

The Management of Non-Invasive Bladder Tumours with Doxorubicin Intravesical Instillation after Transurethral Resection

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علاج سرطان المثانة غير الغازي بحقن الدوكسوروبيسين داخل المثانة بعد تجريف الورم عبر الاحليل

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الملخص: الهدف: تقييم فعالية العلاج بواسطة حقن المثانة بالدوكسوروبيسين في تقليل نسبة النكسة عند مرضى أورام المثانة غير الغازية. الطريقة: أجريت الدراسة في مستشفى الأسد الجامعي باللاذقية (سوريا) وشملت مرضى أورام المثانة غير الغازية الذين عولجوا بتجريف الورم عبر الاحليل ثم حقن الدوكسوروبيسين داخل المثانة. راقبنا المرضى كل 3 أشهر في أول سنتين ثم كل 6 أشهر بعد ذلك. وقد ركزنا في دراستنا على معدل نكسة الأورام. النتائج: شملت الدراسة 85 مريضاً لديهم ورم مثانة غير غازي. لدى 23 مريضاً سرطانة حليمية غير غازية (المرحلة أ) و لدى 62 ورماً يغزو النسيج الضام تحت الظهارة (المرحلة الأولى). 12 مريضاً لديهم أورام جيدة التمايز (درجة أولى) . 48 لديهم أورام متوسطة التمايز (درجة ثانية). 25 كانت سينة التمايز (درجة ثالثة). بلغ معدل النكسة الكلي 23%. وكانت معدلات النكسة 56% في الدرجة الثالثة و 0% في الدرجة الأولى. كانت نكسة الأورام الكبيرة 41% مقابل 17% في الأورام الصغيرة و كانت نكسة الأورام المتعددة 44% بينما نكسة الأورام الوحيدة 18%. بينما كانت نكسة أورام المرحلة أ 30% و 21% من أورام المرحلة الأولى. الخلاصة: بعد متابعة قصيرة الأمد. كان معدل النكسة لدينا 23% مقارنة بـ 54% في دراسة عالمية متعددة المراكز لم تعط علاجاً مساعداً داخل المثانة و بالتالي يبدو أن العلاج المساعد داخل المثانة بالدوكسوروبيسين يقلل نكسة سرطان المثانة السطحي. يبدو أن درجة الورم وحجمه وعدد الأورام هي عوامل إنذارية للنكسة.

مفتاح الكلمات: حقن داخل المثانة . الدوكسوروبيسين . سرطان المثانة غير الغازي.

ABSTRACT Objectives: Evaluation of the intravesical instillation of doxorubicin for its effect on disease recurrence for patients with non-invasive bladder tumour. **Methods:** The study was performed at Al Assad University Hospital in Lattakia, Syria and included patients with non-invasive bladder tumours who were managed with transurethral resection and induction and maintenance therapy with intravesical doxorubicin. They were followed up by cystoscopy every 3 months for 2 years and every 6 months thereafter with special emphasis on recurrence rates. **Results:** The study included 85 patients with non-invasive bladder tumours: 23 with non-invasive papillary carcinoma (Stage Ta), 62 with tumour invading subepithelial connective tissue (Stage T1). Twelve patients had well differentiated tumours (Grade 1), 48 had moderately differentiated (Grade 2), 25 had poorly differentiated (Grade 3) tumours. The total recurrence rate was 23%. The rates of recurrence were 56% in Grade 3 and 0% in Grade 1. The recurrence rate was 41% in patients with large tumours versus 17% in those with small tumours; 44% in those with multiple tumours compared to 18% in those with solitary tumours; 30% of Stage Ta tumours recurred and 21% of Stage T1 tumours. **Conclusion:** In short term follow-up, our rate of recurrence was 23%. Adjuvant intravesical doxorubicin was shown to reduce the recurrence of superficial bladder cancer. Tumour grade, size and number were shown to be prognostic factors for recurrence.

Keywords: Intravesical Instillations; Doxorubicin; Non-Invasive bladder cancer.

Advances in Knowledge

- Intravesical chemotherapy with doxorubicin is effective in the treatment of non-invasive bladder tumours.
- The grade, size, multifocality and stage of tumour are important prognostic indicators.

Application to Patient Care

- With minimal side effects, intravesical instillation of doxorubicin could be used as one of the interventions for non-invasive bladder tumours.

