

## Urethral Strictures Associated with the Management of Non Muscle Invasive Bladder Carcinoma

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### ABSTRACT:

#### BACKGROUND:

Carcinoma of Bladder is a common urological tumor. Urethral strictures with different grades are frequently seen in patients with non muscle invasive bladder cancer .

#### OBJECTIVE:

To elicit the incidence of urethral strictures, their severity and correlation with different factors in patients managed for non muscle invasive bladder tumor.

#### PATIENTS AND METHODS:

In a prospective study from January 2008 to January 2010 ,we followed 98 patients with superficial bladder tumor ,they were all male their age ranged from 38-76 years, all patients diagnosed endoscopically and histologically staged as superficial bladder tumor (excluding invasive bladder tumor),we follow those patients with a history regarding any change in urinary stream then urethroscopically during a period of 1-2 years, we classify urethral strictures that was urethroscopically diagnosed as mild, moderate and sever.

For each urethral stricture case we state the site and severity of the stricture, the number of preceding cystoscopies, duration of TURBT procedure and number of preceding chemotherapy sessions , the type of chemotherapy used and method of treatment required in each case.

#### RESULTS:

During the period of the study , a total of 23 urethral strictures (23.5%) were identified. They were all in the bulbar urethra, they were mild in 10 patients (43.5%), Moderate in 6 patients (26.1%) and sever in 7 patients (30.4%) and 14 patients with urethral stricture had also B.P.H(60.9%).

Prior to the occurrence of stricture; urethroscopy was done once in 55.5% of cases , twice in 26.1% and 3 or more in 17.4%.

Duration of TURBT procedure was  $\leq 20$  mints in 30.4% and  $> 20$  mints in 69.6%.

Intravesical chemotherapy sessions were 0-3 in 17.4% of patients, 6 in 43.5% and more than 6 in 39.1%.

The type of chemotherapeutic agent used was Doxorubicin in 56.5% of patients Mitomycin-c- in 26.1% and both of them (through multiple courses) in 13%.

#### CONCLUSION:

Urethral stricture associated with the management of non muscle invasive bladder tumors is a common and important clinical problem that need to be considered and avoided as far as possible ,Factors that may had a positive impact on the incidence of stricture were : B.P.H , duration of TURBT procedure, the number of intravesical chemotherapy sessions(6 and more) and doxorubicin instillation.

**KEY WORDS:** urethral stricture, bladder tumour, cystoscopy, intravesical chemotherapy .

### INTRODUCTION :

Urethral stricture disease is one of the oldest and most difficult maladies known to the urologist.

While references to the disease and its treatment dates back to the writings of the Hindus, Egyptians and Greeks, the management of this disease has undergone significant change in the last 4 decades<sup>(1,2)</sup>.

By definition ,anterior urethral disease: is a scarring process involving the spongy erectile tissue of the corpus spongiosum {spongiofibrosis} resulting in reducing of the urethral lumen<sup>(3)</sup>.

In contrast posterior urethral stricture; is an obliterating process in the posterior urethra that has resulted in fibrosis &generally the effect of distraction in the area caused by either trauma or radical prostatectomy<sup>(4)</sup>.

Any process that injures the urethral epithelium or the underlying corpus spongiosum to the point that

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healing results in a scar can cause anterior urethral stricture<sup>(5)</sup>. Today most urethral strictures are the result of either Trauma ( including accidents, external violence and iatrogenic trauma through the insertion of catheter, cystoscope or foreign body)<sup>(6)</sup>. Or inflammatory process like gonococcal and non gonococcal urethritis<sup>(7)</sup>, lichen sclerosus-Balanitis xerotica obliterans<sup>(8)</sup>, and inflammatory strictures due to chemical irritation<sup>(9)</sup>.

On the other hand, bladder carcinoma is a common urological tumor and 90% of bladder tumors are urothelial (transitional cell CA)<sup>(10)</sup>.

Transitional cell carcinoma of bladder could be presented in 3 distinct clinical entities:

Superficial (non muscle invasive) tumor, muscle invasive tumor and metastatic tumor<sup>(11)</sup>.

Most of the urothelial CA(55%-60%) are non muscle invasive (stage Ta,T1)<sup>(12)</sup>.

