Multiplicity and History Have a Detrimental Effect on Survival of Patients With T1G3 Bladder Tumors Selected for Conservative Treatment

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Purpose: In the absence of Tis tumor we assessed whether history and multiplicity have a detrimental effect on conservative treatment in carefully selected patients with T1G3 bladder carcinoma.

Materials and Methods: Between January 1976 and December 1999, 165 select patients with T1G3 bladder tumors were conservatively treated with transurethral resection plus adjuvant intravesical therapy. Patients with concomitant or previous Tis, previous T1G3, tumor size greater than 3 cm and more than 3 lesions were excluded from analysis. Repeat transurethral resection was not routinely performed. However, cytology had to be negative for atypia before the start of adjuvant intravesical therapy.

Results: Recurrence-free survival at 1, 3 and 5 years was 71.8%, 55.6% and 45%, respectively. Of the cases 14 (8.4%) progressed with a median progression-free survival of 149 months. A total of 23 patients (14%) died. The 5-year recurrence-free survival rate was 52%, 34% and 15% in cases of single and/or primary, multiple and recurrent tumors, respectively. Median overall survival was 144 months. The 5-year disease-free overall survival rate was 85%, 83%, 79% and 69% in cases of primary, single, multiple and recurrent tumors, respectively. An intact bladder was maintained in 137 patients (83%) with a mean disease-free overall survival of 102.7 months. Patients with recurrent and/or multiple T1G3 tumors showed worse survival ($p = 0.0021$ and 0.0142, respectively).

Conclusions: History and multiplicity are relevant predictors of survival even in highly selected patients with TIG3 bladder tumors that are conservatively treated.

Key Words: carcinoma, transitional cell; survival; chemotherapy, adjuvant; neoplasms, multiple primary; recurrence

T1G3 bladder cancer is classified as a high risk tumor. However, its prognosis is not homogeneous with a 5-year progression rate of 22% to 75%. The most important recognized risk factor is Tis. Unfortunately to our knowledge a specific prognostic analysis of a large number of patients with T1G3 is not available. Patients harboring T1G3 tumors, including single and multiple, primary and recurrent tumors with and without Tis, represent only 9.1% of the population analyzed to create the European Organisation for the Research and Treatment of Cancer risk tables.[1]

Optimal therapy for T1G3 carcinoma remains a matter of controversy. For years immediate cystectomy has been advocated as the best treatment.[2–4] On the other hand, several experiences have been reported with conservative treatment for T1G3 tumors by TUR and adjuvant intravesical therapy.[5–8] A recent meta-analysis showed better efficacy of TUR plus BCG than TUR alone or TUR plus intravesical chemotherapy for preventing the progression of superficial TCCB.[9] However, this analysis included only 108 Ta-T1 G3 tumors of 5,456 cases (2%). Therefore, the results cannot be applied with certainty to T1G3 bladder cancer and the role of BCG for preventing progression and death from this category of tumors has not been definitively proved. Conservative treatment for T1G3 tumors is of immediate efficacy for decreasing recurrence and probably early progression to muscle invasive disease. However, to our knowledge a positive impact on long-term survival has not been demonstrated. Moreover, many studies refer to unselected T1G3 tumors, including patients with associated untoward risk factors.

A conservative approach to T1G3 tumors was recently suggested only for a small proportion of carefully selected patients with a small, single primary tumor in the absence of Tis.[4,10] We expand these criteria by analyzing the long-term prognostic impact of history and the number of lesions on the outcome of carefully selected T1G3 tumors that were conservatively treated.

MATERIALS AND METHODS

From January 1976 to December 1999, 165 selected patients with T1G3 TCCB were conservatively treated with TUR plus adjuvant intravesical therapy. Patients with concomitant or previous Tis, a previous T1G3 bladder tumor, previ-

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ous pelvic radiotherapy and/or systemic chemotherapy, previous unsuccessful BCG therapy, chronic urinary tract infection, tumor greater than 3 cm and more than 3 lesions were excluded from analysis.

All patients underwent excretory urography, cytology, cystoscopy, and TUR of the tumor and the underlying muscular layer. Multiple random cold cup biopsies, including of the prostatic urethra, were performed only in patients with multiple tumors. Patients with concurrent dysplasia and/or Tis on bladder mapping were excluded from study.

Repeat TUR for T1G3 tumors has become a common practice at our institution only since 2000, and it was not performed in the current series. However, patients with positive cytology within 30 days after TUR underwent second-look TUR plus bladder mapping and they were excluded from analysis.