BLADDER CANCER IS THE FOURTH MOST common cancer in men and the tenth most common cancer in women.¹ The most common type of bladder cancer in Syria is urothelial carcinoma, also known as transitional cell carcinoma (TCC). Bladder cancer has various causative factors. Smoking leads to higher mortality from bladder cancer during long-term follow-up, even though in a multivariate analysis the prognostic effect of smoking was weaker than that of other factors, such as stage, grade, size and multifocality of the tumour.² Bladder cancer is also associated with industrial exposure to aromatic amines in dyes, paints, solvents, leather dust, inks, combustion products, rubber, and textiles.³ Approximately 80-90% of patients with bladder cancer present with painless gross haematuria, which is the classic presentation, but 20-30% of patients with bladder cancer experience irritative bladder symptoms.⁴

The diagnosis of bladder cancer ultimately depends on cystoscopic examination of the bladder and histological evaluation of the resected tissue. Small tumours can be resected in one chip where the chip contains the complete tumour plus a part of the underlying bladder wall. Larger tumours have to be resected in fractions.

Approximately 75-85% of patients with bladder cancer present with the disease confined to the mucosa (non-invasive papillary carcinoma [Stage Ta], carcinoma in situ [CIS]), or to the submucosa (tumour invading subepithelial connective tissue [Stage T1]). The management of non-muscle invasive bladder cancer has become more complex with regard to initial investigation, treatment and follow-up.¹

Although a state-of-the-art transurethral resection (TUR) by itself could eradicate a Ta or T1 tumour completely, these tumours recur in a high percentage of patients and progress to muscle-invasive bladder cancer in a significant number of cases. The choice between chemotherapy and immunotherapy largely depends on the risk that needs to be reduced: recurrence or progression. Two meta-analyses demonstrated that BCG (bacille Calmette-Guérin) therapy prevents, or at least delays, tumour progression.⁵ A meta-analysis of European Organization for Research and Treatment

of Cancer (EORTC) and Medical Research Council (MRC) data, comparing intravesical chemotherapy versus TUR alone, demonstrated that chemotherapy does prevent recurrence but not progression.⁶ There is no one superior drug with regard to efficacy. Mitomycin C, epirubicin and doxorubicin have all been shown to have a beneficial effect.⁷ A randomised trial documented that the concentration of the drug instilled was more important than the duration of the treatment.⁸

The treatment may be considered ineffective when a higher grade of T category or CIS appears during therapy. If a recurrence (even of the same grade and T category) is detected after 3 months and 6 months, the therapy may be considered a failure, since few patients will respond to further intravesical therapy.⁹

Severe complications have been reported in patients in whom extravasation of the drug occurred. Thus, an immediate instillation should not be given in extensive TUR procedures.¹⁰

The probability for recurrence and progression at 1 year vary from 15 to 61% and 0.2 to 17%, respectively. After 5 years of follow-up, recurrence and progression rates rang from 31% to 78% and 0.8-45% respectively.¹¹

The aim of the present study was to evaluate the intravesical instillation of doxorubicin for its effect on disease recurrence, patients' tolerance, side effects and the complications of instillation, in patients with non-invasive bladder tumour.

METHODS

The study included 85 patients with non-invasive bladder tumours who reported either to Al Assad University Hospital or the Center of Nuclear Medicine in Tishreen University Hospital, Lattakia, Syria between March 2005 and March 2008. This study was approved by the Internal Review Board (No. 211) of Tishreen University.

The inclusion criteria were as follows: patients with non-invasive transitional cell carcinoma of the bladder who were managed with transurethral resection and induction and maintenance therapy with intravesical doxorubicin. From the original number of 96 patients,

Table 1: Patients' characteristics

	N	%
Patients	85	
Male	83	97.6
Female	2	2.4
Age / year		
Mean	63	
Peak	61 - 70	
Range	34 - 85	
Follow - Up / month		
Mean	11	
Range	36 - 6	
Smoking habit		
L	4	4.7
M	21	24.7
H	60	70.6

L: less than 1 pack/day for 10 years; M: less than 1 pack/ day for 20 years; H: more than 1 pack/day for 30 years

11 were excluded for the following reasons: one patient had adenocarcinoma, two patients underwent only 6 sessions of doxorubicin, 8 patients were treated with a radical cystectomy; one patient had tumours within a diverticulum and 7 patients had invasive bladder cancer on review of histopathology.

After the diagnosis was determined by cystoscopy under local anaesthesia, the patients were admitted to the Department of Surgery and prepared for transurethral resection of bladder tumour (TUR-BT). During the procedure, the tumour characteristics in terms of size ($\leq 2.5\text{cm}$, >2.5) and number (solitary, multiple) were recorded. Intravesical chemotherapy was given routinely to patients with superficial (non-invasive) bladder tumours. We included only the patients with transitional cell carcinoma (TCC); we diagnosed one case with adenocarcinoma, but it was excluded. All patients consented to the adjuvant therapy.

