

The Value of Second Look Transurethral Resection in the Evaluation and Management of Patients with Bladder Tumors

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ABSTRACT:

BACKGROUND:

The role of a routine second transurethral resection in evaluating and management of patients with bladder tumor is defined.

PATIENTS AND METHOD:

From January 2004 to October 2006, 100 patients with new or recurrent bladder tumors underwent repeat transurethral resection within 4-6 weeks after the initial resection, and the results, including the presence of residual tumor and tumor stage, were compared.

RESULTS:

Of 100 cases, 28 (28%) had no tumor and 72(72%) had residual tumor on repeat TUR. Out of 64 cases with superficial (Ta, Tis, T1) bladder tumors, 20(31%) had residual non-invasive tumor and 13 (20%) were upstaged to muscle invasive tumor. Among 36 patients with a muscle invasive tumor, 10(28%) had no residual tumor on re-TURBT. Results of second resection had changed treatment option in 39 patients (39%) from the initial treatment recommendation which was given after the first TUR.

CONCLUSION:

many patients with bladder tumor have residual tumor present after an initial TUR. Routine repeat resection is advised to control noninvasive tumors and to detect residual tumor invasion.

KEY WORDS: bladder tumor, second look TURBT, treatment option.

INTRODUCTION:

Carcinoma of the bladder is the third most common tumor in males and the eighth most common tumor in females ^[1]. At initial presentation approximately 70% of tumors are superficial stage Tis or Ta ^[2]. Invasion into the lamina propria or muscle wall is identified in smaller number of patients, approximately 28% and 24 % respectively; regional or distant metastasis are found in approximately 15%. However, 80% of patients with invasive or metastatic disease have no previous history of bladder cancer ^[3].

Bladder cancers may also be stratified at the time of initial presentation on the basis of grade: about 43% of tumors are classified as grade I, 25% into grade II, and 32% of tumors into grade III ^[4].

Tumor recurrence and progression rates are higher in patients with:

Tumor larger than 10 grams

Multifocal tumor

High grade tumors

Tumors with lamina propria invasion

Tumors invading lymphatic space

Tumors associated with severe urothelial dysplasia or CIS ^[5].

Treatment selection:

Low risk cancer is treated with TUR and intravesical chemotherapy is administered if indicated. ^[5]. The overriding issue is when should high risk superficial cancers be treated conservatively with TUR with or without intravesical chemotherapy, and at which point does a cystectomy become necessary to prevent progression to muscle invasive disease. The problem is that the groups needing conservative or aggressive management are not clearly defined, meaning that there may be considerable over – and under – treatment of these cancers ^[6]. TUR is a diagnostic and therapeutic procedure; it aims not only to determine the type and extent of disease, but also to eradicate all macroscopic superficial and if possible invasive tumors ^[7]. In the majority of cases therapeutic decisions for bladder tumors are based on the results of an initial TUR of primary (first) tumor or a follow-up resection for recurrent tumors ^[7]. TUR should also provide adequate specimens for pathological evaluation of tumor grade and stage (depth of tumor invasion).

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Such information is critical because the pattern of tumor growth, grade, and stage directs therapy and influence prognosis^[8], however, there is reported evidence that this TUR is often not performed to adequate standards^[9]. A finding of tumor invasion on repeated TUR might suggest a change in therapy from the treatment recommended based on results of the first resection^[7]. In addition to removing the exophytic growth, a separate loop resection of the tumor base is recommended^[10]. The TUR should also include the margins of the resection area^[6].

Factors which result in suboptimal specimen collection at TUR are:

Multiplicity of cancer growth

Awkward anatomical location of cancers (within a diverticulum, dome or anterior wall of the bladder)

Trabeculated or thin bladder wall

Incidental perforation and over-enthusiastic use of the diathermy loop^[6].

A TUR technique incorporating 5-ALA photodynamic diagnosis has been examined as a solution to minimize the amount of cancer left behind^[11, 12]. The accurate staging of superficial bladder cancer is crucial, as all superficial cancer carry a risk of progression (pTa 4%, pT1 30%)^[13]. There is also lack of conformity in the actual reporting of the final TUR histology, Factors contributing include poor tissue orientation on prepared slides, and thermal or crush artifact. Thus the true rates of high risk cancers, including pT1G3 that have been reported in published reports is debatable.^[14, 15] Re-TUR could play a key role in managing high-risk superficial bladder cancers by reducing the residual cancer rates and improving the staging accuracy. Early recurrence within 3 months after a TUR has been shown to be a poor prognostic factor^[16].

