

Predictive factors for residual tumor and tumor upstaging on relook transurethral resection of bladder tumor in non-muscle invasive bladder cancer

Tejpal S. Gill, Ranjit K. Das, Supriya Basu, Ranjan K. Dey, Subrata Mitra
Department of Urology, R G Kar Medical College and Hospital, Kolkata, West Bengal, India

Abstract

Context: Relook transurethral resection of bladder tumor (TURBT) improves the diagnostic and therapeutic efficacy of primary TURBT. However, it is still not established as to which category of patients would benefit most from this repeat invasive procedure.

Aims: This prospective interventional study was designed to identify the category of patients with non-muscle invasive bladder cancer who may benefit from a routine relook procedure.

Setting and Design: A total of 52 consecutive patients with biopsy proven non muscle invasive bladder cancer on primary TURBT underwent a relook TURBT between March 2011 and September 2012.

Materials and Methods: The incidence of residual tumor and tumor upstaging on relook procedure was correlated with various histopathological (stage, grade, CIS, presence of muscle) and cystoscopic (type and focality of tumor, any apparent field change) parameters on primary TURBT.

Results: Out of the total 52 patients, 23 (44.2%) had a residual tumor on relook TURBT. 12 (23.1%) were upstaged (of these 9 i.e. 17.3% to muscle invasion). While most of the parameters studied showed a positive correlation with incidence of residual tumor and upstaging to muscle invasion, statistical significance (for both) was reached only for tumor stage ($P = 0.028$ and 0.010), tumor grade ($P = 0.010$ and 0.002) and tumor type (solid vs. papillary; $P = 0.007$ and 0.001). Carcinoma *in situ* showed a significant correlation with incidence of residual tumor ($P = 0.016$) while the absence of muscle in the primary TURBT specimen was significantly associated with upstaging to muscle invasive disease ($P = 0.018$).

Statistical Analysis: The data was analyzed using SPSS software v. 16.0.

Conclusions: Relook TURBT may be especially recommended for high grade and T1 tumors and tumors with a solid/sessile appearance on primary TURBT especially when deep muscle was absent in the primary TURBT specimen.

Key Words: Non muscle invasive bladder cancer, relook transurethral resection of bladder tumor, residual tumor, tumor upstaging

Address for correspondence:

Dr. Tejpal S. Gill, 43- SF, HIG Flats, Rajguru Nagar, Ludhiana - 141 012, Punjab, India. E-mail: drtejpalgill@gmail.com

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INTRODUCTION

Transurethral resection surgery has had the greatest impact on management of bladder cancer and is the single most important modifier of the natural history of this disease.^[1] This is especially true for “non-muscle invasive bladder” cancer. The term “superficial bladder cancer” is no longer preferred as it led to false groupings and some misleading implications.^[2,3] The first

transurethral resection of bladder tumor (primary TURBT) however, often fails to achieve complete tumor clearance or detect deep muscle invasion when it is actually present.^[1,4-8]

Relook TURBT increases the diagnostic and therapeutic yield of primary TURBT. Although some believe that Relook TURBT is must in all cases, a routine clinical application of this repeat invasive procedure is still lacking.^[5] Although numerous studies have been conducted and have shown residual tumor rates ranging from 26% to 83% and tumor upstaging rates as high as 37%,^[9,10] few have attempted to define statistically significant correlations between primary TURBT parameters and relook TURBT outcomes.

We reckoned that the markers that define a “candidate” relook patient should be defined from routine parameters identified in primary TURBT. Thus, seven different parameters were defined in primary TURBT and these were each compared with the three outcome measures of relook procedure to find statistically significant correlations (if any) between them.

MATERIALS AND METHODS

A prospective interventional study was conducted at our institution from March 2011 to September 2012.

A detailed documentation of intra operative findings of primary TURBT was done in all patients. All consecutive patients diagnosed with biopsy proven, non-muscle invasive transitional cell carcinoma (TCC) Bladder were enrolled in the study after taking proper consent. Patients in whom complete resection was not attempted (due to huge tumor burden) during primary TURBT, those with contrast enhanced computed tomography showing evidence of extravesical spread or those not fit or declining to undergo a repeat invasive procedure were excluded from the study.

The patients enrolled in the study were admitted and operated within a span of 2-6 weeks (average 4 weeks) after primary TURBT.^[11] All routine protocols for TURBT anesthesia were followed. Again, a detailed documentation of intra operative findings was done and tissue was sent for histopathological examination. Surrounding suspicious areas (labeled as “apparent field change” in this study) were also biopsied during primary as well as relook TURBT.

Seven parameters (markers) were identified in the primary TURBT procedure. Three were from intraoperative findings and four from the histopathological examination report. The parameters were:

1. Tumor type (i.e. morphological growth pattern- solid/papillary)
2. Tumor focality (unifocal/multifocal)
3. Any apparent field change (present/absent)
4. Tumor stage (T1/Ta)

5. Tumor grade (high grade/low grade)
6. Carcinoma *in situ* (CIS; present/absent)
7. Deep muscle in specimen (present/absent).

