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Prognosis and Treatment of T1G3 Bladder Tumours. A Prognostic Factor Analysis of 121 Patients

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Patients with T1G3 bladder cancer have a considerable risk for recurrence and/or progressive disease. Until now no consensus has been achieved on the optimal treatment. Within the Dutch South Eastern Bladder Cancer Study Group, 155 patients with a T1G3 bladder tumour were seen between 1983 and 1988. After review of histology, 121 could be evaluated and recurrence-free interval was studied with regard to prognostic factors. Prognostic factors such as sex, age, blood group, abnormalities on intravenous urography, pretreatment tumour configuration, number of tumours, number of locations involved in the bladder, voided urine cytology, results of random biopsies and mitotic index were evaluated, using a multivariate analysis with the Cox proportional hazard model. During the follow-up period, 70 (58%) patients had recurrent bladder cancer, and of these 30 (43%) had progression into invasive disease. Of the possible prognostic factors analysed, only multiplicity ($P = 0.03$) and the number of locations of the tumours ($P = 0.03$) were independent prognostic factors in relation to the risk of recurrence. The recurrence-free interval was influenced by the therapy. For T1G3 tumours, additional intravesical immunotherapy/chemotherapy or radiotherapy after transurethral resection (TUR) increased the recurrence-free interval significantly. Because most other parameters did not show additional prognostic value, the T1G3 tumours can be considered as homogeneous with regard to prognosis. Only multiplicity and the number of locations involved added to the prognostic significance of patients with these bladder tumours. In addition, it is advisable to give patients with T1G3 tumours additional treatment after the initial TUR.

Key words: bladder tumours, superficial, prognosis, treatment
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INTRODUCTION

THE CLINICAL course of superficial bladder tumours (Ta-T1, G1-3, Tis) is characterised by its unpredictability. Although it is obvious that the strategy of treatment differs from muscle-invading bladder cancers, no consensus has been reached about their therapy [1]. Transurethral resection (TUR) of all visible tumour remains the cornerstone of treatment, but the initial TUR is followed by a heterogeneous therapy schedule [1, 2]. Different forms of adjuvant treatment have become available in the last decades. Developments in intravesical chemotherapy

and immunotherapy have introduced new treatment options for superficial bladder tumours, which allow therapy to be individualised [3–5].

On the basis of prognostic factors, patients with superficial bladder cancer can be divided in subgroups [6, 7]. Subdivision by tumour stage and grade is most important, and can play a role in the treatment selection, the individualisation of therapy and the development of future studies [8, 9].

Patients with T1G3 tumours are at special risk, because of the high recurrence rate of these tumours and their special tendency to develop muscle-invasive disease [10, 11]. The incidence of T1G3 transitional cell carcinoma of the bladder varies from 6 to 23% of all superficial bladder tumours, recurrences occur in 50–90% of patients, and progression to muscle-invading disease in 25–50% of the patients [6, 10, 11]. Several studies have discussed the term "superficial" for these T1G3 patients. Abel showed the unfavourable outcome of patients with pT1 tumours and suggested the term "superficial" to be reconsidered [12]. Jakse and colleagues defined the 40 T1G3 patients they studied as a high risk group and recommended special caution [10].

Within the Dutch South Eastern Bladder Cancer Study Group, we were able to evaluate the largest series to date of T1G3 bladder tumours for analysis of prognostic factors, treatment and recurrence rates.

PATIENTS AND METHODS

From 1983 to 1988, 2075 patients with newly diagnosed bladder tumours were registered in the Dutch South Eastern Bladder Cancer Study Group. The group is a cooperative organisation of 45 urologists (working in 24 hospitals), five radiotherapy centres and five pathology departments. 155 patients with T1G3 tumours were registered according to the TNM classification and graded according to Mostofi, with a slight modification according to Pauwels [13–15]. To exclude interindividual variations, one pathologist reviewed all slides histopathologically. For 121 patients, the specimens were sufficient for histological characterisation, were correctly staged and could, therefore, be included in the study. Of these, 104 were men and 17 were women, with ages ranging from 37 to 88 years (median 70). All patients underwent complete resection of the tumour including deep resection of muscle, and random biopsies were taken from 79 patients (65%). Carcinoma *in situ* (Tis) was found in 19 of 79 biopsy specimens (24%), and dysplasia in 16 of 79 (20%).

