



Bladder Cancer

Predicting Recurrence and Progression in Individual Patients with Stage Ta T1 Bladder Cancer Using EORTC Risk Tables: A Combined Analysis of 2596 Patients from Seven EORTC Trials

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Abstract

Objectives: To provide tables that allow urologists to easily calculate a superficial bladder cancer patient's short- and long-term risks of recurrence and progression after transurethral resection.

Methods: A combined analysis was carried out of individual patient data from 2596 superficial bladder cancer patients included in seven European Organization for Research and Treatment of Cancer trials.

Results: A simple scoring system was derived based on six clinical and pathological factors: number of tumors, tumor size, prior recurrence rate, T category, carcinoma in situ, and grade. The probabilities of recurrence and progression at one year ranged from 15% to 61% and from less than 1% to 17%, respectively. At five years, the probabilities of recurrence and progression ranged from 31% to 78% and from less than 1% to 45%.

Conclusions: With these probabilities, the urologist can discuss the different options with the patient to determine the most appropriate treatment and frequency of follow-up.

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1. Introduction

Prognostic factors in patients with superficial bladder cancer have been the subject of numerous publications for many years [1–11]. Depending on a patient's characteristics, after transurethral resection (TUR) the probability of recurrence at one year ranges from about 15% to 70% [6]; the probability of progression at five years ranges from about 7% to 40% [5].

The prognostic importance of various factors is not always the same from one publication to another [7]. This may be due to differences in the choice of variables analyzed, their coding, and, in multivariate analyses, the correlation between the factors. Another important source of variability is due to differences in the endpoint assessed: first recurrence or progression.

Typically the goal has been to divide patients into risk groups of good, intermediate, and poor prognosis. After TUR and one immediate instillation of chemotherapy, treatment can then be adapted according to the patient's prognosis, with good prognosis patients receiving either no further instillations or intravesical chemotherapy. In poor prognosis patients the treatment of choice is BCG with maintenance. The treatment of intermediate-risk patients remains controversial [12].

The division of patients into risk groups is problematic. In some cases the same risk group classification has been applied to both recurrence and progression, even though the relative importance of the prognostic factors for these two endpoints is different [7,8]. Thus, a risk group classification may be appropriate for one endpoint but not for another. In addition, the division of patients into risk groups is arbitrary, since the concept of what constitutes a good-risk patient or a poor-risk patient may vary from one clinician to another.

Nomograms have been proposed as a method that avoids the arbitrary division of patients into risk groups [13]. Based on a nomogram, one can calculate the probability of a certain event; for example, the probability of progressing within five years. Alternatively, lookup tables provide the probability of an event based on the prognostic score.

Ideally, one would like to be able to calculate the short- and long-term risks of recurrence and progression based on available clinical and pathological data. Molecular markers have sometimes been used in individual patients to help predict their prognosis, but none are used daily in current clinical practice.

The aim of this paper is to provide simple tables that will allow urologists to easily calculate a superficial bladder cancer patient's probability of recurrence and progression at one and five years after TUR based on a set of routinely assessed clinical and pathological factors. This will then serve as an aid in determining the most appropriate adjuvant treatment after TUR and the frequency of follow-up in an individual patient.

2. Methods

Over the past 30 years the European Organization for Research and Treatment of Cancer (EORTC) has carried out a series of randomized phase III studies that compared prophylactic treatments after TUR in stage Ta, T1, and Tis bladder cancer patients. Seven of these trials are included here [14–19]. Details of these trials, which accrued patients between January 1979 and September 1989, are provided in Table 1.

Individual patient data were merged from these trials for the following variables assessed at entry on study: intravesical treatment, age, gender, prior treatment, prior recurrence rate, number of tumors, tumor size, T category (local and review), presence of concomitant carcinoma in situ (CIS), and grade (local and review; 1973 WHO classification). As review pathology was available for only half the patients, the review assessment was used only if the local pathology was not available. Overall, the difference in prognosis based on local and review pathology was small [20].

