invasive bladder cancer (NMIBC) is a heterogeneous group with differing biological potentials. Tumors invading lamina propria (pT1) have an increased propensity for recurrence and progression. Accurate staging at the time of primary TURBT, including the presence of DM, is crucial to avoid understaging and unnecessary delay in definitive treatment.*
Materials and methods: *We analyzed our maintained bladder tumor database (TURBTs from 2002 to 2009) and selected patients diagnosed with pT1 bladder tumors. Data on surgeon status, tumor characteristics (size, TNM stage 2009, grade, DM presence) and RR-FC were retrieved. Surgeons were stratified into "senior" and "junior" according to the years of prior training.*
Results: *Of the 340 TURBTs for pT1 tumors, "senior" and "junior" surgeons performed 237 (69.7%) and 103 (30.3%), respectively. Overall, 238 (70%) TURBTs had DM in the specimen, including 175 (73.8%) and 63 (61.3%) for the "senior" and "junior" operators, respectively (p = 0.02). The overall RR-FC was 37.4% (n = 127) and was significantly different for DM presence and DM absence (30.7% versus 52.9%; p = 0.01). On multivariate analysis, tumor recurrence was associated with "junior" operator experience independent of the presence or absence of DM (OR = 2.33 [1.45-3.74]) p = 0.01).*
Conclusions: *The presence of DM in a primary TURBT for pT1 NMIBC is directly associated with operator experience, with an associated increased 3 month recurrence rate for "junior" resectionists.*

Key Words: radical cystectomy, survival, prognosis, recurrence, non-muscle invasive bladder cancer, learning curve, urothelial carcinoma

Introduction

Non-muscle invasive bladder cancer (NMIBC) comprises a heterogeneous group in which tumor number, size, grade and pathological stage (pT) are important prognostic factors related to the risk of recurrence, progression and survival.[1,2] Transurethral resection of bladder tumor (TURBT) is the reference treatment of NMIBC.[1,2] The accepted standard for "correct" TURBT are complete macroscopic tumor clearance with specimens of tumor base and resection border sent separately.[3,4] This allows the pathologist to determine the histological type, grade and the presence, depth, and type of invasion (stage).[3,4] A key feature of the pathology report is the presence and/or invasion of lamina propria (LP; pT1) or muscularis propria (MP;

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≥ pT2), the latter being dependent upon the presence of detrusor muscle (DM) in the TURBT specimens.[3-5] It is now well established that a "correct" TURBT positively influences recurrence and progression and that the presence of DM and the recurrence rate at first cystoscopy (RR-FC) are independent factors to determine "quality" of TURBT.[6,7] A European Organization for Research and Treatment of Cancer (EORTC) study noted a significant interinstitutional variation in RR-FC after TURBT among TaT1 tumors, which was directly linked to initial TURBT quality.[8,9] Furthermore, the absence or presence of DM on initial TURBT appears to be a surrogate marker for resection quality and is directly linked with the surgeon's experience.[7] This suggests that a "learning curve" may exist for TURBT akin to the one that has been proven and widely discussed for minimally invasive procedures.[10]

The heterogeneity within NMIBC is best illustrated by comparing pTa and pT1 tumors. Both the clinical behavior and molecular biology differ. LP-invasive tumors have a greater propensity for recurrence and progression, which can influence long term survival, and have underlying genotypic changes similar to true muscle invasive bladder cancer (MIBC).[11-13] Thus, a thorough and accurate initial TURBT is even more pertinent in this subgroup of NMIBC.[6,14] It is international consensus that when a patient is diagnosed with a pT1 tumor, a "second-look" TURBT is advocated within 4-6 weeks.[2,15] This is for accurate staging purposes as upstaging (to ≥ pT2), with its ramifications for treatment choice, occurring in 10%-30%.[16,17] Early repeat TURBT is especially indicated in pT1 tumors without DM in the specimen, as a significant chance of under-staging exists. Delaying the diagnosis of MIBC ultimately leads to a delay in definitive treatment for eligible patients. It is consistently reported that a treatment delay > 12 weeks from time of TURBT to radical cystectomy (RC) negatively impacts on cancer-specific and overall-survival.[18,19]

In light of this knowledge, we hypothesize that operator experience influences the presence of DM on TURBT for pT1 bladder tumors and that a "learning curve" exists for TURBT in this important cohort of patients. We aim, in this current study, to assess the quality and the oncologic outcomes of TURBTs performed by "senior" and "junior" urologists for pT1 tumors at a single institution.