Treatment was instituted according to the preference of the members of the study group, and given immediately after the histological diagnosis. The patients were treated by eight different regimes, but mainly by TUR only (48 patients), TUR and radiotherapy (17 patients), and TUR and intravesical immunotherapy or chemotherapy (51 patients). In 16 of the 19 Tis patients, adjuvant treatment was given. 5 patients underwent a cystectomy after primary diagnosis. The radiotherapy was given as external radiation of 44 Gy on the pelvic region and, in addition, external radiation of 66 Gy as a boost on the bladder region. The intravesical therapy consisted of mitomycin-C (30 mg in 50 ml saline), given once a week for 1 month, and thereafter once a month for a total of 6 months after TUR or BCG (Bacillus-Calmette-Guerin) (BCG-Tice or BCG-R.I.V.M.), given once a week for 6 consecutive weeks. Median follow-up for recurrence and survival was 4 years (range 3–8).

Blood group, abnormalities on intravenous urography (IVU) (visible tumour in the bladder and/or dilatation of the upper urinary tract), tumour configuration, number of tumours, number of tumour locations, cytological results of voided urine, biopsy results and mitotic index were analysed as prognostic factors. The bladder was divided into 11 distinct regions, namely the trigone, right ureteral orifice, left ureteral orifice, right wall, left wall, anterior wall, posterior wall, dome, bladder neck, prostatic urethra and prostate. Maligant cytology was defined as an increase of the nuclear–cytoplasmic ratio, hyperchromatosis of the nuclei, polymorphic nuclei and cells, and the appearance of papillary structures. The mitotic index of the tumour expresses the number of mitotic figures per 10 high power (×40) fields of neoplastic tissue. As criteria for counting mitosis, we used the recommendations of Baak [16].

A recurrence was defined as a histologically-proven bladder tumour after TUR, progression was defined as the development of muscle-invasive disease.

Statistical methods

Recurrence curves were computed with the actuarial method. To test the equality of curves for several groups, we used log rank tests. We explored the possibility of intergroup differences in important confounding prognostic variables (regarding recurrence) by estimating β in Cox's proportional hazard model. The cut-offs for the various variables were taken with allowance of number of patients in order to obtain statistical significance.

RESULTS

Of the 121 patients with T1G3 bladder tumours, 70 (58%) had recurrent bladder cancer during the follow-up period, and 30 of the 70 (43%) showed progression into muscle-invasive tumours. During the follow-up period, 41 patients (34%) died, 15 of them (36%) from bladder carcinoma. Death due to bladder cancer was not influenced by treatment. Of the patients who died of other causes, 2 were known to have recurrent superficial bladder cancer at the time of death.

Results of a multivariate analysis of pretreatment prognostic factors are given in Table 1. Of the measures examined, multiplicity ($P = 0.03$) and location of the tumours in more than one region ($P = 0.03$) were both independent prognostic factors for time to recurrence, especially in patients with multiple tumours located in different regions of the bladder. Additional prognostic significance for blood group, abnormalities on IVU, pretreatment tumour configuration, cytological results from voided urine, biopsy results or mitotic index ($P > 0.05$) was not found.

Table 2 compares type of therapy with rate of recurrence and progression. Adjuvant treatment prolonged the time to first recurrence significantly ($P = 0.001$) (Table 2, Figure 1). Patients with TUR only showed a shorter recurrence-free interval than patients with TUR plus radiotherapy or TUR plus bladder instillations. No significant difference was seen between TUR plus radiotherapy and TUR plus intravesical immunotherapy or chemotherapy ($P = 0.34$). In this study, additional treatment was not found to be of use, especially in multiple cancers.