The following endpoints were assessed:

1. Time to first recurrence (disease-free interval): time from randomization to the date of the first bladder recurrence. Patients who were still alive and without recurrence were censored at the date of the last available follow-up cystoscopy. Deaths before recurrence were analyzed as a competing risk.
2. Time to progression to muscle invasive disease: time from randomization to the date of first increase to stage T2 or higher disease in the bladder. Patients who were still alive and without muscle invasion were censored at the date of

Table 1 – Trials included in prognostic factor analysis

EORTC trial number	Treatment after TUR	Number patients randomized
30781	Oral Pyridoxine, Placebo [14]	291
30782	Thiotepa, Doxorubicin, Cisplatin [15]	356
30791	Epodyl, Doxorubicin, Control [16]	443
30831	Mitomycin C [17]	517
30832	Doxorubicin [17]	448
30845	Mitomycin C, BCG (no maintenance) [18]	361
30863	Epirubicin, Water [19]	512
Total		2928

the last available follow-up cystoscopy. Deaths before progression were analyzed as a competing risk.

The prognostic importance of recurrence at the first follow-up cystoscopy at three months on the time to progression was also evaluated. Extravesical recurrence was not analyzed since these data were not routinely collected.

Time to event distributions were estimated by means of cumulative incidence functions to properly take into account the patients who died (competing risk) before recurrence or progression [21]. They were compared using the stratified univariate and multivariate Cox proportional hazards regression model with stratification by study and the presence or absence of intravesical treatment.

Based on the coefficients of the variables in the multivariate model, a weight (score) for each level of each variable was obtained. The weights that corresponded to a given patient's characteristics were summed. Patients were then divided into four groups according to their total score. For each group, cumulative incidence estimates of the probabilities of recurrence and progression at one year and five years were calculated along with their 95% confidence intervals.

To assess model accuracy (discrimination) at one and five years, Harrell's bias corrected concordance index c , $0 \leq c \leq 1$, was calculated. Models were refit 200 times with the bootstrap resampling technique. The concordance index is the percentage of patient pairs in which the predicted and observed outcomes are in agreement; i.e., the probability that for two patients chosen at random, the patient who had the event first had a higher probability of having the event according to the model. $C = 0.50$ represents agreement by chance; $c = 1.0$ represents perfect discrimination [22].

All statistical analyses were done in SAS version 9.1.3 and in R version 2.2 with the Design software package version 2.0-12.

3. Results

Two thousand, nine hundred twenty-eight patients were randomized in the seven EORTC trials included here. Excluding the ineligible patients, 2596 (89%) eligible patients with stage Ta T1 bladder cancer, with or without concomitant CIS, were included in this analysis.

3.1. Patient characteristics

The main characteristics of the patients are given in Table 2. Seventy-eight percent received intravesical treatment, mainly chemotherapy. In one study, patients were randomized to receive either chemotherapy or six induction instillations of BCG. The median age was 65 years and almost 80% were male.

Patients tended to have favorable characteristics: 54% were primary; however, among recurrent patients, slightly more than half had a prior

Table 2 – Trial and patient characteristics

	Number (%)
Study	
30781	270 (10.4)
30782	313 (12.1)
30791	414 (15.9)
30831	451 (17.4)
30832	391 (15.1)
30845	327 (12.6)
30863	430 (16.6)
Intravesical treatment	
No	561 (21.6)
Yes	2035 (78.4)
Age (years)	
≤60	859 (33.1)
61–70	890 (34.3)
71–80	690 (26.6)
>80	118 (4.5)
Unknown	39 (1.5)
Gender	
Male	2044 (78.7)
Female	515 (19.8)
Unknown	37 (1.4)
Prior treatment	
No	2358 (90.8)
Yes	187 (7.2)
Unknown	51 (2.0)
Prior recurrence rate	
Primary	1405 (54.1)
Recurrent, ≤1 rec/yr	505 (19.5)
Recurrent, >1 rec/yr	645 (24.8)
Unknown	41 (1.6)
Number of tumors	
1	1465 (56.4)
2–7	836 (32.2)
≥8	255 (9.8)
Unknown	40 (1.5)
Tumor size	
<1 cm	920 (35.4)
<3 cm	1167 (45.0)
≥3 cm	464 (17.9)
Unknown	45 (1.7)
T category	
Ta	1451 (55.9)
T1	1108 (42.7)
Unknown	37 (1.4)
Carcinoma in situ	
No	2440 (94.0)
Yes	113 (4.4)
Unknown	43 (1.7)
Grade	
G1	1121 (43.2)
G2	1139 (43.9)
G3	271 (10.4)
Unknown	65 (2.5)
T1 G3	
No	2361 (90.9)
Yes, No CIS	172 (6.6)
Yes, with CIS	22 (0.8)
Unknown	41 (1.6)