Materials and methods

Population

We analyzed our maintained bladder tumor database (TURBTs from 2002 to 2009) and selected patients diagnosed with pT1 bladder tumors. The following data was retrospectively retrieved: age, gender, surgeon status, tumor characteristics (size, TNM stage, grade, presence or absence of DM) and RR-FC. The following exclusion criteria were used for the current study: biopsy of bladder tumor, invasive tumor at diagnosis. Informed consent was obtained from each patient following local ethics committee (Assistance Publique - Hôpitaux Paris; APHP) approval of the study. In case of multifocal tumors, only the largest one was considered in the current study.

TURBT

TURBTs were systematically performed using white-light cystoscopy and standard resection equipment, as described previously.[4,20] Particular attention was made to resect, and submit to pathology separately, distinct parts of the macroscopic tumor. This included the tumor bulk, tumor base and resection margin. Surgeons were stratified into "senior" and "junior" urologists. The urological training program in France prior to becoming a certified urologist consists of a minimum of 5 years specific training in urology (3 years as a "resident" and 2 years as "chef de clinique; CCA"). A "resident" has continuous operative supervision whereas a CCA is an autonomous position with no senior supervision. So for the purposes of this study, "junior" surgeons were young certified urologists (i.e. "CCA") and the "senior" surgeons were certified urologists. The operative surgeon specified tumor size. We did not routinely administer intravesical chemotherapy immediately postoperatively.

Pathological evaluation

All original TURBT specimens were examined by dedicated genitourinary pathologists and processed according to standardized procedures.[21] Tumors were staged according to the 2009 International Union Against Cancer TNM classification. Also, pT1 tumors were subdivided into two groups: those with (T1b) or without tumor invasion of the muscularis mucosae layer of the lamina propria (pT1a) [5]. Tumor grading was assessed according to both the 1973 World Health Organization guidelines and the 2002 WHO–International Society of Urological Pathology grading systems.[22] Histological type and the presence or absence of DM was documented. For the purpose of the study, the pathologic database of pT1 tumors was re-analyzed and representative slides were re-examined by both a senior and junior pathologist in a blinded fashion and compared to the pT stage, grade and DM status of the initial report.

Follow up regimen

The patients follow up schedule was altered from routine clinical care and was specifically for the purpose of this study and consisted systematically of a control cystoscopy at 3 months post surgery. Patients in whom DM was present on original TURBT underwent an outpatient flexible cystoscopy and patients without DM in original TURBT specimen underwent cystoscopy and mandatory re-resection under formal anesthesia. All patients diagnosed with a pT1 tumor received a full induction course (x6) of bacillus-Calmette Guerin (BCG) according to French guidelines.[23] Also, patients underwent physical examination, cystoscopy and urine cytology. Recurrence was defined as either pathologically confirmed tumor on the re-TURBT specimen or macroscopic tumor at 3 month control cystoscopy.

Statistical analysis

Student's t test was used to compare continuous variables, and a chi-squared test was used to compare categorical variables. Univariate and multivariate logistic regression analyses were carried out to determine associations between the variables using a Bayesian method. For the construction of stochastic model (Basialab), we analyzed recurrence, resection by "senior" or "junior" urologist, presence of DM, size of tumor and association with other variables. A p value of less than 0.05 was considered significant. The statistical analysis was performed using SPSS V.17 (SPSS Inc., Chicago, IL, USA).

Results

Population

Overall, 340 patients within our database had pT1 tumors. Patient and tumor characteristics and surgeon status are described in Table 1. Briefly, 68 (21%) patients were female and 254 (79%) male. The median patient age was 69 years (range 33 to 98).

pT1 tumors

Of the 340 pT1 tumors, 182 (53.5%) and 124 (36.5%) cases were classified as pT1a or pT1b, respectively. In 34 (10%) cases, the pathologist could not make a distinction due to lack of muscularis mucosae in the specimen. DM status according to pT stage and the surgeon experience is displayed in Table 2. According to the 1998 WHO/ISUP classification, 323 (95%) and 17 (5%) had high (G3) or low grade carcinoma, respectively. Fifty-nine patients (17.3%) had associated carcinoma in-situ (CIS).