Management of non muscle invasive bladder tumor requires frequent transurethral interventions; The first cystoscopy for diagnosis and transurethral resection of the tumor(TURBT) usually followed by multiple weekly sessions of intravesical chemotherapy or immunotherapy<sup>(13)</sup>, and finally frequent check cystoscopies should be done at intervals according to the initial stage, grade and risk group<sup>(14)</sup>.

### PATIENTS & METHODS:

In this prospective study ,from January 2008 to January 2010, we followed 98 patients admitted and treated at Al-Yarmouk Teaching Hospital urology unit for having bladder carcinoma.

They were all male subjects, their age range from 38-76y with a mean  $59.30 \pm 10.58$ .

All were required to have a cystoscopically and histologically proven superficial transitional cell carcinoma of the bladder to be enrolled in this study( muscle invasive tumors were excluded).

For all the patients and after having the cystoscopic diagnosis ,transurethral resection of the tumor done(using 24 F resectoscope) and in most of them this is followed by 6 weeks course of intravesical chemotherapy (either mitomycin or doxorubicin according to the availability), using small caliber Foley catheter (12-14fr) which is removed after evacuation of the drug at the end of session .

All urethral strictures in this study were diagnosed by urethro cystoscopy (during the follow up check scopes for a period of 1-2 years) and usually preceded by a history of change in urinary stream of those patients .

According to the urethroscopy appearance We classify urethral stricture as a follows:

1. Mild: when we see a thin opalescent mucosal fold opened easily by the passage of the scope.

2. Moderate : when we see a more thick iris constriction in the lumen of urethra.

3. Sever: when we see a more sever narrowing with hardness in the lumen of urethra.

For each urethral stricture case we state age of the patient, any coexistent Benign prostatic hyperplasia (BPH) ,the site and severity of the stricture , ,the No. of preceding cystourethroscopes, duration of the TURBT procedure the No. of preceding chemotherapeutic sessions , the type of chemotherapy used, and the method of treatment required in each case .

From these collected data statistical analysis done to elicit the incidence of urethral stricture and its correlation with different variables.

statistics conducted by using ANOVA ,and pearson Chi-Square(x2) with p value considered to be significant if it is equal or less than 0.05.

### RESULTS:

During the period of the study, a total of 23 urethral strictures were identified in the 98 male patients with superficial bladder tumor enrolled in this study , which constitutes an incidence of 23.5% .

Patient age ranged from 38-75 years with a mean age  $59.30 \pm 10.58$  (table 1).

Among those patients with urethral stricture ,14 patients had also B.P.H (60.9%), but only 7 patients (30.4%) had a history of retention of urine.

The urethral stricture was bulbar in all patients and it was mild stricture in 10 cases (43.5%), moderate in 6 cases (26.1%) and sever in 7 cases (30.4%) .

Prior to the diagnosis of stricture , 13 patients had been subjected to a single check cystoscopy (56.5%) ,6 patients (26.1%) had twice , while 4 patients (17.4%) had 3 or more cystoscopies prior to the occurrence of stricture (table 2).

Duration of TURBT procedure, was equal or less then 20 minutes in 7 patients (30.4%) and more than 20 minuts in 6 patients (69.6%).Regarding intravesical chemotherapy prior to the occurrence of stricture ,4 patients (17.4%) received 0-3 sessions , 10 patients (43.5%) received 6 sessions and 9 patients (39.1%) received more than 6 sessions {through repeated courses in case of recurrence} (table 3).

Intravesical Doxorubicin used in 13 cases (56.5%), Mitomycin C in 6 cases (26.1%) and 3 patients (13.0%) received both drugs (through multiple courses).while 1 patient (4.3%) received no chemotherapy(table 3).

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Thirteen strictures (56.5%) were managed by optical urethrotomy while 10 cases (43.5%) were mild strictures and opened just by introducing the cysto scope.

Then , the incidence and severity of urethral

strictures were correlated with :BPH, the number of pre stricture cystoscopy, the duration of TURB.T procedure, the number of sessions and type of intravesical chemotherapy received prior to the occurrence of stricture as shown in table 4.