Tumor size was not included because firstly, tumors found to be very large and unresectable on primary TURBT were excluded from the study and secondly, it is a known fact that size is not a very strong predictor of invasiveness.

Solid/sessile type was defined on the basis of morphological growth pattern of the tumor as seen on cystoscopy i.e. tumors with a broad base, solid looking and with a sessile growth pattern. The term “field change” should not be confused with the fact that TCC bladder may be associated with a field effect leading to spatial and temporal multifocality. It is rather a term we defined on the basis of personal experience referring to common incidence of surrounding tissue edema, hyperemia etc., with or without a clear demarcation which often looks suspicious. We were curious about the clinical significance of this observation and hence included it in the study parameters.

Three outcome measures were defined for the relook procedure.

1. Incidence of residual disease
2. Incidence of tumor upstaging
3. Incidence of upstaging to muscle invasive disease

The collected data was analyzed using SPSS software v. 16.0. Chi-square and Fisher’s exact test were used to determine statistical correlation between test parameters and outcome measures of relook procedure.

RESULTS

A total of 52 patients were enrolled in the study over a period of 1½ years and underwent a relook procedure. There were 42 males and 10 females. Age range was 35-85 years with mean age was 60.19 years.

The tumor characteristics on primary TURBT and their distribution in the study group are shown in Table 1. The outcome of relook TURBT is shown in Table 2 and depicted graphically in Figure 1. In our study, the incidence of residual

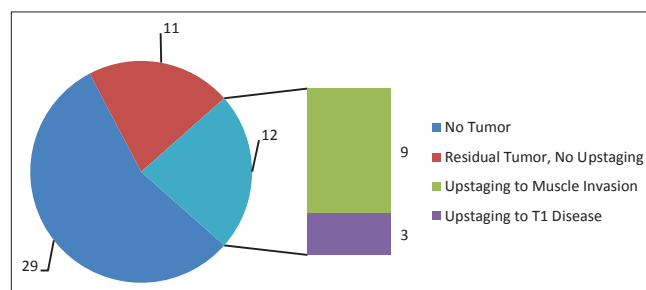


Figure 1: Outcome of relook transurethral resection of bladder tumor (total 52 patients)

Table 1: Tumor characteristics on primary TURBT

Parameter	Distribution in study group
Tumor stage	Ta=27 T1=25
Tumor grade	Low grade=24 High grade=28
Tumor type	Papillary=41 Solid/sessile=11
Tumor focality	Unifocal=38 Multifocal=14
Any field change	Present=10 Absent=42
Carcinoma <i>in situ</i>	Present=8 Absent=44
Muscle in specimen	Present=36 Absent=16

TURBT: Transurethral resection of bladder tumor

Table 2: Outcome of relook TURBT

Outcome measure	Present	Absent	Incidence %
Residual tumor	23	29	44.2
Tumor upstaging	12	40	23.1
Upstaging to muscle invasion	9	43	17.3

TURBT: Transurethral resection of bladder tumor

tumor was 44.2%. The incidence of tumor upstaging was 23.1% overall while upstaging to muscle invasive diagnosis occurred in 17.3% of patients. As shown in the graph, out of 12 patients who showed tumor upstaging, nine were upstaged to muscle invasive disease while three were upstaged from Ta to T1 disease. For the nine patients diagnosed with muscle invasion, there was a radical change in treatment protocol. Five of these underwent radical cystectomy while three opted for bladder preservation protocols. One of these later underwent radical cystectomy. One patient was unfit for any kind of therapy and was kept on conservative management.

Contingency tables (2 × 2) were constructed for each study parameter. Incidence of residual tumor, stage progression and progression to muscle invasive disease was calculated for each subset of patients as depicted in Table 3. The study variables (markers) in primary TURBT were compared with the outcome measures of relook TURBT to look for any statistically significant correlations. The level of significance in the study was kept at $P < 0.05$.

The summary of statistical correlations is shown in Table 4.

As shown in the table, tumor type, tumor grade and tumor stage showed a statistically significant correlation with all three outcome measures of relook TURBT i.e. incidence of residual tumor, tumor upstaging and upstaging to muscle invasive diagnosis. The presence of CIS was significantly associated with high incidence of residual tumor while the lack of deep muscle in the primary TURBT specimen was significantly associated with tumor upstaging and upstaging to muscle