TABLE 1. **Patient and tumor characteristics**

pT1 stage	**n = 340**
Gender (n = (%))	
Male	268 (79%)
Female	72 (21%)
Median age (years) [range]	69 [33-98]
Operator experience	
Junior	103 (30.3%)
Senior	237 (69.7%)
Size	
< 3 cm	101 (26.9%)
> 3 cm	239 (73.1%)
Stage (%)	
pT1x	33 (9.7%)
pT1a	183 (53.9%)
pT1b	124 (36.%)
Stage (%)	
Low	17 (5%)
High	323 (95%)
Recurrence [number (%)]	204 (60.4%)

Operator experience

"Senior" surgeons performed 237 of the 340 (69.7%) TURBTs for pT1 tumor. "Junior" surgeons performed 103/340 (30.3%).

TABLE 2. **Presence or absence of detrusor muscle in regards to stage and surgeon's experience**

		Senior	**Junior**	**Total**
pT1x		21	13	34 (10.0%)
	DM+	16	4	21
	DM-	5	8	13
pT1a		129	53	182 (53.5%)
	DM+	102	30	132
	DM-	27	23	50
pT1b		87	37	124 (36.5%)
	DM+	57	29	86
	DM-	30	8	38
pT1		237 (73.1%)	103 (30.3%)	340
	DM+	175	63	238 (70%)
	DM-	62	40	102 (30%)

DM = detrusor muscle

DM status

Overall, 238 (70%) TURBTs had DM in the specimen. In the group of "senior" urologists, 175 (73.8%) cases displayed DM compared to 63 (61.3%) for the "junior" operators (p = 0.02), see Table 2.

3 month RR-FC

At the 3 month first cystoscopy (FC), 127 (37.4%) patients experienced tumor recurrence. When analyzing RR-FC in respect of DM status, the RR-FC for DM presence and DM absence was significantly different (30.7% versus 52.9%; p = 0.01). Of the 102 patients with lack of DM on original TURBT, 8 (8%) patients were upstaged to MIBC (≥ pT2) at the 3 month control cystoscopy/re-TURBT.

Regression analyses

On univariate and multivariate analysis, tumor recurrence was associated with "junior" operator experience independent of the presence or absence of DM (OR = 2.33 [1.45-3.74] p = 0.01). Neither age, gender, larger tumors, tumor location or association of CIS was associated with DM status or operator experience.

Discussion

The primary TURBT is unarguably the most important part of the diagnostic process for a newly presenting bladder tumor and it is vital that it is done correctly and to a high standard the first time. Obtaining a complete and representative specimen for formal histological analysis allows for efficient informed management decisions to be made based on key prognostic pathological variables, namely stage, grade, size, multiplicity and associated CIS. There have been critical technological advances in the last 20 years that have revolutionized endoscopic urologic surgery and now with digital video equipment, modern resectoscopes and angled telescopes we can strive to set contemporary standards of care for such operations as TURBT.[4] A surrogate marker of resection quality is the presence or absence of DM in the TURBT specimen. The overall reported rate of absence of DM after primary TURBT for clinically NMIBC is approximately 30%.[7,24] The imperativeness of the presence of DM varies for the grade and stage of the tumor. A small, solitary, exophytic, clinically low grade pTa tumor differs in the necessity for DM in the specimen compared to a large, clinically high-grade tumor with surrounding unstable urothelium. The 2011 European Association of Urology (EAU) guidelines on NMIBC clarify this point when they state "a second TUR should be considered when the initial resection is incomplete, for example, when multiple and/or large tumors are present, or when the pathologist has reported that the specimen contains no muscle tissue (TaG1 excluded)".[1] The discussion between patient and physician after the initial TURBT essentially centers on the lack or depth of invasion. It is this factor that dictates future management. In the case of pT1 bladder tumor, the presence of DM in the specimen is paramount given we are now aware that a significant proportion (10%-30%) will be upstaged on repeat TURBT.[15,17] This necessity to perform a repeat TURBT due to lack of DM in what could actually be a MIBC adds an undue delay before the definitive diagnosis is made. This almost certainly will impact negatively on long term cancer outcomes given the quoted "window of opportunity" of 12 weeks from time of TURBT to RC.[18,19,25] One limitation of the current study was the bias introduced with the follow up regimen since patients with DM in the resection were followed by cystoscopy and those without underwent a second resection.

