

Surgically treated transitional cell carcinomas of the bladder

The role of radical surgery

Muneer A. Al-Ali, MBChB, FRCS, Dawoud M. Kashmoula, MBChB, FICMS, Loay F. Haddad, MBChB, FICMS.

ABSTRACT

Objectives: To assess the treatment outcome and differentiate between the individual behavior of the tumor stages that were studied (Ta, T1, and T2a) with special reference to T2a tumors.

Methods: This study was carried out at Al-Rasheed Military Hospital, Baghdad, Iraq, during a 12 year period. Fifty-six patients with Ta, T1, and T2a (superficial invasion of muscularis propria) transitional cell carcinomas of the bladder, have been retrospectively analyzed. They were treated surgically with either transurethral of the bladder tumor (N=45) or radical surgery (N=11). Tumors with frequent recurrences or multifocal or extending to the ureter or vesical outlet were treated with radical surgery. No adjuvant intravesical chemotherapy or bacillus calmette-guerin therapy was practiced.

Results: All Ta tumors were controlled by transurethral of the bladder tumor treatment. Seventy-five percent of T1 tumors were controlled by transurethral of the bladder treatment and 25% qualified for radical surgery according to our criteria. Sixty percent of T2a tumors were controlled by transurethral of the bladder treatment and 40% warranted radical surgery. No stage progression occurred

in Ta and T1 lesions, but 27% of T2a lesions (superficial invasion of muscularis propria) progressed to T2b (deep invasion of muscularis propria). All grade 2a lesions of all stages under study were controlled by transurethral of the bladder treatment. Of 6 patients with T2a grades 2b and 3 tumors, 5 patients (83%) qualified for radical surgery. No distant metastasis occurred during the observation period, which ranged from 4 months to 12 years (mean 51 months). Seventy-five percent of all patients, 78% of the transurethral of the bladder treatment group and 64% of the radical surgery group are alive and free of disease for 5 years or more.

Conclusions: Radical surgery is indicated for T1 and T2a bladder carcinomas if they were multifocal, or extending to the ureter or the vesical outlet or frequently recurring within the first year, specially if they were T1 tumors of grade 3 or T2a tumors of grades 2b and 3. Transurethral resection is justifiable for grades 1 and 2a, low risk T2a tumors.

Keywords: Bladder, cancer classification, systectomy, grading, transurethral resection.

Saudi Med J 2002; Vol. 23 (6): 695-699

Bladder cancer (Ca) is the 2nd most frequent cancer in Iraq in both sexes.¹ There is an increased risk of Ca-bladder in areas where schistosomiasis is endemic like Arabian areas

including Iraq, and Africa.² Bladder cancer is known to be a heterogeneous disease with different behavioral processes. This had led various authors to give different descriptions to the same lesion. To

From the Department of Urology, (Al-Ali), The Royal Hospitals of St Bartholomew and The London, London, United Kingdom and the Department of Urology and Transplantation, (Kashmoula, Haddad), Al-Rasheed Military Hospital, Baghdad, Iraq.

Received 2nd February 2002. Accepted for publication in final form 24th February 2002.

Address correspondence and reprint request to: Dr. Muneer Al-Ali, Consultant Urologist, Department of Urology, The Royal Hospitals of St Bartholomew and The London, London, E1, United Kingdom. Tel. +44 (208) 8833010. Fax. +1 (775) 7432764. E-mail: alalimun@hotmail.com

