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pTa high grade urothelial bladder cancer: is there a role for second transurethral resection?

[Autor's unedited version]

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Introduction Evidence for second transurethral resection of bladder tumour (TURBT) for pTa High grade lesion is limited. This study aims to examine the role of a second TURBT in the pTa high grade group and to generate recurrence and progression data for this group.

Materials and methods We retrospectively studied the clinical profile and outcome of all patients diagnosed with pTa high grade lesions at first TURBT, between the years 2006-2015. First, in patients who underwent a complete first TURBT, we calculated the proportion of patients with positive findings on second TURBT. Secondly, we assessed whether those who underwent a second TURBT had a longer recurrence free survival compared to those who underwent a single TURBT.

Results 112 patients had a pTa high grade urothelial bladder tumor (WHO 2004 classification) at first TURBT, out of whom 43 (38.3%) had a second TURBT. Indications for second TURBT were high grade lesions (n = 36), absence of detrusor muscle (n = 2), and incomplete resection (n = 5). Out of the 36 patients who had a complete first TURBT and underwent a relook second TURBT, 7 patients had positive findings (3 carcinoma in situ, 2 pTa low grade lesions and 2 pTa high grade lesions) and there was no upstaging. Of the 5 patients with an incomplete first TURBT, one upstaged to pT1 on second TURBT. Of
the 81 patients who followed up with us, 25.9% had a recurrence and 8.6% progressed. The estimated median recurrence free survival was 60 months (95% CI 29.2-90.7) for the

whole group and 76 months vs. 45 months for the second and single TURBT group respectively – a difference that was clinically, though not statistically significant. Multiple (≥2) tumours had a lower recurrence free survival (HR of 4.60, CI 1.67–12.63, p = 0.003).
Conclusions 19.4% patients with pTa high grade tumours who had a second TURBT after a complete first TURBT had a positive finding. Multiple tumours are four times as likely to recur as solitary tumours. The role of a second TURBT in this group needs to be studied in larger patient cohorts before a recommendation regarding its lack of clinical utility can conclusively be made.

INTRODUCTION

With the wider adoption of the classification proposed by the World Health Organisation (WHO) and International Society of Urological Pathology (ISUP) in 2004, all grade 3 tumours and many of those previously classified as grade 2 tumours (according to the 1973 WHO classification) have been upgraded to the high grade group [1]. As a result, the pTa high grade group is more heterogenous as compared to the pTaG3 group [2]. This has potential implications in terms of clinical management i.e. treatment guidelines for pTaG3 (1973 WHO classification) may not apply to the pTa high grade group [3].
According to the European Association of Urology guidelines (2017), pTa high grade alone (especially if the first resection was complete and detrusor muscle was present in the histopathological specimen) is no longer an indication for second transurethral resection of bladder tumour (TURBT) and the WHO 2004 pathological classification is not yet incorporated into prognostic models (i.e. treatment guidelines are still based on the 1973 WHO classification) [4]. The omission of pTa high grade group from the list of indications for second TURBT is due to a lack of studies addressing the outcomes of second TURBT in in this group. Likewise, for the WHO 2004 pathological classification to be incorporated into prognostic models, we need a robust systematic review of outcomes, which is only possible if individual studies report outcome data in time to event format. The paucity of such studies has been clearly highlighted by the European Association of Urology guideline panel in a recent systematic review [5].
This study had two main objectives, namely, to examine the role of a second TURBT in the pTa high grade group and to generate recurrence and progression data for this group in time to event format, so that the WHO and ISUP 2004 classification can be incorporated into prognostic models.

MATERIAL AND METHODS

Selection of the study population: We used the institutional pathology data base as the starting point for data collection, and searched for all histopathological reports of pTa high grade (reported as per the WHO 2004 classification), pTaG2 and pTaG3 (reported as per the WHO 1973 classification) urothelial bladder tumours from 01/01/2006–31/03/2015. All reports which were initially reported using WHO 1973 classification were reviewed and reclassified by a single dedicated uropathologist (RMK) according to the WHO 2004 classification (Figure 1). An attempt was also made to arbitrarily classify the slides into two categories: those with ≥20% high grade (HG) lesion and those with <20% HG lesion, in an attempt to see if this sub-classification would help in predicting clinically relevant outcomes.
For selecting the study population that would constitute the basis for this study, histopathology reports with the following characteristics were excluded (details are given in Figure 1):

1. All reports of second TURBT. (Since the study population was defined as those who were diagnosed with pTa high grade lesion after first TURBT, second TURBT reports were excluded.)
2. Presence of concomitant higher stage lesion.
3. Presence of synchronous upper tract lesion.
4. Non-representative initial TURBT biopsy.
5. First TURBT done elsewhere and slides sent for review to our institution, as clinical details of resections were not available.