PATIENTS AND METHODS:

From January 2004 to October 2006, 100 patients from all geographical regions in Iraq with bladder cancer were studied. The patients were classified as having a new tumor diagnosis or recurrent bladder tumor. All of the patients were submitted to initial TUR which was standardized as to technique since surgery was performed by highly expert surgeon, furthermore, information regarding whether tumor resection was complete or incomplete was also available. A separate loop biopsy from the tumor base was taken and labeled for the histopathologist

to look specifically for muscle invasion. All of the histopathological specimens were analyzed by the same histopathologist who was encouraged to report on the status of the muscularis propria in all TUR specimens analyzed. The tumors were identified as solitary or multiple. The tumors were classified as Ta-papillary non-invasive, Tis-carcinoma in situ, T1 lamina propria invasion or T2 any muscle invasion. In case of T1 tumors, the presence or absence of muscles (muscularis propria) in the specimen was noticed. Tumors were graded as low (I) or high (II&III) grades. Each patient had received at least a tentative recommendation for treatment of bladder tumor(s) based on the findings of the first TUR, which consist of follow up cystoscopy, intravesical therapy or cystectomy. All patients were advised to have a second TUR before discussing the treatment options, which was done within 4-6 weeks after the initial TUR. The follow up TUR was performed by the same surgeon in Al-Kadhemia teaching hospital under general anesthesia. All gross tumors as well as any suspicious or edematous areas from previous biopsy sites were thoroughly resected and care was taken to include muscle in the specimens. Again separate loop biopsy from the tumor base was taken and labeled for the histopathologist to look specifically for muscle invasion. The findings of the second TUR were used exclusively to recommend a final treatment strategy, which either agreed in general with the first recommendation (conservative or radical treatment) or represent a change in treatment option from that recommended. A change in treatment was defined as a follow-up TUR and intravesical therapy rather than cystectomy or immediate cystectomy and in some cases systemic chemotherapy, in favor of the conservative therapy.

RESULTS:

Out of 120 cases evaluated, 20(17%) declined and 100(83%) agreed to have another TUR. There were 81 men and 19 women evaluated, out of whom 13(13%) presented predominantly with Tis, 12(12%) Ta tumor, 39(39%) T1 tumor and 36(36%) T2 tumor. Out of the patients evaluated, 43(43%) had a solitary tumor and 57(57%) had multiple tumors. Ta tumors were low grade in 3 and high grade in 9 patients, Tis T1 and T2 tumors were all high grade. Table 1 compares tumor stage after a second TUR with the presenting tumor stage.

PATIENTS WITH BLADDER TUMORS

Table 1. Comparison of bladder tumor stage after first and second transurethral resection with P value results.

Stage at first TUR	No. of patients	No. of patients with each tumor stage at second TUR (%)					P VALUE=
		T0	Ta/Tis	T1	T2	T3-T4	
Tis	١٣	5(38)	4(31)	3(23)	1(8)	-	P<0.001
Ta	١٢	3(25)	5(42)	3(25)	1(8)	-	P<0.001
T1:	٣٩	9(23)	11(28)	8(21)	11(28)	-	P<0.001
T1 Muscle	٢٤	6(25)	8(33)	5(21)	5(21)	-	P<0.001
T1 No muscle	١٥	3(20)	3(20)	3(20)	6(40)	-	P<0.001
T2	٣٦	10(28)	5(14)	2(5)	18(50)	1(3)	P<0.001
Totals	١٠٠	28(28)	72(72)				

Sixty four patients (64%) presented with superficial (Ta, Tis, T1) tumors, 8(12%) had a primary (first) tumor and 56(88%) had a recurrent tumors. Out of 36 patients (36%) with T2 tumors, 31(86%) presented with a primary invasive tumor and 5(14%) had a recurrent invasive tumor. Out of the 100 case evaluated, 28(28%) had no tumor (T0) on re-TUR procedure and 72(72%) had residual tumor. Out of the 25 cases with Ta or Tis disease, 6(24%) had lamina propria invasion (T1) detected and 2(8%) were upstaged to muscle invasive tumor. Among the 39 cases with T1 tumor, 8(21%) had residual T1 tumor and 11(28%) had a T2 tumor. Out of 15 T1 case without any muscle present in the initial TUR, 6(40%) had muscle invasion on a re-TUR compared with 5 of 24(21%) patients who did have muscle identified in the original specimen.