A week after the TUR, the first session of doxorubicin was administered. All sessions were conducted on an outpatient basis. Each session began by emptying the bladder of any residual urine by a urethral catheter. Then we instilled 50mg of doxorubicin diluted with 50mL normal saline, and removed the catheter. We asked the patient to rest in a bed for 105 minutes by taking right lateral, left lateral, prone and supine positions, and then walking in the hall for another 15 minutes before voiding out the drug. The session was

Table 2: Tumour characteristics

	N	%
Primary or recurrent		
primary	73	85.9
recurrent	12	14.1
Size		
$\leq 2.5\text{cm}$	63	74.1
$>2.5\text{cm}$	22	25.9
Multifocality		
solitary	67	78.8
multiple	18	21.2
Stage*		
Stage Ta	23	27.1
Stage T1	62	72.9
Grade**		
Grade 1	12	14.1
Grade 2	48	56.5
Grade 3	25	29.4

*Ta: Non-invasive papillary carcinoma

T1: Tumour invades subepithelial connective tissue

**Grade 1: well differentiated

Grade 2: moderately differentiated

Grade 3: poorly differentiated

repeated weekly 4 times then monthly 11 times. We further excluded any patient who was not given this regimen or was not given the maintenance therapy. Two patients received only 6 sessions of doxorubicin, therefore they were excluded.

The rationale for the selection of doxorubicin was its local availability. Doxorubicin also represents an important drug for adjuvant intravesical chemotherapy. Although BCG is considered the first choice as intravesical adjuvant therapy, it is not always available in the present setting. Secondly, BCG is not relevant for most patients in our study since we had no cases of CIS.

Mainly, we followed up the patients by using cystoscopy every 3 months in the first two years and every 6 months after that. We also performed a cystoscopy when patients had documented haematuria.

RESULTS

The study included 85 patients with non-invasive bladder tumours. Table 1 shows the demographic characteristics of the study sample. The majority of the patients were males (97.6%). The mean age was 63 ± 9.6 years; the range was 34-85 years and the peak

Table 3: Factors of recurrence

	N	%
Total recurrence	20	23.5
Stage*		
Stage Ta	7	35
Stage T1	13	65
Grade**		
Grade 1	0	0.00
Grade 2	6	30
Grade 3	14	70
Size		
≤2.5cm	11	55
>2.5cm	9	45
Multifocality		
Solitary	12	60
Multiple	8	40

*Ta: Non-invasive papillary carcinoma
T1: Tumour invades subepithelial connective tissue

**Grade 1: well differentiated
Grade 2: moderately differentiated
Grade 3: poorly differentiated

incidence was between 61 and 70 years.

Our patients were compliant to the treatment; usually attending for the cystoscopy on the specified date. The follow-up of the patients continued successfully for up to 36 months (average 11 months). Smoking was the common risk factor for developing bladder cancer among our patients. Most patients were heavy smokers (71%), defined as smoking more than 1 pack per day for 30 years or more. Table 2 gives the full clinical and histopathologic characteristics of the tumours after TUR-BT, of which 85.9% were primary and 14.1% recurrent.

Morphologically, most tumours were small, defined as less than 2.5cm. We considered the total volume when there was more than one tumour. The percentage of small tumours was 74%; 79% of tumours were solitary and the rest multiple.

Microscopically, CIS was not diagnosed in any case and the tumours were staged as Ta and T1 (27% and 73%), respectively. Grade 2 (G 2) tumours (moderately differentiated) were the predominant type (56%) followed by Grade 3 (G3) poorly differentiated tumours (30%). The rest were Grade 1 (G1) tumours (well differentiated tumours). A total of 86% of our patients were diagnosed and treated for the first time, while 14% had been diagnosed and treated before, but had

Table 4: Progression & mortality rates

	N	%
Mortality	2	2.3
Progression	2	2.3
Stage* Ta to stage T1	1	1.2
Stage T1 to stage T2	1	1.2

*Ta: Non-invasive papillary carcinoma
T1: Tumour invades subepithelial connective tissue

**Grade 1: well differentiated
Grade 2: moderately differentiated
Grade 3: poorly differentiated

not been given intravesical adjuvant therapy.

It is known that adjuvant intravesical chemotherapy mainly affects the recurrence rate; therefore, we studied its relation to the tumours' characteristics [Table 3]. The tumours recurred in 20 patients (23.5%). Of these, tumours recurred in 35% of patients with Ta and in 65% of patients with T1. No G1 tumours recurred, but 70% of G3 tumours recurred while only 30% of G2 tumours did. As to the link between size and recurrence, 45% of big tumours recurred, but only 55% of small tumours. Multifocality affected the recurrence rate in the same way as size, with only 60% of solitary tumours recurring, while 40% of multiple tumours recurred.