Clinical details of patients who were finally classified as pTa high grade on first TURBT were extracted from the hospital information system. All patients' follow up data was collected up to 30/8/2016.

Surgical and intravesical [mitomycin C and Bacillus Calmette Guerin (BCG)] administration protocols: Steps of TURBT included cystoscopy with 30 and 70 degree scopes, bimanual examination, resection of the tumour and the surrounding area, and a separate deep muscle resection biopsy. Resections were carried out both by consultants and trainees under supervision.

Intra-vesical mitomycin C when administered was instilled immediately after surgery at a concentration of 40 mg/40 ml. Patients underwent a second TURBT 2–6 weeks after the first TURBT. Intra-vesical BCG when administered was given two weeks after TURBT at a dose of 80 or 120 mg weekly for 6 weeks (induction phase) and monthly for 12 months (maintenance phase).

Definition of variables:

Induction BCG group: those who received induction intravesical BCG +/- maintenance BCG for less than 12 months.

Maintenance BCG group: those who received induction followed by at least 12 months of maintenance intravesical BCG.

Maintenance intravesical Mitomycin C group: those who received five to six monthly intravesical instillations after TURBT.

Multiple tumours: ≥2 tumours.

Complete first TURBT: TURBT with no gross residual tumour at the end of first resection and presence of detrusor muscle reported in the histopathology specimen (according to EAU 2017 guidelines, a second TURBT is no longer indicated in this group, and this study sought to test this assumption by examining outcomes in patients fulfilling this criteria who were offered a second TURBT)

Follow up schedule: Patients were advised to follow up three monthly for the first two years, six monthly for the next three years and yearly thereafter.

Outcomes: To assess the value of a second TURBT we looked at two aspects. First, we calculated the proportion of patients who had positive findings on the second TURBT after complete first TURBT. Second, we determined whether the group who had a second TURBT had a higher recurrence free survival.

Thus, the primary aims of the study were:

To calculate the proportion of patients having tumours on the second TURBT in those diagnosed with pTa high grade tumours after complete first TURBT.

To determine if the group that underwent second TURBT had lower recurrence free survival as compared to the group that underwent single TURBT.

To generate recurrence and progression data for the pTa high grade group in time to event format.

Secondary analysis: Baseline variables such as multiplicity (≥2 tumours), size of tumour, presence of ≥20% HG lesion, past history of urothelial tumours and maintenance BCG were checked for association with recurrence free survival. Potential bias due to

differential loss to follow up was assessed and reported.

Statistical analysis

Data was tabulated using the Statistical Package for Social Sciences-16 (SPSS-16). Proportions and percentages were used to analyze baseline characteristics and outcomes of the second TURBT. Recurrence free survival was calculated using Kaplan Meier (KM) survival curve. Various possible prognostic factors were analyzed using Cox Regression. During diagnostics of multivariate analysis of the Cox model, multiplicity (≥2 tumours) violated the proportionality assumption, hence, instead of a non-parametric Cox model, exponential distribution was used to model the hazard and the hazard ratios (95% CI) were presented. Loss to follow up bias was analyzed by calculating differential loss to

RESULTS

Study flow: Shown in Figure 1.
A total of 112 patients met inclusion criteria and 81 had followed with us, the mean duration of follow up was 24.1 ±18.3 months.
Various subsets of this study population of 112 patients were used to answer the primary aims of the study. Of the 112 patients, those patients who had undergone complete first TURBT (n = 36) (Figure 1 and 2) followed by second TURBT served as the subset for analysing the proportion of patients with positive findings on second TURBT. For analysing the impact of second TURBT on recurrence free survival, we included all patients who had followed up with us (n = 81, 72.3%, Figure 1) and compared the outcomes between those who had undergone a second vs. single TURBT.
The study group's baseline parameters, clinico-histopathological profile, treatment received, and comparison between those who followed up and those who did not (differential loss to follow up analysis), are shown in Table 1. The patients who followed up and those who were lost to follow up were comparable in all respects except that a higher proportion in the latter group had detrusor muscle in the histopathology specimen on first TURBT.