Table 3: Outcome rates according to tumor characteristics

Parameter	Type	Outcome rate (% age (positive/negative))		
		Residual tumor	Stage progression	Progression to muscle invasion
Tumor stage	Ta (27)	29.62 (8/19)	11.11 (3/24)	3.70 (1/26)
	T1 (25)	60 (15/10)	36 (9/16)	32 (8/17)
Tumor grade	Low (24)	25 (6/18)	4.16 (1/23)	0 (0/24)
	High (28)	60.7 (17/11)	39.29 (11/17)	32.14 (9/19)
CIS	Absent (44)	36.36 (16/28)	18.18 (8/36)	13.63 (6/38)
	Present (8)	87.5 (7/1)	50 (4/4)	37.5 (3/5)
Muscle in specimen	Present (36)	36.11 (13/23)	13.88 (5/31)	8.33 (3/33)
	Absent (16)	62.5 (10/6)	43.75 (7/9)	37.5 (6/10)
Type of tumor	Papillary (41)	34.15 (14/27)	14.63 (6/35)	7.32 (3/38)
	Solid/sessile (11)	81.82 (9/2)	54.55 (6/5)	54.55 (6/5)
Focality	Unifocal (38)	36.84 (14/24)	18.42 (7/31)	13.16 (5/33)
	Multifocal (14)	64.29 (9/5)	37.71 (5/9)	28.57 (4/10)
Field change	Absent (42)	38.1 (16/26)	19.05 (8/34)	14.29 (6/36)
	Present (10)	70 (7/3)	40 (4/6)	30 (3/7)

CIS: Carcinoma *in situ*

Table 4: Summary of statistical correlations

Parameter	Level of significance (P value)**		
	For residual tumor	Tumor upstaging	Upstaging to muscle invasion
Tumor stage	0.028	0.033	0.010*
Tumor grade	0.010	0.003	0.002*
Tumor type	0.007*	0.011*	0.001*
Focality	0.077	0.267*	0.229*
Field change	0.087*	0.212*	0.349*
Carcinoma <i>in situ</i>	0.016*	0.072*	0.130*
Muscle in specimen	0.077	0.031*	0.018*

*Analyzed with Fisher's exact test as the expected cell counts were <5, **values marked in red are significant

invasive diagnosis. Other variables while showing a positive correlation did not achieve statistical significance. These include tumor focality and apparent field change for all three outcome measures, CIS for tumor upstaging and upstaging to muscle invasion and absence of muscle in the specimen for residual tumor incidence.

DISCUSSION

One of the key questions that comes to one's mind while managing patients with non-muscle invasive bladder tumor diagnosed on primary TURBT is- Should I subject this patient to a repeat invasive procedure? This question became the starting point of our investigation as we attempted to better define the role of relook TURBT in non-muscle invasive bladder cancer.

A better way to ask the above mentioned question would be:

1. What is the chance that I would find residual/unresected tumor in this patient?
2. What is the chance that I would find muscle invasion that went undiagnosed in the primary procedure (i.e. false negatives) thus leading to a drastic change in disease prognostication, management and outcomes?

3. Are there any disease variables in this patient which may place him at a greater risk for the above two outcomes?

Our study attempted to deal with all three of these questions. We found a 44.2% incidence of residual tumor, a 23.1% incidence of tumor upstaging and a 17.3% incidence of upstaging to muscle invasive diagnosis. This is a rather high incidence, but it is in fact in congruence with all other investigations in this field.^[1,4-8]

The reasons for such high rates of residual tumor and missed muscle invasion have been speculated by many and are probably multifactorial.^[1,12]

Regarding the third question, our study showed that patients with stage T1 tumors, high grade tumors and tumors with a solid/sessile growth pattern were significantly associated with a high incidence of residual disease as well as upstaging to muscle invasion. Presence of CIS was associated with high incidence of residual disease while absence of muscle in the primary TURBT specimen was associated with significant upstaging to muscle invasion.

Our study is relatively unique in the sense that it is a focused attempt at defining the “candidate” patient for relook TURBT on the basis of routine clinical, intra operative and histopathological parameters. Most of the previous studies in this field have done this but not in a focused way usually analyzing other corollaries as well.^[13] Dwivedi *et al.*^[14] performed a similar study combined with analysis of tumor ploidy by flow cytometry and found the incidence of stage and grade up-migration leading to change in treatment in 41.6% patients. Herr,^[1] reported that 75% of patients with superficial bladder tumors (Ta, T1 and Tis) had a residual tumor on relook TURBT and 29% of these were upstaged to muscle invasive tumor. He also included select cases of T2 tumors in his study in an effort to retrieve some patients for bladder preservation protocols.

One drawback of our study is that there was limited follow up and the survival data were not analyzed but since the prognostic ramifications of incomplete resection and of missed muscle invasive disease are well established, we felt that this was not necessary.^[1,13,15] Furthermore, the number of patients enrolled in this study is probably less than desirable but we felt that it was enough to determine relevant statistical correlations. Still, we feel that a larger, multicenter study with a similar design may be able to provide more robust associations.

CONCLUSION

Going by the high incidence of residual disease and missed muscle invasion after primary TURBT, a relook procedure

seems to qualify as an important adjunct in patients with non-muscle invasive disease on primary resection. It seems that relook TURBT may be highly desirable in any patient with high grade Ta disease, T1 disease and those with solid/sessile type of tumor growth pattern especially if deep muscle was not found in the primary resection specimen.

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