The maximum follow-up time was 36 months (average 11 months). In such a short-term study we therefore could not obtain a valid conclusion on progression rates and mortality [Table 4]. We had 2 patients where the tumours progressed. In the first case, the tumour was a big multiple recurrent Stage T1, G2 tumour. Within 3 months, it became Stage T2 and G2. This patient underwent radical cystectomy and is still in good health. The other case was that of a multiple small recurrent Ta G2 tumour; in 6 months it became a T1, G2 tumour. The patient is under the intensive follow-up and the TUR has been performed. Two patients died, the first was an 85 year old heavy smoker, who worked in the cigarettes industry for 40 years. The other was 65 years old, and the cause of mortality is unclear.

Our patients tolerated the adjuvant chemotherapy well. Table 5 shows the side effects seen during the session or during follow-up. To avoid the complications of extravasation, we waited for a week after TUR for instillation of doxorubicin and avoided an instillation when there was significant haematuria. The catheter was placed by expert physicians without trauma of

Table 5: Adverse drug reactions

	N	%
Side Effects	22	25.9
Urinary frequency	14	16.5
Dysuria	12	14.1
Hematuria	12	14.1
Urinary tract infection	8	9.4
Intolerance of drug	1	1.2
Allergic reactions	0	0.00

the urethra. To avoid allergic reactions on the external genitalia, we withdrew the catheter slowly and then placed gauze on the meatus.

One patient had severe urinary tract infection (UTI) and did not tolerate the adjuvant therapy: in the urine culture there were colonies of *E.coli* (more than 1,000,000) and after that *klebsiella* was discovered. He was treated with appropriate antibiotics, but the irritative voiding symptoms continued and were very severe; therefore, he decided to stop the adjuvant therapy after 9 months, He remained recurrence free during the 18 months of follow-up. Mild or moderately severe urinary tract infection (UTI) occurred in 9.4% of patients and were effectively treated by antibiotics. Haematuria occurred in 12% without any tumour seen by cystoscopy. Cold biopsy of bladder was performed in two cases and they showed chronic inflammation. The irritative voiding symptoms were the most common side effects; especially dysuria and frequency of urine (interval between micturition less than 2 hours) 14% and 16.4%, respectively.

In summary, all patients, except one, tolerated the adjuvant intravesical chemotherapy.

DISCUSSION

Doxorubicin intravesical administration mainly affects the recurrence rate; therefore, we concentrated on evaluating the disease recurrence as well as side effects, complications and patients' tolerance of the instillation. Males were more dominant in this study compared to other studies.¹² This could be explained by the low incidence of smoking in women, and the fact that women rarely deal with the carcinogenic agents.

We notice that our patients were younger than in other studies by 5-6 years. We reviewed the medical literature and noticed that the lower limit is always 40 years, indicating a worrying trend in bladder cancer

occurrence in our region.¹² All patients were smokers and community awareness raising about the dangers of smoking is imperative since it is an important risk factor for non-invasive bladder tumours.

A major limitation of our study was the pathological testing, because the pathologists did not use one system; some used the WHO 1973 classification, but others used the WHO 2004 classification. We therefore compared the corresponding grades between the two systems, and reclassified all patients according to WHO 1973 since this classification is better known.

We compared our rate of recurrence with the published rate of recurrence without the intravesical adjuvant therapy (54%),¹³ and found that the recurrence free survival in our study was 77%.

As to the grade, we notice that the grade of tumour is an important indicator of recurrence: more than half of the patients with G3 (56%) had recurrence during follow-up, but none with G1. This accords with the opinion that G3 is a relative indication for radical cystectomy.¹⁴ The size and number of tumours also are shown; they are important indicators of recurrence, but less important than the grade. A total of 41% of patients with tumours greater than 2.5cm recurred and 44% of patients with multiple tumours recurred.

Saika et al. noted that only the adjuvant therapy (chemotherapy or immunotherapy) played an important role in the recurrence rate, when the non-invasive tumours were G3, while the size, multifocality and morphology did not play a role in terms of the recurrence rate.¹⁴ This difference to our results is perhaps unreal and could be occasioned by the fact that the tumours were high grade. Cheng et al. showed in long term follow-up (17 years) that adjuvant intravesical doxorubicin did not improve the recurrence rate of superficial bladder cancer, compared with controls on long-term follow-up. Tumour size and grade were shown to be prognostic factors for recurrence and progression respectively¹⁵, therefore we acknowledge the importance of long term follow-up in order to get valid conclusions.

CONCLUSION

Intravesical chemotherapy is safe and tolerable for non-invasive bladder tumours and has reduced tumour recurrence rates, especially when the grade is low, but it probably has no positive impact on disease progression or survival. Hence we must continue following up these patients for a long time. Also we sug-

gest the use of another drug such as mitomycin C in future trials for comparison with the current study's results. The tumour grade, size and number are important prognostic factors in the recurrence.

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