Table 2 (Continued)

	Number (%)
Recurrence at 3 months	
No	2070 (79.7)
Yes	313 (12.1)
Unknown	213 (8.2)
Recurrence	
No	1356 (52.2)
Yes	1240 (47.8)
Progression	
No	2317 (89.3)
Yes	279 (10.7)
Survival	
Alive	1743 (67.1)
Dead	853 (32.9)
Cause of Death	
Alive	1743 (67.1)
Malignant disease	262 (10.1)
Other	461 (17.8)
Missing	130 (5.0)
Total = 2596 patients.	

recurrence rate of more than one per year. Fifty-six percent had a single tumor, in 80% the maximum tumor diameter was smaller than 3 cm, 56% were Ta, 10% were grade 3, and 4% had concomitant CIS.

3.2. Selection of variables in the Cox multivariate models

Variables that represented the prior recurrence rate, number of tumors, tumor size, T category, grade, and CIS were included in the final multivariate models for time to first recurrence and time to progression. Prior treatment was not included because only 7% of the patients were previously treated. In addition, it was correlated with the prior recurrence rate and the type of previous treatment

could not be taken into account. Age and gender were likewise not retained in the final models, as they were not significant at the 5% level and their inclusion did not improve either model's discrimination or calibration.

3.3. Time to first recurrence

Based on a median follow-up of 3.9 years and a maximum follow up of 14.8 years, 1240 of 2596 patients (47.8%) had at least one recurrence. The median time to first recurrence was 2.7 years.

As indicated in Table 3, the following variables were identified to be of prognostic importance in the univariate analysis: prior treatment, prior recurrence and prior recurrence rate, number of tumors, tumor size, T category, grade, and the presence of CIS.

The variables included in the multivariate model were coded as (Table 4): prior recurrence rate (primary, ≤ 1 recurrence per year, >1 recurrence per year), number of tumors (single, 2 to 7, ≥ 8), tumor size (<3 cm, ≥ 3 cm), T category (Ta, T1), CIS (no, yes) and grade (G1, G2, G3). For this model, Harrell's bias corrected concordance index c was 0.66 at both one and five years.

Based on the coefficients of these variables in the multivariate model, a score for each patient was calculated, from 0 (best prognosis) to 17 (worst prognosis) as shown in Table 5. Patients were then divided into four groups according to their score. Fig. 1 presents the time to first recurrence for each group.

Table 6 presents the probabilities of recurrence at one year and five years and their 95% confidence intervals according to the patient's score. The

Table 3 – Univariate analysis of time to first recurrence and time to progression

Variable	Recurrence		Progression	
	HR	<i>p</i> value	HR	<i>p</i> value
Age: ≤ 65 years, >65 years	1.10	0.089	1.36	0.012
Gender: male, female	1.00	0.986	0.92	0.580
Prior treatment: no, yes	1.31	0.013	1.19	0.442
Tumor status: primary, recurrent	1.67	$<.0001$	1.36	0.036
Prior recurrence rate: primary, recurrent ≤ 1 rec/yr, recurrent >1 rec/yr	1.42	$<.0001$	1.19	0.027
Number of tumors: single, multiple	1.96	$<.0001$	1.86	$<.0001$
Number of tumors: single, 2 to 7, 8 or more	1.71	$<.0001$	1.48	$<.0001$
Tumor size: <3 cm, ≥ 3 cm	1.34	$<.0001$	1.94	$<.0001$
T category: Ta, T1	1.37	$<.0001$	2.80	$<.0001$
Carcinoma in Situ: no, yes	1.40	0.008	4.19	$<.0001$
Grade: G1, G2, G3	1.29	$<.0001$	2.40	$<.0001$
Grade G3: no, yes	1.42	$<.0001$	3.88	$<.0001$
T1G3: no, yes no CIS, yes CIS	1.48	$<.0001$	4.00	$<.0001$
Recurrence at 3 months: no, yes	NA	NA	3.11	$<.0001$

Table 4 – Multivariate analysis of time to first recurrence and time to progression