**Table 1: Age distribution of the patients**

	No Cases of stricture	%
Age (years) <50	3	13.0%
50--59	9	39.1%
60--69	5	21.7%
=>70	6	26.1%
Mean±SD (Range)	59.30±10.58	38-75

**Table 2: Number of pre stricture cystoscopies and duration of TURBT in stricture cases**

Number of cystoscope	No	%
Once	13	56.5%
Twice	6	26.1%
Three& more	4	17.4%
Mean±SD (Range)	1.70±1.02	1-5
Duration of TURBT		
	No	%
≤20 minutes	7	30.4%
>20 minutes	16	69.6%

**Table 3: Number of sessions and type of chemotherapeutic agents installed prior to the occurrence of stricture**

Number of sessions	No	%
0--3	4	17.4%
6	10	43.5%
>6	9	39.1%
Mean±SD (Range)	8.35±5.20	0-18
Chemotherapy		
	No	%
Doxorubicin	13	56.5%
Mitomycin	6	26.1%
Both	3	13.0%
No	1	4.3%

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**Table 4: The association of stricture severity with different parameters.**

	Mild		Moderate		Severe		P value
	No	%	No	%	No	%	
Number of cystoscope							
Once	6	46.2%	2	15.4%	5	38.5%	0.596
Twice	2	33.3%	3	50.0%	1	16.7%	
Three& more	2	50.0%	1	25.0%	1	25.0%	
Mean±SD	1.80±1.32		1.83±0.75		1.43±0.79		0.726
Duration of TURBT							
≤20 minutes	3	42.9%	1	14.2%	3	42.9%	0.592
>20 minutes	7	46.7%	5	33.3%	4	20.0%	
BPH							
Yes	7	50.0%	4	28.6%	3	21.4%	0.500
No	3	33.3%	2	22.2%	4	44.4%	
Number of sessions							
0--3	1	25.0%	-	-	3	75.0%	0.301
6	5	50.0%	3	30.0%	2	20.0%	
>6	4	44.4%	3	33.3%	2	22.2%	
Mean±SD	9.00±5.83		9.00±3.29		6.86±5.96		0.682
Chemotherapy							
Doxorubicin	4	30.8%	5	38.5%	4	30.8%	0.678
Mitomycin	3	50.0%	1	16.7%	2	33.3%	
Both	2	66.7%	-	-	1	33.3%	
No	1	100%	-	-	-	-	

\* The Pearson Chi-Square statistic is significant at the 0.05 level for percentages and ANOVA test for comparing means.

### DISCUSSION:

-Carcinoma of the bladder is a common urologic tumor all over the world (6.6% in men and 2.4% in women)<sup>(15)</sup> and management of this tumor takes a large area in the practice of almost all urologists.

Superficial (non muscle invasive) tumor constitute 55-60% of urothelial tumors.

-The management of superficial bladder cancer (with the aim of cure and bladder preservation) is basically done through frequent transurethral interventions, starting from the first diagnostic cystoscopy ± T.U.R.B.T, followed by the transurethral installations of chemotherapy or immunotherapy which usually delivered in multiple sessions for weeks.

In addition all patients must be followed by frequent check cystoscopies for years, for the early diagnosis of recurrence and progression.

-During all these transurethral interventions, there is always a possibility of iatrogenic urethral injury which may end in urethral stricture formation.

-Occurrence of a urethral stricture in a patient with superficial bladder tumor will adds more to the patients burden, and will make the management and follow up procedures (which are all depend on the urethral access to the bladder) more difficult.

More over, there is also a possibility of re implantation of tumor cells at the site of urethral injury and the dissemination of tumor cells through

the suprapubic cystostomy tract needed in case of retention which may shift the tumor to an advanced stage.

The aim of this study (which to our knowledge is the first in this aspect) is to elicit the real size of this important clinical problem in our practice, and to study all the possible etiological factors and their impact on the severity of stricture.

We found an incidence of 23.5% urethral stricture in the 98 patients we followed in a 2 years period, this high incidence reflects the importance of this clinical problem and approves our observations and concern of this problem many years before conducting this study.

All these urethral strictures were indentified during the follow up check cystourethroscopies, while uroflowmetry couldn't be used because of the high incidence (60.9%) of coexistent BPH in our patients which may lead to misinterpretation.