Indications for second TURBT (Figure 2)

Forty three patients underwent second TURBT. Indications were: presence of high grade tumours (relook TURBT after complete first TURBT, n = 36, 83.7%), absence of detrusor in the initial specimen (restaging TURBT, n = 2, 4.6%) and incomplete resection in the first TURBT (completion TURBT, n = 5, 11.6%).
Primary aim (a): Proportion of patients having tumours on the second TURBT in those with complete first TURBT.
Tumours were found in seven (19.4%) patients undergoing relook TURBT after complete first TURBT (n = 36) and there was no upstaging. The histopathological reports pertaining to these 7 TURBTs and the sites of recurrence have been detailed in Table 2.
We failed to find predictors for presence of tumours on second TURBT. There was no association between tumour size, multiplicity, presence of concomitant carcinoma in situ (CIS) on the first TURBT, immediate mitomycin C instillation or the history of previous urothelial lower tract tumours with the presence of tumours on relook TURBT (after complete first TURBT, n = 36) in our data set.
Outcomes in patients undergoing restaging and completion second TURBT (Figure 2)
There were no positive findings in the group undergoing restaging TURBT (n = 2) Figure 2).

Only one patient in the completion TURBT (n = 5) group was upstaged to pT1 tumour after completion TURBT, the remaining four were staged as pTa high grade. The patient who was upstaged to pT1 after second TURBT was not included in the survival analysis.
Primary aim (b) Effect of Second TURBT on recurrence free survival:
Thirty two (32) patients in the second TURBT group (mean follow up duration, 20.9 ±15.6 months), and 49 patients in the single TURBT group (mean follow up duration, 26.2 ±19.7 months) followed up with us. Seven out of 32 patients who followed up after two TURBT's had a recurrence as compared to 17 out of 49 patients after single TURBT. The median estimated recurrence free survival in the second TURBT group was 76 months vs 45 months in the single TURBT group. This difference though clinically impressive was not significant on statistical analysis (Table 3).
Primary aim (c) Recurrence and progression in time to event format:
Of the 81 patients who followed up after first or second staging TURBT, 21 (25.9%) had histopathologically proven recurrences. Three patients had a suspicious growth on cystoscopy or positive cytology on follow up, however they were lost to follow up thereafter without undergoing formal TURBT. Of those with histopathologically proven recurrences, eight were pTa low grade, five were pTa high grade and one had CIS. Seven patients (8.6%) had progressed, one to pT1 low grade, four to pT1 high grade, one to pT2 and one presented with metastasis. Median estimated recurrence free survival on Kaplan Meier estimate was 60 months (95% CI 29.2–90.7 months) (Figure 3). The number of patients who progressed were too few for regression analysis.

Secondary outcomes

Multiple (≥2) tumours at initial resection were likely to have 4.6 times shorter recurrence free survival and this was statistically significant. Maintenance BCG instillation showed a trend towards protective effect on recurrence free survival which failed to reach statistical significance (Table 3). Median estimated recurrence free survival was 60 months for maintenance BCG group vs 40 months in all other patients. So, maintenance BCG for at least one year added around 1.5 years of recurrence free survival. In relative terms (relative risk or hazard ratio), patients who did not complete maintenance BCG for at least one year had three times shorter recurrence free survival. The probability that we have arrived at this value by chance was 7% which was above the conventional level of 5%(two sided), hence it was not considered statistically significant. Presence of ≥20% HG lesion/history of urothelial tumours, did not affect recurrence free survival (Table 3).

DISCUSSION

Outcomes of second TURBT

The role of second TURBT has been well studied; however most of the evidence comes from T1 tumours [6–9] or is based on the 1973 WHO histopathological classification. There is only one other study, by Lazica et al [10], that reports the outcomes of a second TURBT in the pTa high grade group. Our study population was similar to theirs, in that 54% of the tumours were multifocal and 40% were ≥3 cm.
Lazica et al did not specify the indications for second TURBT in their study [10]. They subjected two patients with extensive bladder tumours to cystectomy after the first TURBT and the final biopsy was pTa high grade. In our series, four out of five such patients after completion (second) TURBT were reported as pTa high grade. This illustrates the presence of a variety of pTa high grade which though extensive, does not progress to invasion of lamina propria, and should not be clubbed with other high grade

tumours that show tendency for early progression. Further clinical studies are indicated to determine the specific histological and/or genetic markers that can distinguish this group of tumours.