	Recurrence		Progression	
	HR (95% CI)	p value	HR (95% CI)	p value
Tumor status: primary, recurrent	–	–	1.48 (1.07, 2.03)	0.016
Prior recurrence rate: primary, recurrent ≤1 rec/yr, recurrent >1 rec/yr	1.35 (1.24, 1.46)	<.0001	–	–
Number of tumors: single, multiple	–	–	1.70 (1.29, 2.24)	0.0002
Number of tumors: single, 2 to 7, 8 or more	1.56 (1.42, 1.71)	<.0001	–	–
Tumor size: <3 cm, ≥3 cm	1.54 (1.32, 1.80)	<.0001	1.89 (1.40, 2.55)	<.0001
T Category: Ta, T1	1.21 (1.07, 1.37)	0.003	2.19 (1.67, 2.86)	<.0001
Carcinoma in situ: no, yes	1.19 (.924, 1.52)	0.180	3.41 (2.32, 5.01)	<.0001
Grade: G1, G2, G3	1.17 (1.07, 1.28)	0.001	–	–
Grade G3: no, yes	–	–	2.67 (1.99, 3.59)	<.0001

probability of recurrence for patients with a score of zero (all good factors) is 15% at one year and 31% at five years while for patients with a score of 10 or higher, it is 61% at one year and 78% at five years.

As an example, Table 7 presents the calculation of the score for a patient with three small (<3 cm in diameter), recurrent (not more than one per year) Ta G1 tumors without CIS. This patient has a 38% chance of recurrence at one year and a 62% chance of recurrence at five years.

3.4. Time to progression

Two hundred seventy-nine of 2596 patients (11%) progressed to muscle invasive disease.

The following variables were identified to be of prognostic importance in the univariate analysis (Table 3): age, prior recurrence and prior recurrence rate, number of tumors, tumor size, T category, the presence of concomitant CIS, and grade.

The variables included in the multivariate model were coded as (Table 4): tumor status (primary, recurrent), number of tumors (single, multiple), tumor size (<3 cm, ≥3 cm), T category (Ta, T1), CIS (no, yes) and grade (G1/G2, G3). For this model, Harrell’s bias corrected concordance index c was 0.74 at one year and 0.75 at five years.

A score was calculated for each patient, from 0 (best prognosis) to 23 (worst prognosis), as shown in Table 5. Patients were then divided into four groups according to their score. Fig. 2 presents the time to progression for each group.

Table 6 gives the probabilities of progression at one year and five years and their 95% confidence intervals according to the patient’s score. The probability of progression for patients with a score of zero (all good factors) is 0.2% at one year and 0.8%

Table 5 – Weights used to calculate the recurrence and progression scores

Factor	Recurrence	Progression
Number of tumors		
Single	0	0
2 to 7	3	3
≥8	6	3
Tumor size		
<3 cm	0	0
≥3 cm	3	3
Prior recurrence rate		
Primary	0	0
≤1 rec/yr	2	2
>1 rec/yr	4	2
T category		
Ta	0	0
T1	1	4
CIS		
No	0	0
Yes	1	6
Grade		
G1	0	0
G2	1	0
G3	2	5
Total score	0–17	0–23

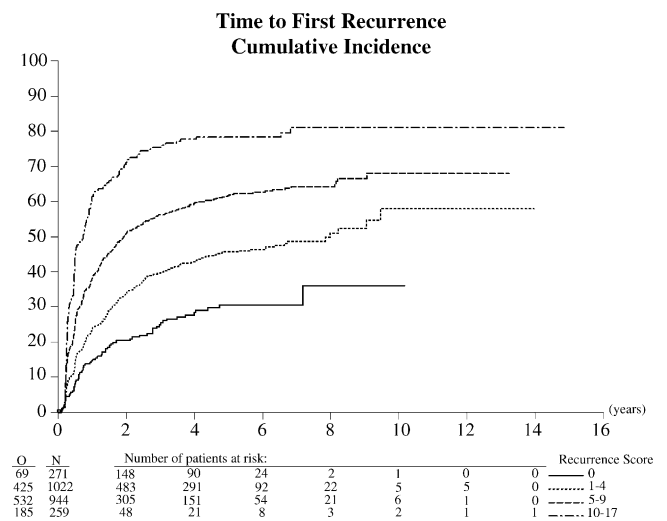


Fig. 1 – Time to first recurrence by recurrence score. O = Observed number of recurrences, N = Number of patients.