Out of the 64 cases with superficial bladder cancer (Ta, Tis, T1) at presentation, 17(27%) had no tumor (T0) found, 20(31%) had non-invasive (Ta) tumor, 14(22%) had persistent submucosal (T1) tumor and 13(20%) were upstaged to muscle invasive cancer. Among the 36 patients with T2

tumor 10(28%) had no tumor (T0) identified and 21(58%) had tumor invasion confirmed on re-TUR. If we exclude diffuse Tis and T2 tumors because a complete TUR for such tumors is less likely and considered only the 51 patients with papillary Ta or T1 tumors, then 12 (24%) had no tumor (T0) identified and 39(76%) had residual tumor. Out of the 12 who had no evidence of tumor after the second TUR, 5(42%) had had a solitary tumor resected initially compared with only 7(58%) with multiple tumors. Table 2 shows the presence or absence of residual tumor by initial tumor type and whether the findings after contemporary re-TUR resulted in a change in treatment or not. Overall, results of the second TUR changed treatment in 39 patients (39%). Treatment changes included cystectomy rather than intravesical therapy in 19 cases up-staged from non-invasive to invasive tumors, repeat resections rather than immediate cystectomy in 19 cases for T0 disease and systemic chemotherapy rather than cystectomy in 1 case judged to be inoperable.

Table 2. Change in treatment of bladder tumors after second transurethral resection

Stage at first TUR	No. of patients	No. of patients with each tumor stage after second TUR		No. Treatment Change (%)	Reason for treatment change[No.]
		T0	T any		
Tis	١٣	٥	8	4(31)	T1[3] T2[1]
TaG1	٣	١	٢	٠	-
TaG2,G3	٩	٢	٧	4(44)	T1[3] T2[1]
T1	٣٩	٩	٣٠	20(51)	T2[11] T0[9]
T2	٣٦	١٠	٢٦	11(31)	T4b[1] T0[10]
Totals	١٠٠	28(28)	72(72)	39(39)	

Statistical analysis:

PATIENTS WITH BLADDER TUMORS

Data were arranged and tabulated in number, percent and probability of significance.

The presence of residual tumors of any stage and the absence of these tumors after doing the second TUR was measured by using the fisher's exact probability test with P value < 0.05 considered the level of significance. Out of thirteen patients who had Tis, on re-TUR five of them show down staging into T0 (no tumor found) with P value < 0.05 and four of them were up-staged to a higher stages (T1, and T2) with P value < 0.05 so we can conclude that re-TUR done for Tis tumors is of significance in regard to both down and up staging of those tumors. Out of twelve patients with a Ta tumor stage, three of them were shown to have down staging on re-TUR to T0 stage with P value < 0.05, while four of them were upstaged to T1 and T2 stages with P value < 0.05 so it can be postulated that re-TUR done for Ta tumors is of significant in regard to both down and up staging of those tumors. Out of thirty nine patients with T1 tumor stage, twenty patients were shown to have down staging on re-TUR with P value < 0.05 and eleven of them were upstaged into T2 tumor stage with P value < 0.05 so it can be postulated that re-TUR done for T1 tumors is of significant in regard to both down and up staging of those tumors. Out of thirty six patients with T2 tumor stage, seventeen of them were shown to have down staging on re-TUR into either T0, Ta, Tis or T1 stage with P value < 0.05 and only one patient was upstaged into T3 tumor stage with P value > 0.05 so we say can say that re-TUR done for T2 tumors

is of significant in regard to down staging of these tumors on re-TUR. So in reviewing these results one might find in accordance to fisher's exact test that re-TUR for each stage is of high significance with P value < 0.001 in regard to the presence or absence of residual tumors.

DISCUSSION:

A majority of patients diagnosed with new or recurrent bladder tumors after the first TUR have a significant tumor load based on the findings of a contemporary second resection, furthermore, repeat resection revealed residual tumor invasion in a third of patients which led to a change in treatment. Most urologists would agree in general that ideally initial TUR of bladder tumor should be thorough and complete but there are many factors that confound adequacy of resection, including multiplicity of disease, capability and preservice of the resectionist, quality of specimens provided and pathological analysis. In our study we tried to address some of these factors but the overall results should be interpreted while keeping these factors in mind. However, complete TUR may be neither feasible nor possible in all cases even in the best hands.