Seven (19.4%) patients had a positive finding on the second TURBT after complete first TURBT as compared to 41.4% in the series by Lazica et al [10]. In both studies the recurrences most commonly involved primary tumour resection sites. In our study 4/7 (57.1%) patients had tumours outside the field of initial resection as compared to 24/36 (66.6%) in the series by Lazica et al. Unlike Lazica et al, in whose series five (5.7%) patients were upgraded to pT1 after second TURBT, there was no upstaging on second TURBT in patients in whom complete resection could be carried out in the first TURBT in our study.

The differing rates of positive outcomes may be due to differences in tumour characteristics (biology of the tumour) or the quality of TURBT [11]. Useful surrogate markers of the latter are completeness of resection and the presence of detrusor muscle in the specimen [12]. Other important factors include accuracy of the initial reporting, inter-observer differences between pathologists [13], and timing of the second TURBT after the first TURBT. Though all these factors are quantifiable and have a direct impact on the outcome of second TURBT, some of them were not reported in the study by Lazica et al (eg. in 50% of the patients, the presence of detrusor muscle in histopathological specimen was not reported), which makes direct comparison between the two studies difficult.

In either case (poor quality of first TURBT/aggressive tumour), these findings highlight the need for all centres to continue performing a second TURBT in order to audit and improve the quality of the first TURBT. The data thus generated would help identify a select group of patients who would most benefit from this procedure and better sub-classify this group.

In our study population we were unable to identify any predictors of positive outcomes on the second TURBT unlike Lazica et al. This absence of statistical association may be due to the fact that fewer patients in our study underwent a second TURBT (36 vs. 87) and the proportion of second TURBT procedures with positive findings was less than half that of Lazica et al [10].

In light of the above findings we suggest that the European Association of Urology guidelines re-include pTa high grade group as an indication for second TURBT.

Recurrence and progression

The data available for the pTa group regarding recurrence and progression are mostly from studies using the 1973 WHO system of grading [12]. The high grade group (WHO and ISUP 2004 classification) contains two groups with different progression potential and immunohistochemical marker profiles [2]. This fact is clearly evident in our study group, only 25.9% of whom had histologically proven recurrences, while 8.6% progressed to a higher stage. Differential loss to follow up bias was minimal as both groups (those who followed up and those lost to follow up) were comparable except that the latter group received a better quality of first TURBT (significantly higher detrusor muscle present). It is therefore unlikely that loss to follow up bias resulted in lower recurrence or progression rate in our study group.

We compared our results with the following two well conducted studies. Herr et al. [14] reclassified and studied the 15 year outcome of pTa high grade group and found a progression rate of 39%. The treatment protocol did not specifically mention the type (induction/maintenance), dosage or duration of BCG therapy. Holmang et al. [2] applied the WHO/ISUP 2004 classification to an older data set of patients of pTa stage and found

a recurrence rate of 73% and progression rate of 23% at five years, though patients did not receive intra-vesical BCG. Second TURBT was not performed in either of these studies. Although confounders like duration of follow up, use of second TURBT and use and duration of maintenance BCG make direct comparison of data difficult, one common outcome is the varied natural history and response to treatment modalities: 8-39% may progress over a median follow up period of 1–15 years, though the majority do not progress even without intra-vesical BCG [2]. Hence, the question remains - do all patients in the pTa high grade group belong to the intermediate or high risk group to warrant intra-vesical BCG? Hopefully the adoption of the newer WHO 2016 classification [15] system and genetic prognostic markers [16] would better sub-classify this heterogeneous group.

Impact of second TURBT in terms of recurrence free survival: To the best of our knowledge there is no published literature in the English language that looks at the evidence of second TURBT prolonging recurrence free survival in the pTa high grade group. In our study we did find a clinically relevant difference in estimated recurrence free survival (76 vs. 45 months) though statistical significance was not demonstrated. Multi-institutional studies with larger patient numbers are needed to confirm if this difference is due to chance or whether statistical significance was not reached due to the small sample size of the present study (underpowered study).

Similarly, data on other parameters affecting recurrence free survival specifically in the pTa high grade group alone is lacking, however our findings are similar to those from studies recruiting non-muscle invasive urothelial tumours of the bladder (pTa and pT1). Like CUETO (based on the data of patients who received a single TURBT and intra-vesical BCG for ≤1 year) and the latest EORTC nomogram (based on the data of patients who underwent two TURBTs and maintenance BCG for 1-3 years), our study showed that multiple tumours remained the most important prognostic indicator, whereas tumour size was not a useful factor for prognostication of recurrence [17, 18]. In our study, patients receiving maintenance BCG showed a trend towards lower recurrence, though statistical significance could not be demonstrated. The efficacy of this intervention is well established in literature [19].