Table 6 – Probability of recurrence and progression according to total score

Recurrence score	Prob recurrence 1 year (95% CI)	Prob recurrence 5 years (95% CI)
0	15% (10%, 19%)	31% (24%, 37%)
1-4	24% (21%, 26%)	46% (42%, 49%)
5-9	38% (35%, 41%)	62% (58%, 65%)
10-17	61% (55%, 67%)	78% (73%, 84%)

Progression score	Prob progression 1 year (95% CI)	Prob progression 5 years (95% CI)
0	0.2% (0%, 0.7%)	0.8% (0%, 1.7%)
2-6	1.0% (.4%, 1.6%)	6% (5%, 8%)
7-13	5% (4%, 7%)	17% (14%, 20%)
14-23	17% (10%, 24%)	45% (35%, 55%)

at five years; for patients with a score of 14 or more, it is 17% at one year and 45% at five years.

The patient in Table 7, who has small, recurrent, Ta G1 tumors, has a 1% chance of progression at one year and a 6% chance of progression at five years.

Fig. 3 presents the time to progression in T1 G3 patients according to their score. The prognosis of patients with T1 G3 tumors is not homogeneous, but worsens as their score increases; the probability of progression ranges from 4% to 20% at one year and from 20% to 48% at five years.

The most important prognostic factor in patients with T1 G3 tumors is the presence of concomitant CIS. Fig. 4 shows that in T1 G3 patients without CIS, the probability of progression is 10% at one year and 29% at five years; in T1 G3 patients with CIS, the corresponding figures are 29% and 74%, respectively.

The prognostic importance of recurrence at the first follow-up cystoscopy on the time to progression was also assessed. One hundred eighty-one of 2070

Table 7 – Calculation of the total score (hypothetical example) Patient with 3 small (less than 3 cm diameter), recurrent (not more than 1 per year), Ta G1 tumors without CIS

Factor	Recurrence	Score	Progression	Score
Number of tumors				
Single	0		0	
2 to 7	3	3	3	3
≥8	6		3	
Tumor size				
<3 cm	0	0	0	0
≥3 cm	3		3	
Prior recurrence rate				
Primary	0		0	
≤1 rec/yr	2	2	2	2
>1 rec/yr	4		2	
T category				
Ta	0	0	0	0
T1	1		4	
CIS				
No	0	0	0	0
Yes	1		6	
Grade				
G1	0	0	0	0
G2	1		0	
G3	2		5	
Total	-	5	-	5

Recurrence score	Prob recurrence 1 year (95% CI)	Prob recurrence 5 years (95% CI)
5	38% (35%, 41%)	62% (58%, 65%)

Progression score	Prob progression 1 year (95% CI)	Prob progression 5 years (95% CI)
5	1% (.4%, 1.6%)	6% (5%, 8%)

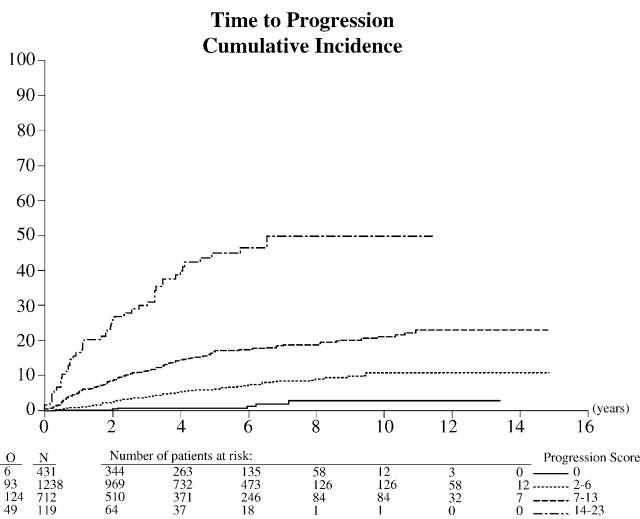


Fig. 2 – Time to progression by progression score. O = Observed number of progressions, N = Number of patients.

patients (8.7%) without a recurrence at three months progressed compared to 80 of 313 patients (25.6%) with a recurrence at three months. In a multivariate model, its importance was similar to that of the two most important prognostic factors for progression, the presence of CIS and the presence of grade 3 tumors.

4. Discussion

The most important prognostic factors for recurrence are the number of tumors, their size, and the prior recurrence rate. The most important prognostic factors for progression are the T category, grade, and the presence of CIS, factors that represent the biological aggressiveness of the disease.