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Table 1. Prognostic factors

Prognostic factor	Number	β	*P* value
Age (years)			
⩾ 70	62	0.15	0.54
< 70	59		
Sex			
Male	104	0.19	0.57
Female	17		
Blood group			
O+	33	0.21	0.47
Other	66		
IVU			
Normal	79	0.02	0.93
Abnormal	42		
Tumour configuration			
Papillary	93	0.11	0.72
Solid	27		
Tumour number			
Solitary	74	0.53	0.03
Multiple	45		
Number of regions			
1	52	0.54	0.03
> 1	69		
Cytological results			
Malignant	39	0.57	0.10
Normal	33		
Biopsy			
No Tis	60	0.14	0.65
Tis	19		
Mitoses (number)			
< 10	46	0.10	0.68
⩾ 10	70		

Table 2. Treatment, recurrence and progression

	n	Median time to first recurrence (months)	Recurrence during follow-up (%)	Progression of recurrences (%)
All patients	121	12	58	43
TUR only	48	11	75	36
TUR + intravesical	51	19	55	50
TUR + radiotherapy	17	25	35	50
		($P < 0.05$)	($P < 0.05$)	(n.s.)

TUR versus TUR + adjuvant treatment: $P < 0.05$ for median time to first recurrence and recurrence during follow-up. TUR + intravesical versus TUR + radiotherapy: not significant (n.s.) for median time of first recurrence and recurrence during follow-up.

Mainly during the first year of follow-up, there was a relatively high actuarial risk of recurrence after TUR alone (64%). The incidence of recurrent progressive disease was not influenced by treatment type ($P = 0.74$). It should be noted that the three treatment arms were completely matched with regard to the other prognostic factors.

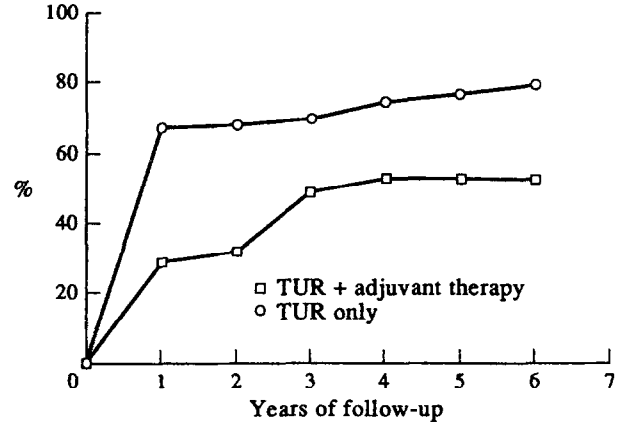

Figure 1. Actuarial risk of recurrent disease.

DISCUSSION

The prognosis of superficial bladder cancer mainly depends on the risk of recurrent disease. In the majority, the recurrences will remain superficial, but about 10 to 15% of patients will show progression into muscle-invasive disease [6]. This cancer has an overall recurrence rate of 50–70%, while progression into muscle-invasive disease occurs in 2–40% [6].

From several reports on prognostic factor analysis, we noticed the clear heterogeneity of the superficial tumours [6, 7]. It must, therefore, be questioned why superficial bladder tumours have been classified mainly as a single group, leading to treatment protocols being developed and results being evaluated on that basis [1, 3]. The most significant prognostic factors in superficial bladder cancer are tumour stage and grade [8, 9]. Combining these factors, a subgroup of T1G3 tumours can be defined. Although considered superficial, this tumour is associated with a high risk of recurrence and progression and, therefore, death. However, the number of T1G3 patients, as a subdivision of superficial bladder tumours, studied in the literature is small [6, 7]. Several studies underline the high tendency to develop recurrent disease for these tumours [10, 11]. Although T1G3 transitional cell carcinomas of the bladder are known to have a worse prognosis than other superficial bladder tumours, consensus about their treatment is lacking. Treatment regimens range from TUR only to radical cystectomy.