consider a lesion as superficial is perhaps more of a semantic than of a clear prognostic value. Some considered T2a lesion (superficial invasion of muscularis propria) as superficial,³ while others even doubted T1 lesion as superficial.⁴ The World Health Organization (WHO) Ingenierburo fur Systemberatung und Planung (ISP) Consensus Classification Committee⁵ has recommended that the term "superficial bladder cancer" should not be used as it lumps together 3 biologically different lesions; non-invasive papillary neoplasia and carcinoma with lamina propria invasion. Lapham et al⁶ have recommended that empirical distinction into superficial and muscle invasive is better discouraged in keeping with the TNM staging. Dalbagni et al⁷ recommend the use of terms; organ confined and nonorgan confined. The main intention of the TNM system is to assist the clinician in planning the treatment for patients with bladder cancer and to provide prognostic information by calculating the treatment results on universally accepted units. On the other hand reports of inter-individual and intra-individual variation between pathologists may explain some of the difficulties in comparing results of treatment and prognosis from different centers.^{8,9} In addition, the clinical dilemma with superficial transitional cell carcinoma (TCC), is to distinguish those patients who will develop new tumors which may become invasive and life threatening from those who will either have no further recurrence or else new occurrences at superficial level only.¹⁰

In this study we have retrospectively analyzed the surgical treatment (transurethral resection or radical surgery) of Ta, T1, and T2a transitional cell tumors. Our aim is to assess the treatment outcome and differentiate between the individual behavior of the tumor stages under study, especially that of T2a tumors.

Methods. Fifty-six male patients whose age ranged from 24 years to 81 years (mean 36 years) were treated for Ta, T1 and T2a TCC of the bladder during a period of 12 years at Al-Rasheed Military Hospital, Baghdad, Iraq. Another 26 patients of similar stages were not included in the study due to incomplete data or follow up. One hundred and seventeen patients with more advanced disease have been treated during the same period. Twenty patients (35.5%) gave history of schistosomiasis. Twenty-one patients had Ta, 20 had T1 tumors and 15 had T2a tumors. Tumor stage, grade and type of treatment are shown in **Table 1**. Classification was based on the most recent TNM staging system¹¹ and the WHO grading system. Grade 2 lesions which have shown clinical heterogeneity in previous reports were subcategorized to "a" and "b" as proposed by Carbin et al¹² who considered grades 1 and 2a as low grades and grades 2b and 3 as high grades. Earlier pathological specimens were accordingly reviewed.

The follow up period ranged from 4 months to 12 years (mean 51 months). No adjuvant intravesical chemo or bacillus calmette-guerin (BCG) therapy was practiced, due to limited resources.

Treatment policy and techniques. Forty-five patients were treated with TUR of the bladder treatment (BT). Nine patients underwent radical cystectomy, 3 of whom had previous TUR-BT. Two patients with ureteric extension underwent wide partial cystectomy, total nephro-ureterectomy and ipsilateral pelvic nodal clearance. TUR-BT was performed down to the muscle layer using continuous flow Olympus resectoscope. Patients had check cystoscopy one-month post-TUR-BT, at 3-monthly intervals for the first 6 months, 6 monthly for a year and yearly thereafter unless recurrences were found when they were followed up as if newly presenting. Patients with T2a tumors underwent re-resection one month later to ensure that there is no residual tumor or higher stage.¹³ Radical cystectomy was performed for tumors which were multifocal or involving the bladder neck and urethra. Tumors, which frequently recurred during the first year, were also treated by radical cystectomy. Bilateral ureterosigmoidostomy was the type of diversion preferred by the patients for cultural reasons. Patients whose lesions had extended into the ureter, were treated with wide partial cystectomy, total nephro-ureterectomy and clearance of the ipsilateral pelvic lymph nodes.

Results. Of 48 patients who were treated with TUR-BT, 27 (56%) were controlled by single resection and 21 (44%) had recurrence, 18 of whom required further resection for up to 6 times (average of 3 resections/patient), and 3 underwent radical cystectomy for rapidly recurring tumors. All Ta tumors number (N)=21 and 75% of T1 tumors (N=15) were controlled by TUR-BT. Five of T1 tumors (25%) qualified for radical surgery. Sixty percent of T2a tumors (N=9) were controlled by TUR-BT, while 6 (40%) qualified for radical surgery, 5 (83%) of whom were of grades 2b and 3. Of 11 patient who underwent radical surgery, 9 underwent radical cystectomy (3 of whom after an initial TUR-BT) and 2 underwent wide partial cystectomy, total nephro-ureterectomy and ipsilateral pelvic nodal clearance. Indications for radical surgery, stage and grade are shown in **Table 2**. Histopathological examination of the cystectomy specimens of 4 patients (26.5%) with T2a tumor (2 of grade 2b and 2 of grade 3) revealed T2b lesions, which indicated stage progression. No stage or grade progression occurred to any of the Ta or T1 lesions. Forty-two patients (75%) were alive and free of disease for 5 years or more after treatment, 35 of whom were of the TUR-BT group (78%) and 7 of the radical surgery group (64%). None of the patients developed distant metastasis during the observation period. One patient who had undergone radical cystectomy died of metabolic disturbances.