Previous studies have identified these same factors to be of prognostic importance for recurrence or progression. However, there is currently no simple

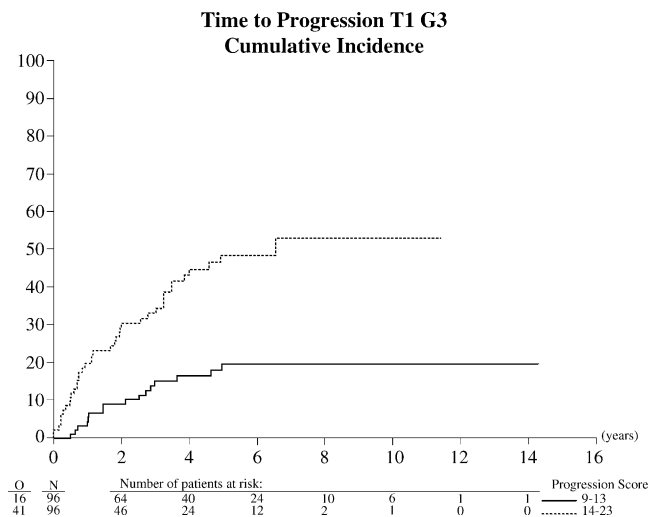


Fig. 3 – Time to progression in T1 G3 patients by progression score. O = Observed number of progressions, N = Number of patients.

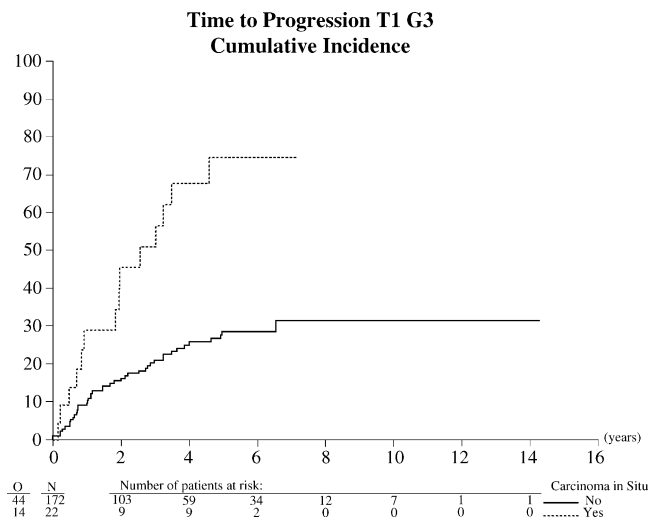


Fig. 4 – Time to progression in T1 G3 patients by carcinoma in situ. O = Observed number of progressions, N = Number of patients.

scoring system based on universally assessed clinical and pathological factors that allows urologists to easily predict the risk of short- and long-term recurrence and progression to muscle invasive disease. The present study provides such a system.

The separation of recurrence and progression enables us to discuss the implications of both endpoints with the patient. For tumors with a high risk of recurrence but a low risk of progression (i.e., multiple recurrent Ta G1 tumors), either intravesical chemotherapy or BCG might be given. However, the choice is somewhat subjective. How important is a probability of recurrence of 35% at one year? What are the risks of BCG side effects? The clinician can decide between intravesical chemotherapy and intravesical BCG for each patient based on the circumstances.

For other tumors that have a high risk of both recurrence and progression (i.e., multiple recurrent T1 G3 tumors), intravesical BCG with maintenance might initially be tried. However, a high risk of progression may also be an argument to convince a patient that an early cystectomy should be performed. But how high a probability is required? Is a 15% chance of progression at one year a sufficient reason to perform a cystectomy? Although the 95% confidence intervals for progression in the patients with the highest progression scores are wider than for the other prognostic groups, clearly these patients do very poorly.

The poor prognosis of T1 G3 patients has been the subject of a number of recent publications [23–30] that discuss the appropriateness of intravesical treatment as opposed to immediate cystectomy. As suggested by some authors [11,23–26,31], Fig. 3

confirms that the prognosis of T1 G3 patients is not uniform but that the risk of progression depends on the patients' other characteristics. In particular the presence of concomitant CIS confers a particularly poor prognosis, with one year and five years progression probabilities of 29% and 74%, respectively (Fig. 4). In such patients a cystectomy should be seriously considered very early in their treatment since progression in patients with a history of superficial bladder cancer is associated with a very poor prognosis [32].