We were able to study the largest number of patients with T1G3 tumours published to date. From our study of 121 histologically reviewed T1G3 superficial bladder tumours, it became evident that adjuvant treatment decreases recurrence rate and increases the recurrence-free interval significantly. The prophylactic use of adjuvant intravesical immunotherapy or chemotherapy has been stated to improve treatment results [4, 5]. Like others, we believe that this kind of adjuvant treatment should not be given for every superficial bladder tumour, but is advisable for T1G3 tumours [1, 10, 11]. Radiotherapy is not widely used for superficial bladder tumours. Although this study was not performed in a randomised, prospective way, the results indicate the beneficial effect of radiotherapy on recurrence-free interval, as has been stated by others [17, 18]. Patients with T1G3 bladder tumours need to be treated with special caution. Additive treatment is demanded. A more aggressive approach such as cystectomy may be necessary in the long term, especially in patients with good life expectancy. However, the decision on this radical option may be delayed by intravesical instillations after the initial TUR. Herr and

colleagues concluded, in a well-documented randomised study, that in high-risk patients intravesical BCG can delay disease progression, prolong the period of bladder preservation and increase the overall survival [19].

Other factors that were shown to be of importance were multiplicity of tumours, ureteral obstruction, abnormality in random biopsy and cytology results [7, 20–22]. In our study, factors such as blood group, abnormalities on IVU, tumour configuration, results of cytology and random biopsy, and mitotic index did not show additional prognostic significance. In our opinion, this is because our patients were homogeneous for stage and grade, which are superior indicators for prognosis, and could have masked the less important prognostic value of the other characteristics. Only multiplicity and tumour location in different regions of the bladder were independent prognostic factors. With the use of the multivariate analysis, only factors that give additional prognostic significance are of value. This may be the reason why our results differ from those of others who studied all different superficial bladder tumour categories. The result of this study that patients with multiple tumours located in different regions of the bladder were especially at risk for recurrence may underline the hypothesis that these patients have diffuse premalignant or malignant changes of the bladder, which are not visible at the time of the initial TUR. This could be confirmed by the use of flow cytometry, which has shown aneuploid stem cells of normal appearing mucosa in patients with bladder cancer [23]. One would expect that patients with multiple tumours would particularly benefit from the additional treatment. However, in this study we were not able to confirm this.

More sophisticated techniques such as flow cytometry, karyometry and tumour-associated antigen expression have been studied recently, but are not yet of clear prognostic value for the daily clinical practice [24–26]. They make it possible to subdivide patients with superficial tumours into individual prognostic categories.

In conclusion, from the results of this study, it is advisable to give patients with T1G3 bladder tumours additional treatment after the initial TUR. Because of the high recurrence and progression rate, the term "superficial" should be reconsidered or used with caution, with consequences for treatment decisions. Patients with T1G3 tumours must be classified and categorised separately. To evaluate these T1G3 tumours together with other superficial tumours is justified considering the heterogeneity of these tumours with regard to the risk of recurrence and progression. Additional treatment, especially intravesical immunotherapy and chemotherapy, is advisable to prolong the recurrence-free interval, and to improve the survival of patients with T1G3 bladder tumours. Association with bad risk factors, such as multiplicity and location of the tumour(s) in different regions of the bladder, might necessitate a more aggressive treatment like cystectomy, especially in patients with good life expectancy. In developing future treatment protocols, the heterogeneity of the "superficial" bladder tumours must be considered. In particular, the stage, histological grade, multiplicity and the number of locations in the bladder of superficial tumours must play a role in study design. In these studies, the optimal treatment for high-risk superficial bladder tumours has to be elucidated in prospective randomised protocols, which are now in progress in Europe (EORTC Genito-urinary Group) and in the U.S.A.

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