We did not find ≥20% high grade lesion to be associated with lower recurrence free survival. In the absence of complete specimens (as only slides and blocks were available for review), our uropathologist was able to classify only 41 out of 81 patients who followed up. Further we realized that a better way of analyzing this would have been to prospectively classify these specimens with % of HG lesions as a continuous rather than dichotomous variable and determine what cut off had maximum predictive value.

This retrospective review has many shortcomings. Not all patients underwent second TURBT, treatment protocols such as the dosage of intra-vesical BCG changed from 120 to 80 mg in clinical practice during the period of review, and the follow up period was comparatively short. Despite no differential loss to follow up, follow up bias may exist as only 72.3% followed up with us. However, the strengths of this study are that it reports outcomes of a focused group (pTa high grade) in time to event format (i.e. time to recurrence, hazard ratio and multivariate adjustments). Further, the parameters that define the quality of the first TURBT are clearly specified in the present study. To the best of our knowledge, this is first study which looks at various factors affecting recurrence free survival in a focused pTa high grade group.

Implications of our study: We should continue to perform a second TURBT in the pTa high grade group as it detects residual disease in a significant minority and serves as an important quality control for the first TURBT. Each institution should analyse the outcomes of second TURBT to improve the quality of the first TURBT and determine which subset of patients would most benefit from it. We need studies with larger patient numbers to confirm the benefits of a second TURBT in terms of recurrence free survival

in pTa high grade group. Since the pTa high grade group has variable outcomes, we need to sub-classify it better to identify patients who would benefit from more aggressive treatment regimens. Multiple tumours can act as one of the prognostic markers for recurrence in this subgroup.

CONCLUSIONS

Approximately one fifth of patients with pTa high grade tumours had a positive finding on second TURBT after undergoing complete first TURBT. Multiple pTa HG tumours are four times as likely to recur during follow up as solitary tumours.

Conflicts of interest

The authors declare no conflicts of interest.

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Table 1. Baseline characteristics and clinico-pathological profile of the study population and differential loss to follow up analysis

Variable		Overall (n=112)	Follow up group (n=81)	Lost to follow up (n=31)	p value
Mean age in years (SD)		57.3(11.5)	57.8 (10.4)	56.2 (13.9)	0.52
Males		86.6(%)	86.4%	87%	1
Smoking history	Current smokers	21.4(%)	18.5%	29%	0.34
	Reformed smokers	19.6%	18.5%	22.5%	
History of urothelial tumour	Lower tract	30.4%	29.6%	32.2%	0.80
	Upper tract	0.9%	1.2%	0	
Solitary tumours		45.5%	45.8%	61.3%	0.139
Size < 3 cm		59.8%	56.7%	67.7%	0.29
Detrusor muscle present in the first TURBT		89.3%	85%	100%	**0.035**
Complete resection during first session		94.6%	96.2%	90.3%	0.35
Concomitant Carcinoma in situ		9.8%	12.3%	3.2%	0.29
Immediate post-operative MMC instillation		68.8%	69.1%	67.7%	0.88
Second TURBT		38.3%	39.5%	35.4%	0.69

Maintenance MMC instillation	7.1%	7.4%	6.4%	1
Induction intravesical BCG	16.1%	18.5%	6.4%	0.15
Induction + Maintenance BCG (at least one year)	19.6%	23.4%	12.9%	0.21

TURBT – transurethral resection of bladder tumour; MMC – mitomycin C, BCG – bacillus Calmette Guerin

Table 2. Outcomes of relook TURBT (second TURBT done in view of high grade lesion)

Findings on second relook TURBT		**Outcome (n=36)**
Tumours on Second relook TURBT		7 (19.4%)
Pathological grade and stage	Carcinoma in situ	3
	pTa low grade	2
	pTa high grade	2
	pT1 high grade	0
Site of recurrences	Primary site	3
	Other	2
	Both primary and other	2