This analysis has concentrated on the use of clinical and pathological factors that are commonly assessed and have been found to be of prognostic importance in previous publications. However, other factors may also be considered. In T1 patients, the depth of lamina propria invasion; i.e., whether the tumor is superficial to, into, or beyond the muscularis mucosae (T1a, T1b, T1c), has been related to the risk of progression to muscle invasive disease [31,33]. The depth of lamina propria invasion was not collected in the EORTC studies. In two multivariate analyses of time to progression, bladder neck involvement [34] and involvement of the trigone or the posterior wall [5] were associated with a worse prognosis. Recently, lymphovascular invasion [35] and micropapillary transitional cell carcinoma [36] have both been shown to be associated with a very poor prognosis; early cystectomy was advocated in each case.

Molecular markers such as p53, Ki-67, NMP22, and Cox-2 have some promise; however, they have not been sufficiently validated to be used day to day at this time [13,26,33,37–40].

The tables in this paper provide a simple tool that uses commonly assessed factors to determine a patient's risk of recurrence and progression. However, these trials date from the pre-BCG maintenance era and approximately 20% of the patients initially received no intravesical treatment [41]. Likewise, fewer than 10% of the patients received an immediate instillation of chemotherapy after TUR [42] and a second look TUR was not yet practiced in high-risk patients [43]. This has several consequences:

First, the characteristics and prognoses of patients who nowadays recur at three months despite an immediate postoperative instillation and a second look TUR will probably not be the same as those encountered in this study. Also, recurrence at three months is not assessed at the same time as the other factors but after the induction instillations. For these reasons it was not included in the multivariate model for progression.

Second, the recurrence and progression rates reported here may be higher than those found in current clinical practice, especially in high-risk patients where maintenance BCG, which reduces the percentage of patients who recur and progress by about 15% and 4%, respectively, is now often applied [44,45]. There are conflicting reports about whether the prognostic importance of the factors identified here would remain the same after treatment with BCG [3,7,10,31,46–47].

Despite these limitations, these tables provide the clinician and the patient with a good starting point for discussing the pros and cons of the therapeutic options. Clinicians are therefore encouraged to apply these tables retrospectively to provide an external validation of these results, and prospectively to aid in the treatment decision process.

Electronic versions of these risk calculators and tables for Windows 2000 and XP, Palm and Windows handheld devices can be downloaded at <http://www.eortc.be/tools/bladdercalculator>.

5. Conclusions

Based on the six clinical and pathological factors presented in this paper, a superficial bladder cancer patient's short- and long-term probabilities of recurrence and progression can easily be calculated with a simple scoring system. Armed with these probabilities, the clinician can discuss the options with the patient to determine the most appropriate treatment: one immediate instillation only, intravesical chemotherapy, intravesical BCG with maintenance, or cystectomy. In this way the treatment

and the frequency of follow-up can be tailored to the patient's prognosis and wishes.

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Editorial Comment

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This is an excellent article that analyzes two of the most important therapeutic problems of non-muscle-invasive bladder cancer such as the poor definition of risk groups and the separation of recurrence and progression risks for these patients. Although differentiation in three risk groups is very practical from a clinical point of view and implies different therapeutic strategies for each, there are borderline patients for whom suitable therapy is difficult to establish. For instance, the behaviour of patients included in the intermediate risk group associated with good prognostic factors can be similar to that of patients in the low-risk group. They could be treated with one immediate instillation of a chemotherapeutic agent only. Conversely, patients with recurrent or multiple tumours included in the intermediate-risk group could be moved to the high-risk group according to the number of recurrences per year or the number of tumours. However, the precise cut-off remains unknown. Moreover, in these patients, indicating when intravesical chemotherapy or BCG should be recommended is difficult. On the other hand, the risk groups associate recurrence and progression rates in the same group, whereas in some cases there is obviously a clear dissociation between both factors.

The present work, to some extent, sorts out both problems by creating two tables that are probably less precise than nomograms, but that are extremely useful for general use. Nevertheless, these tables should be retrospectively and prospectively validated according to geographic area.

Despite the obvious advantages of the tables proposed by the authors, some concerns arise. Most of the patients were treated with intravesical chemotherapy and a small percentage with BCG. The question of whether the prognostic factors identified in this article would be the same if a greater percentage of patients had been treated with BCG is open. Certainly, the most accepted indication for intravesical BCG is for high-risk patients and is debatable in intermediate risk patients. Thus, this issue should be analysed in other series for the homologation of the risk groups that the authors rightfully propose.