Between 1976 and 1999, 503 nonmuscle invasive bladder cancers (27.5%) were classified as T1G3 tumors. Of these 503 patients 165 (32.8%) with T1G3 TCCB fulfilled the current selection criteria. Of the 338 excluded patients (67.2%) 146 (29%) had more than 3 lesions and 62 (12.3%) had lesions greater than 3 cm. Tis was detected by mapping and/or by persistent positive cytology after TUR in 80 patients (15.9%), while previous Tis and a T1G3 tumor were recorded in 41 (8.1%) and 131 (26%), respectively. In 121 patients (24%) the coexistence of 2 or more mentioned factors was recorded.

A centralized repeat review of specimens was not performed. The pathological evaluation was done in all cases by the same 2 well trained pathologists. Histological examination in all patients had to show tumor invasion of the lamina propria and a tumor-free underlying muscular layer. No distinction was made of the level of lamina propria infiltration in relation to the muscularis mucosae. Tumors were multiple in 69 patients (41.8%) and recurrent in 43 (26.1%). Table 1 lists patient characteristics. Written informed consent was obtained from all patients.

Starting 14 to 30 days after TUR intravesical adjuvant chemotherapy, mainly doxorubicin, epirubicin and mitomycin C, or immunotherapy with BCG was given for 1 year. Every 3 months all patients underwent cytology, cystoscopy and biopsy of every suspicious bladder lesion. If a superficial tumor (category Ta-T1) recurred, TUR and bladder mapping were repeated. Subsequently intravesical therapy was continued for 1 year. Patients went off study if Tis, T1G3 or invasive tumor (T category greater than T1) was detected.

Statistical Analysis

Statistical analysis was performed by one of us (RA). History, number of tumors and adjuvant therapy were considered. Recurrence, progression and survival were estimated by the Kaplan-Meier method. Differences between subgroups were compared using the log rank test. For survival analysis death from any cause was considered an event and survivors at last followup were censored. This methodology was also adopted to analyze recurrence-free and progression-free survival. The distribution of parameters for all variables was examined and differences were assessed by the chi-square and Fisher exact tests (p value) and the OR. The ϕ coefficient was used as a measure of association derived from the Pearson chi-square statistic. On multivariate analysis stepwise selection of logistic regression was used to find significant variables (residual chi-square test) related to events (recurrence, progression and survival).

TABLE 1. *Patient characteristics*

No. pts	165	
Age:		
Median	68	
Mean (range)	66	(31–83)
No. tumors (%):		
Primary	122	(73.9)
Recurrent	43	(26.1)
Single	96	(58.2)
Multiple	69	(41.8)

TABLE 2. *Results*

Event	No. Pts (%)	Median Mos From TUR (range)	No. Outcome (%)
Lost to followup	25 (15.2)	41 (12–90)	
Recurrence:	75 (45.5)	11 (3–80)	Recurrent NMI tumors,
Primary	50 (41.0)		Ta in 35 (46.7),
Recurrent	25 (58.1)		T1 in 32 (42.6),
Single	33 (34.4)		T1G3 in 23 (30.6),
Multiple	42 (60.9)		Tis in 8 (10.7)
Progression:	14 (8.4)	12 (4–149)	
Primary	8 (16.0)		
Recurrent	6 (24.0)		
Single	5 (15.2)		
Multiple	9 (21.4)		
Cystectomy:	10 (6.0)	23 (3–72)	Bladder retraction in 1
Primary	5 (4.1)		
Recurrent	5 (11.6)		
Single	5 (5.2)		
Multiple	5 (7.2)		
Death:	23 (14.0)	44 (4–144)	Bladder Ca in 9 (5.5)
Primary	11 (9.0)		
Recurrent	12 (27.9)		
Single	8 (8.3)		
Multiple	15 (21.7)		

RESULTS

Table 2 lists results. During an observation period of 30 years 25 patients (15.2%) were lost to followup after a mean observation period of 41 months. The recurrence-free survival rate at 1, 3 and 5 years was 71.8%, 55.6% and 45%, respectively.

Recurrent tumors were stage T1 in 32 patients (19%) and again T1G3 in 23 (14%). In an additional 8 patients (5%) asynchronous bladder Tis was found. Median time from initial TUR to the first recurrence was 11 months. The recurrence rate was between 34% and 60% according to tumor characteristics with a median recurrence-free survival of 47 months. The 5-year recurrence-free survival rate was 45% (fig. 1). It showed great variation according to tumor history and multiplicity ($p = 0.05$ and 0.0007, respectively, table 3).

In 14 patients (8.4%) muscle invasive progression was noted at TUR for recurrent tumor. Median time between initial TUR and progression was 12 months. The 5-year progression-free survival rate was 91%. Median progression-free survival was 149 months. Six patients with progression underwent cystectomy, 2 underwent radiotherapy and 6 underwent only extensive TUR due to poor general status in 3 and to an additional lesion in the remaining 3. Not enough statistical power was attained to demonstrate a significant difference in the progression rate according to tumor characteristics.