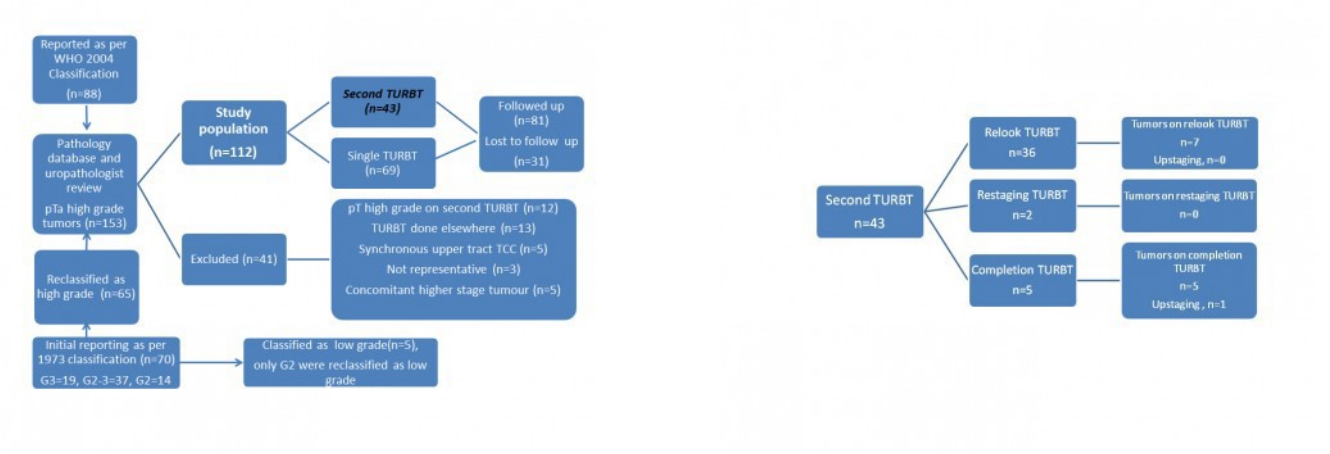
TURBT – transurethral resection of bladder tumour

Table 3. Factors affecting recurrence free survival

			Recurrence free survival		Univariate analysis		Multivariate analysis	
Variable		Events /total	Median (months)	P value	Hazard Ratio (95% CI)	P value	Hazard Ratio (95% CI)	P value
Multifocal	No	6/37	68	0.004	Ref	0.011	Ref	**0.003**
	Yes	18/44	30		3.38(1.32-8.41)		4.60(1.67-12.63)	
Size(in cm)	< 3	15/46	60	0.41	Ref	0.45	Ref	0.15
	≥3	9/35	76		0.73(0.32-1.66)		0.5(0.19-1.29)	
BCG maintenance	No	21/62	40	0.12	Ref	0.12	Ref	0.07
	Yes	3/19	60		0.38(0.11-1.28)		0.33(0.09-1.11)	
Second TURBT	No	17/49	45	0.65	Ref	0.64	Ref	0.53
	Yes	7/32	76		0.81(0.34-1.96)		0.74(0.3-1.86)	

History of urothelial tumour	No	17/56	45	0.51	Ref	0.71	Ref	0.46
	Yes	7/25	60		1.18(0.49-2.85)		0.68(0.25-1.88)	
% of high grade tumour ≥ 20%	No	5/15	68	0.34	Ref	0.71		
	Yes	9/26	36		1.23 (0.41-3.67)			

TURBT – transurethral resection of bladder tumour; BCG – bacillus Calmette Guerin



bladder cancer patients.

Fig. 1 Study flow detailing the procedure followed for selection of cases for inclusion in the study

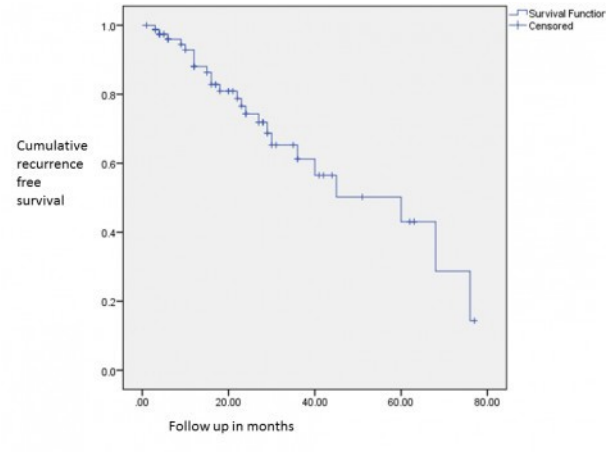


Fig. 3 Median estimated recurrence free survival on Kaplan Meier estimate in pTa high grade urothelial

Figure2
Outcomes of second TURBT. Relook TURBT: Indication being presence of high grade tumour in the first (complete) TURBT histopathological specimen; Restaging TURBT: Indication being absence of detrusor in the initial specimen; Completion TURBT: Indication being incomplete resection in the first TURBT.