Along the same line, patients with T1G3 tumours associated with carcinoma in situ in this article have a progression rate at one and five years of 29% and 74%, respectively. In these cases the authors suggest that a radical cystectomy should be strongly considered as initial treatment. However, we do not know the impact of BCG on these progression rates. Recent articles confirm the poor prognosis of T1 tumours associated with carcinoma in situ when patients are treated with BCG [1,2]. Nonetheless, this issue should also be

validated in other large studies. Another hypothesis is that progression might be significantly reduced in patients treated with BCG at one year but not necessarily at five years, according to the data from Sylvester's meta-analysis [3]. This would lead to a more conservative initial management. The clinical response would then be evaluated at three months (first cystoscopy) as an additional factor in decision-making for radical cystectomy. All these comments are simply speculative. More studies should be undertaken to confirm the outcome of the present work, which is an important contribution to the international literature for non-muscle-invasive bladder cancer.

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Editorial Comment

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I wish to congratulate the authors for their important contribution to standardized classification of the risk of recurrence and progression in patients with non-muscle invasive bladder cancer. The compiled data from more than 2500 patients with Ta, T1, or Tis bladder cancer were used to develop a stratification scheme. The latter relies on six risk factors: tumor focality, size, T-stage, grade, presence of concomitant carcinoma in situ, and prior rate of recurrence. Each risk factor has two to three intensity levels and contributes to the cumulative recurrence and progression score. The internally validated recurrence predictions are 66% accurate at one and five years; progression predictions are 74% and 75% accurate, respectively. This stratification scheme allows the practicing urologist to easily determine the risk of recurrence and progression; however, even though highly detailed information was used, 34% of recurrence

predictions and 24–25% of progression predictions will incorrectly discriminate between the presence and absence of the outcome of interest. These results are comparable to a previously published nomogram, where recurrence predictions were 75% accurate, when age, gender, and cytology were used and 81% accurate, when NMP22 was added [1]. The two models are complementary, as the current model is ideally suited for baseline predictions and the nomogram is ideally suited for risk assessment at variable times during follow-up. Both tools are clearly superior to clinical “guesstimates” and their use should be strongly encouraged in patient counseling, clinical practice, and clinical trials.

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Editorial Comment

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Patients seem to like numbers in this information age. Nomograms and the so-called lookup tables as we have here are useful aids to help us convey prognostic information to our patients. In this article the authors have arduously queried their extensive European Organization for Research and Treatment of Cancer data set and provided some information in tabular form that will tell our patients with Ta and T1 urothelial

tumors of the bladder their chances of recurrence and progression given some key data such as number of tumors, grade, and carcinoma in situ. This will be useful in terms of decisions about adjuvant therapy and, more importantly, abandoning a bladder preservation approach. Of course there are other variables such as patient comorbidity and risks of major surgery that will be used to make any final decision. One caveat is that accurate information is required that presupposes excellence in the endoscopic resection and pathologic interpretation of the submitted material.

Editorial Comment

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As pointed out in this manuscript, tumor recurrence and progression in patients with non-muscle invasive bladder cancer are distinct events that require different rules for prognostication. The population used for these analyses consisted of patients enrolled in seven EORTC studies. Most (54%) had primary tumors, and 78% received intravesical therapy, mainly chemotherapy. Immediate single-dose chemotherapy after transurethral resection (TUR) was used infrequently. The treatment of patients with Ta and T1 bladder cancer continues to evolve. Advances since these patients were treated include BCG maintenance, second look TUR, more frequent use of perioperative chemotherapy, and increased awareness of adverse pathologic features such as invasion of the

muscularis mucosae, lymphovascular invasion, and micropapillary histology. Four groups of patients were defined based on recurrence or progression score. Patients with low risk of recurrence can be defined and will benefit from less intensive follow-up and therapy. The risk of progression in the four groups at one year ranged from 0.2% to 17%, which approaches two orders of magnitude. Currently, most patients at high risk of progression receive BCG with maintenance. As stated in the manuscript, how high a risk is required for immediate cystectomy is unclear. Perhaps new biomarkers will more precisely reveal when intravesical therapy should be avoided and replaced with immediate cystectomy. Although far from perfect, these tables provide useful information. As newer forms of therapy and validated biomarkers become incorporated into clinical practice, these prognostic tables will need to be revised.