Table 1 - Tumor stage, grade and type of treatment.

Stage (N)	Grade (N)	Treatment
Ta (21) T1 (20)	G1 (21) G1 (7)	21 TUR-B 4 TUR-B 2 Radical cystectomy (1 after TUR-B) 1 Partial cystectomy total nephro-ureterectomy and nodal clearance
	G2a and b (9)	9 TUR-B
	G3 (4)	2 Radical cystectomy 2 TUR-B
T2a (15)	G1 (3)	1 Radical cystectomy 2 TUR-B
	G2a (6)	6 TUR-B
	G2b (4)	2 Radical cystectomy 1 Partial cystectomy total nephro-ureterectomy and nodal clearance 1 TUR-B
	G3 (2)	2 Radical cystectomy (After TUR-B)
G - group, TUR-B - transurethral resection of the bladder tumor		

Table 2 - Type of surgery and indication, tumor stage and grade of the radical surgery group of patients (N=11).

N of Patients	Type of Surgery	Indication of Surgery	Grade (N)	Stage
3	Radical cystectomy	Frequent recurrences after TUR-B	G3 (1) G3 (2) T2a*	T1
3	Radical cystectomy	Extension to bladder neck and prostatic urethra	G1 (2) T1 G2b (1)	T2a*
3	Radical cystectomy	Multifocal lesions	G3 (1) G1 (1) G2b (1)	T1 T2a T2a***
2	Partical cystectomy total nephro-ureterectomy and nodal clearance	Ureteric extension	G1 (1) T1 G2b (1)	T2a
N - number TUR-B - transurethral resection of the bladder, G - grade * - cystectomy specimen revealed T2 lesion ** cystectomy specimen revealed involvement of the ipsilateral iliac lymph nodes				

Discussion. To date the most important factors are easily assessed at TUR and comprise the number of the tumors, the previous recurrence rate, the size of the tumors and the grade of the anaplasia. For progression, grade is the most important factor while T1 has a worse prognosis than Ta.¹⁴ Using these factors patients can be divided into 3 groups: the lowest risk group with Ta G1, single, <3 cm tumor with a recurrence rate of <1/year; a high risk tumor of T1 G3, multifocal, large, highly recurrent and Tis; and other tumors of intermediate risk.¹⁴⁻¹⁶ Grade 3 lesions need particular attention as they have a life-long high risk of progression.¹⁷ At 5 years half of these tumors become invasive and 20% of patients present with metastasis and other urologists have also advocated an early cystectomy for grade 3 lesions.¹⁴ However, many studies show that conservative treatment with BCG installations can prevent such a course in most of these patients.^{13,18-20} Grade 2a tumors, which were shown by others to have markedly different recurrence rate and prognosis from grade 2b tumor,²¹ were all controlled by TUR-B in our series, regardless of the stage. We practiced radical cystectomy for multifocal lesions even though "superficial", as such tumors were shown to have a greater chance of recurrence than single tumors and the disease-free interval is shorter.²² Rapidly