Who can say with certainty that a T1 tumor has been completely resected? Re-TUR dose not guarantee complete resection but it reduces the uncertainty of clinical understaging, especially among superficial bladder tumors^[8]. Others have also shown that residual tumor is often discovered on routine second TUR.

Table 3 shows residual cancer and cancer upstaging rates in the re-TUR series

Table 3. Residual cancer and cancer upstaging rates in the re-TUR series

Reference	Number of patients	Re-TUR at, weeks	Residual cancer %	Upstaging (muscle invasion)%
Klan et al.[17]	46	1-2	44	2
Herr et al.[7]	150	2-6	76	29
Brauers et al.[18]	42	4-6	64	0
Schwaibold et al.[19]	60	4-6	55	10
Schips et al.[20]	110	4-6	36	0
Grim et al.[21]	83	Mean 7	33	4

Initially there was much skepticism of the high residual cancer rates (44%) reported by Klan et al.^[17], additional reported evidence also suggested this as shown in the table above, all of these studies also suggested that re-TUR is a safe procedure, as no significant morbidity or mortality was reported. In Klan et al. study they reported that 20 of 46 patients with T1 tumors (44%) had residual tumor on the second specimen, including 7 with Ta, 12

with T1, and 1 with T2 tumors, and 40 had no tumor visible at cystoscopy. They did not mention how the findings of the second TUR influenced management but they speculated that residual tumor may be an important cause of early tumor recurrence.

Mersdorf et al.^[22] believed that a second TUR is a must. Among 49 cases with Ta tumors resected 31% had residual Ta tumors and 14% were up

staged to muscle invasive tumors. Out of 45 cases T1 tumors 16% had residual T1 tumors on repeat resection and 24% were up staged to muscle invasion. The authors advised a second TUR to resect tumor completely and to detect carcinoma in situ.

Vogeli et al. ^[23] reported on 215 patients of whom 37% with Ta tumors and 43% with T1 tumors had residual malignant tumor on second TUR .Repeat resection revealed a higher tumor stage in 9% of these patients .The authors suggest that early tumor recurrence might be diminished by a repeat resection.

Should patients with bladder tumors be advised to undergo a routine re-TUR and, if so, how should the findings influence treatment? Results of a repeat TUR must be interpreted as part of a focused strategy for managing bladder tumors in an individual patient. Result of a repeat TUR were often the deciding factor for or against bladder preservation. Out of the majority of patients with multiple or recurrent Ta tumors , those with T1 tumors and in selected patients with T2 tumors a re- TUR is advised even by the same urologist who performed the first TUR . A second TUR reduces tumor burden and may facilitate conservative therapy, for example, BCG is more effective against carcinoma in situ than multifocal papillary tumors and it is most effective against minimal residual disease after maximal resection of all visible tumors. TUR alone is sufficient therapy for a solitary T1 tumor if a re-TUR shows no evidence of residual invasion or carcinoma in situ, whereas BCG might be indicated if residual tumor is found ^[24]. Multiple recurrent T1 tumors may provide an indication for either conservative therapy or cystectomy but muscle invasion that is discovered after a second TUR will likely be treated by cystectomy. On the other hands , a patient with a muscle invasive (T2) tumor who had no evidence of residual tumor on re-TUR may elect to defer immediate cystectomy in favor of close follow up , which occurred in up to 20% of patients with muscle invasion , and the long term follow up of such patients justifies a conservative approach^[25].

CONCLUSION:

A significant proportion of patients have residual tumor on a routine contemporary second TUR after initial resection of primary and recurrent bladder tumors. In many of these cases tumor invasion of the submucosa or muscle is found only on re-TUR procedure.

Re-TUR is especially appropriate for patients with high risk superficial transitional bladder cancer for the following reasons:

Residual cancers are found in 33-76% of patients after their first TUR for Ta and T1 bladder tumor.

Errors in staging of bladder cancers are common and occur as a result of deficiencies in sampling and analysing after a TUR.

A T0 status of superficial bladder cancers at re-TUR seems to confer a favorable effect on cancer recurrence and progression in the short to medium term.

Patients with Multifocal Ta tumor may benefit from re-TUR to reduce tumor burden and facilitate intravesical therapy and to detect carcinoma in situ.

The re-TUR could be used to distinguish between patients for whom watchful waiting and bladder preservation is appropriate from those who need an early cystectomy for disease control.

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