The stricture was in the bulbar segment of the urethra in all patients, which means that Bulbar urethra is the commonest segment affected by different insults, and this is comparable to what is mentioned in the literatures<sup>(16)</sup>.

The highest incidence of stricture was in the age group 50-59 years (9 cases) but there was no

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statistically significant correlation between age groups and severity of stricture( table 1.)

Among patients with urethral stricture , 14 patient had also B. P.H (60.9%) and seven of them (30.4%) gave a history of retention of urine.

This co-incidence of B.P.H is expected in the age group of patients enrolled in this study and it possibly had an impact on the etiology of stricture especially in those with retention of urine with the possible catheterization related trauma , also mentioned in many studies<sup>16,17</sup>,In addition large prostate with a high bladder neck make manipulation of the scope in the urethra during cystoscopy or TURB.T more difficult and some time may be even traumatic . but there was no statistically significant correlation with the severity of stricture(table4).

When we correlate the incidence of stricture with the number of previous check cystoscopies , we found the highest incidence (13 cases , 56.5%) in the group of patients exposed to one check cystoscope and also the highest incidence of sever stricture in this group (5 from 7) which means that the correct technique and handling of cystoscope rather than the number of cystoscope , is the determinant factor for the possibility of having trauma and stricture.

This fact is also concluded in other studies<sup>17,18</sup>.

We Also noticed a higher incidence of stricture, the more prolonged time of the TURB.T procedure (69.6% for > 20 minuts VS 30.4% for ≤ 20mints), which may be explained by the prolonged friction between resectoscope sheath and urethral mucosa, but there was no significant correlation with the severity of stricture(table 4).

When we study the impact of intravesical chemotherapy , we found a higher incidence of stricture in the patients received 6 sessions (10 cases ,43.5%) and in those with more than 6 through multiple courses (9 cases ,39.1%) than in patients with 0-3 sessions (4 cases , 17.4%)(table3). This result may reflect the significant impact of chemotherapy on the etiology of stricture which is explained by the tendency of the tissues exposed to prolonged chemotherapy for fibrosis which is also noticed in other studies<sup>18</sup>,and of course, more sessions means more urethral catheterizations .

We also found that 13 cases of stricture (56.5%)were in the group treated with doxorubicin , while only 6 cases of stricture (26.1%) diagnosed in the mitomycin group(table3).

More over , cases of stricture in the doxorubicin group were more than mild (moderate or sever) in 70% of cases , while these cases of moderate and sever strictures constitute 50% in the mitomycin group and there was only mild stricture in the patient received neither of them (table4).

These results elicit a possible correlation of doxorubicin with the incidence and severity of urethral stricture . when we search the literature, we couldn't find any article studied this correlation with doxorubicin.

In spite of all our above mentioned observations and possible correlations, they were all statistically insignificant because of the relatively low number of cases .

The treatment was feasible in all the cases of urethral stricture encountered in our study .

Mild strictures were opened just by introducing the cystoscope while moderate and sever strictures managed by optical urethrotomy , which was needed to be repeated in few cases of sever stricture.

### CONCLUSION:

- 1-Urethral strictures in patients with superficial bladder tumors is a common and important clinical problem that need to be well considered and avoided as far as possible by the managing medical personnel.
- 2-It is hard to determine the exact cause of the stricture because patients underwent different multiple transurethral interventions essential for the management of their bladder tumors ,all may have an impact on the etiology of stricture.
- 3-Factors that might had a positive impact on the incidence of stricture were : B.P.H ,duration of TURBT procedures ,the number of intravesical chemotherapy sessions(6 and more) and doxorubicin instillation.

### RECOMMENDATIONS:

- 1- As urethral strictures in patients with bladder carcinoma are mainly iatrogenic in origin , so it should be dealt with as a preventable morbidity:
  - a- by implementing an education program for the nursing staff regarding the proper technique of urethral catheterization and instillation of intravesical chemotherapy.
  - b-residents in urology and even junior urologists should take extra care during cystoscopic procedures, adhering to the strict rules of gentle , aseptic insertion of the scope with sufficient lubrication to minimize urethral injuries.
- 2- The positive correlation of doxorubicin with incidence and severity of strictures found in this

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study, need to be well addressed in a more large study in the future.

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