Intuitively, you would assume that if the presence of DM is a valid surrogate marker for resection quality, then the experience of the endoscopic operator would be directly proportional to the presence of DM. Mariappan et al prospectively evaluated 356 patients who were judged to have had a complete first TURBT (2005-2006).[7] Overall, DM was present in 241/356 (67.7%) patients and in 167 (72.6%) and 67 (56.8%) for "senior" and "junior" surgeons, respectively (OR = 2.0 [1.3-3.2] p = 0.003). On multivariate analysis, large tumors (> 3 cm), high grade tumors (G3) and surgery by "senior" urologists were independently associated with the presence of DM in the resected specimens. Multivariate logistic regression analysis revealed that stage pT1 (OR 3.0; 95%CI 1.3-9.3: p < 0.01), absence of DM (OR 2.2; 95%CI 1.0-4.5: p = 0.04) and resection by "junior" surgeon (OR 2.1; 95%CI 1.1-3.9: p = 0.03) were independent predictors of early tumor recurrence. The RR-FC when DM was absent and present was 44.4% and 21.7%, respectively (OR 2.9; 95%CI: 1.6-5.4; p = 0.0002). Resections carried out by "junior" surgeons were associated with a two-fold increase in risk of early recurrence (OR 2.0; 95% CI:1.1-3.6; p = 0.02). Of the 59 T1 tumors, DM was present in 85.7% (n = 35) and 54.1% (n = 24) for "senior" and "junior" surgeons, respectively. RR-FCs were 81.3% and 34.9% when DM was absent and present, respectively (OR 8.1; 95%CI 1.7-42.9: p = 0.002).

This discrepancy in standard of TURBT related to operator experience is corroborated by other studies. Brausi et al reported RR-FCs of 8% and 28% when certified staff members and trainees carried out resections, respectively.[26] They demonstrated by following a program of specific TURBT training that there was an

increased ability to resect DM and a reduction in RR-FC. Similarly, Jesuraj et al reported significant surgeon-related differences in the ability to resect DM, which were more pronounced in higher grade/stage tumors.[27] DM was seen in 45.8% of resections by "juniors" compared with 67.3% of resections by "seniors".

Herein, we describe for 340 pT1 tumors how operator experience influences the presence of DM and recurrence. DM was present overall in 70% (n = 238) and in 73.8% (n = 175) and 61.3% (n = 63) of TURBTs performed by "senior" and "junior" surgeons, respectively (p = 0.02), Table 2. These figures support the theory that operator experience is directly related to TURBT quality if you use the presence of DM as the surrogate marker. Also, when we correlated operator experience with tumor recurrence using multi-variable analysis, increased recurrence was linked with "junior" operator status independent of DM presence (OR 2.33; p = 0.01). When analyzing RR-FC in respect of DM status, the RR-FC for DM presence and DM absence was significantly different (30.7% versus 52.9%; p = 0.01). This data supports our hypothesis that a "learning curve" for TURBT exists when you specifically analyze the presence of DM and the 3 month RR-FC after TURBT for primary pT1 bladder tumors.

We would like to address a few self imposed constraints and limitations of our study. First and foremost, this study was not designed to evaluate the role of re-TURBT, upstaging or survival outcomes for pT1 NMIBC. We would like to clarify our choice to specifically focus on pT1 bladder tumors and 3 month RR-FC. Firstly, this decision was made due to distinct phenotypic and biological differences between pT1 and pTa NMIBCs. We feel, in accordance with the EAU guidelines that the presence of DM in a TURBT specimen is of paramount importance in pT1 tumors specifically due to the potential for understaging in the absence of DM and subsequent delay of definitive treatment, with deleterious consequences, that a repeat TURBT creates. Secondly, the result of the first follow up cystoscopy is an established independent prognostic variable in NMIBC and a valid endpoint for the purpose of our study.[1-3,12]

The information presented cautions all urologists performing and teaching endoscopic surgery to be vigilant on adhering to now prescribed standards of care for TURBT to ensure we get the primary TURBT correct at the first time of asking. Structured training and adequate supervision are imperative for "junior" operators. This will guarantee accurate and efficient staging and avoid any unnecessary potentially dangerous delay that the need for a repeat TURBT due to the lack of DM will generate.

Conclusion

The presence of DM in a primary TURBT for pT1 NMIBC was directly associated with operator experience. Tumor recurrence was associated with junior operator experience independent of the presence or absence of DM. This could negatively impact on long term outcomes especially in the situation of disease understaging and treatment delay that lack of DM on TURBT could create. □

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