recurring lesions within the first year were also treated by radical surgery as they were shown to have poor prognosis.²³ We treated tumors extending into the ureteric orifice by wide partial cystectomy, total nephro-ureterectomy and ipsilateral pelvic nodal clearance. Kato et al²⁴ have shown that such tumors herald an invasive intramural ureteric tumor. In an European Organization for Research and Treatment of Cancer study (EORTC),²⁵ progression occurred in 21% of patients with tumors at the bladder neck and in only 9% when it was in another site (P<0.05). Fijii et al²⁶ in a series of 277 patients also stressed the significance of bladder neck involvement as an independent risk factor for the prognosis of "superficial" TCC, at multivariate analysis. To improve survival, some workers had even added adjuvant therapy to surgery in cases of extension to the ureter or vesical outlet. Birch et al²⁷ have shown that upstaging occurred in one 3rd of selected patients with superficial carcinoma of the bladder who have undergone radical cystectomy. Upstaging occurred in 26.5% of our cases. Birch et al²⁷ and Jakse et al²⁸ noted that T one tumors that are initially grade 3 have a worse prognosis than other "superficial" TCC's with recurrence rate of 80% and progression rate of 60%. More recently the need for radical surgery in some superficial bladder tumors is

emphasized. Freeman et al²⁹ stated that radical cystectomy should be considered a viable alternative to continued conservative measures for selected patients with aggressive "superficial" bladder tumors. Skinner³⁰ has treated grade 3 T1 tumors, which showed mutation of P53 by radical cystectomy. However, Liyama et al³¹ have shown that grade 3 lesions of early stages of bladder cancer can be treated with TUR-BT with or without adjuvant therapy. In fact, 2 (50%) of our 4 patients with grade 3 T1 tumors were controlled by TUR-BT without adjuvant therapy, and the other 2 (50%) qualified for radical cystectomy. It is remarkable that grade 1 and 2a, T2a tumors behaved differently from grade 2b and 3, T2a tumors, but similar to Ta and T1 namely 88% was controlled by TUR-BT. T2a tumors lie in a grey zone with behavior and prognosis, which have to be identified. Such identification will prevent under or over-treatment of T2a tumors and help distinguish patients requiring early radical treatment in the course of the disease, from those who are amenable to transurethral resection. Such stratification of patients will also determine the need for adjuvant treatment.³² Dalbagni et al⁷ showed that cancers invading the superficial muscle wall (T2a) can behave similarly to those invading deep muscle wall (T2b) and that 25% of patients with muscle invasive tumor on TUR treatment, had either superficial disease or no tumor on the final pathological specimen. They suggested a conservative approach for a subset of patients with muscle invasive tumors. Cheng et al³² conducted a univariate and multivariate analysis which showed that only tumor size is predictive of prognosis and that the subclassification of T2 bladder carcinoma by depth of muscle invasion is of no prognostic value, but their analysis did not include grading. The possible effect of intravesical bladder sparing therapy on recurrence velocity and horizontal spread in our cohort of patients remains speculative as we did not practice such treatment due to limited resources.

The EORTC-Genito Urinary (GU) group and the British Medical Association working party³³ have performed a combined analysis of completed trials using meta-analysis techniques. The statistical power of the tests used to compare treatments is increased as data are available from 6 randomized trials comprising 2535 patients. In all of these trials TUR-BT alone was compared with TUR-BT followed by intravesical chemotherapy using different drugs. There was a significant difference ($P < 0.01$) in the disease-free interval in favor of adjuvant treatment. However, although statistically different, less than 10% of patients randomized to adjuvant treatment were disease-free at follow up. The time of progression to muscle invasive disease in the 2 treatment groups and the overall duration of survival were not significantly different ($P > 0.1$). Intravesical BCG was not addressed in this combined analysis.

We have put together all factors that could affect prognosis in a workable policy. This series might also provide a rare model for comparison with patients who were treated with intravesical bladder-sparing therapy.

In conclusion, radical surgery is indicated for high risk T1 bladder carcinomas (namely if they are multifocal or extending to the ureter or the vesical outlet or frequently recurring within the first year) especially if they are of grade 3. Conversely, transurethral resection is justifiable for grade 1 and 2a, low risk T2a tumors.

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