Prognostic Factors in Non–Muscle-Invasive Bladder Tumors
I. Clinical Prognostic Factors: A Review of the Experience of the EORTC Genito-Urinary Group
II. Biologic Prognostic Markers

Karl-Heinz Kurth,*, Richard J. Sylvester

*Department of Urology, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands

European Organization for Research and Treatment of Cancer Data Center, Brussels, Belgium

Abstract

Objectives: To summarize the most important clinical prognostic factors of non–muscle-invasive bladder cancer, as assessed by the European Organization for Research and Treatment of Cancer (EORTC) Genito-Urinary Group, to present biologic markers involved in urothelial cell carcinoma, and to address their prognostic value.

Methods: On three occasions between 1983 and 2006, prognostic factors were assessed based on individual patient data. Patients were included in one (308 patients), two (576 patients), or seven (2596 patients) EORTC trials. The literature on biologic markers for superficial bladder cancer was reviewed and screened for prognostic factors with independent predictive value.

Results: Multivariate statistical techniques revealed that number of tumors, prior recurrence rate, tumor size, and G grade were the most important prognostic factors for recurrence. For invasion tumor grade, recurrence rate at entry, and size of the tumor determined prognosis. An index was computed reflecting the risk for invasion. From the combined analysis of seven EORTC trials, a scoring system was developed based on six factors: number of tumors, tumor size, prior recurrence rate, T category, carcinoma in situ, and grade. The probabilities of recurrence and progression ranged at 5 yr from 31% to 78% and from <1% to 45%.

Markers that characterize the histology and cellular appearance of a tumor may predict disease recurrence, but they are not ready for use in daily decision-making.

Conclusion: Urologists can discuss treatment options with patients after using this scoring system to calculate the probabilities of recurrence and progression.

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1. Introduction

Non–muscle-invasive bladder cancer (NMIBC) comprises a spectrum of disease processes. Prognostic variables that predict recurrence and muscle invasion can be used to identify patients who require adjuvant therapy after transurethral resection or additional surgery and, conversely, patients for whom the potential toxic effects and costs of adjuvant chemotherapy or immunotherapy can be spared.

Patient characteristics influence the outcome of all forms of cancer. Approximately 70–80% of patients with newly diagnosed bladder cancer present with superficial bladder tumors (ie, stage Ta, Tis, or T1). In non–muscle-invasive urothelial bladder cancer, prognostic factors may have a more important influence on the further development of the disease after transurethral resection than the choice of adjuvant chemotherapy or immunotherapy.

Investigation of the clinical course of patients with NMIBC requires the selection of a specified time in their disease history, called time zero. Patients are characterized at time zero and the disease is subsequently assessed with respect to different end points (Table 1).

To study the influence of adjuvant therapy on the time to first recurrence or time to invasion, time zero is specified as the time of entry (date of randomization) into a study after complete transurethral resection (TUR). Time zero can be any other suitable point in time. For example, if the study is designed only for a group of patients with no recurrence at the time of the first follow-up cystoscopy after complete resection of all visible tumors (usually planned at 4 wk or 3 mo after TUR), time zero then is the date at which this first cystoscopy was performed.

Prognostic variables are not evaluated irrespective of their association with other known variables or the end point of interest. Multivariate statistical procedures are used to study the relative importance of different variables with respect to the end points examined. Complete follow-up is important in prognostic studies because patients who are lost to follow-up may have experienced a different outcome as compared with those who remained. All patients in a study should be assessed at the same frequency, using the same set of tests. For example always use a flexible endoscope or always use a rigid endoscope with 0°, 30°, and 70° optics and barbotage for cytology. A small recurrent lesion near the bladder neck may be recognized earlier and more easily if a flexible endoscope is used rather than a rigid cystoscope.

Over the past 30 yr, the European Organization for Research and Treatment of Cancer Genito-Urinary Group (EORTC-GU Group) has carried out and published a series of studies on the prophylactic intravesical therapy of NMIBC to investigate the appropriate choice of drugs and the optimal conditions and schedules for intravesical therapy to prevent recurrence and progression after surgical resection [1–13].

The first analysis of prognostic factors based on a randomized clinical trial was reported in 1983 by Dalesio et al [14]. In this study 308 patients with stage Ta/T1 carcinoma of the bladder were treated to compare the efficacy of TUR alone or followed by bladder instillations of thiotepa or VM-26 (teniposide) for 1 yr. With the recurrence rate as the primary end point of interest, the data from this trial were used to assess the prognostic importance of the following factors at entry into the study: number of tumors, prior recurrence rate, tumor size, grade, age, treatment group assigned, and, finally, the interval between TUR at entry into the study and the start of intravesical treatment. Using multivariate statistical techniques it was found that the number of tumors at presentation was the most important prognostic factor followed, in order of importance, by the recurrence rate at entry and the size of the largest tumor. Of particular note was the discovery that patients with fewer than one recurrence per year at entry had a prognosis similar to patients with primary tumors, whereas those with a higher recurrence rate did uniformly poorly. These results showed that patients with stage Ta/T1 carcinoma of the bladder form a heterogeneous group and that more aggressive therapy should be considered for patients with a poor prognosis.

In a second assessment of prognostic factors, data from two similar trials (30790, 30782) were pooled together to facilitate the analysis of recurrence, invasion, and survival [15]. Data on 576 patients, all of whom received intravesical chemotherapy, were analyzed. No association was found between the adjuvant treatment group assigned and either recurrence, invasion, or survival. Thus, the drugs

<table>
<thead>
<tr>
<th>Table 1 – End points in studies for superficial bladder cancer</th>
</tr>
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<tbody>
<tr>
<td>Time to first recurrence (synonymous: disease-free interval)</td>
</tr>
<tr>
<td>Recurrence rate per year</td>
</tr>
<tr>
<td>Recurrence rate per year taking the first follow-up cystoscopy as time zero</td>
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<tr>
<td>Recurrence at first follow-up cystoscopy at 3 mo</td>
</tr>
<tr>
<td>Tumor rate per year</td>
</tr>
<tr>
<td>Time to muscle invasion (synonymous: progression to ≥T2)</td>
</tr>
<tr>
<td>Survival – death due to any cause</td>
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<tr>
<td>Death due to malignant disease</td>
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selected were equally effective (doxorubicin 50 mg, cisplatinum 50, or thiotepa 50 mg all dissolved in 50 ml saline or ethoglucid 13 g dissolved in 100 ml water weekly for 1 mo and monthly for 1 yr). The 576 patients were followed from 3 mo to 8.6 yr, with a median of 4 yr. Thirty-eight percent of the patients were newly diagnosed before entering the trial; 310 patients were category Ta and 266 were category T1. Using the 1973 World Health Organization (WHO) classification, 10% were graded G3, 46% G2, and 44% G1. Their diagnoses date from 9 wk to 9.6 yr before entry, with a median of 2.4 yr.

Table 2 shows how patient characteristics are correlated with each other. For example, primary patients tend to have larger and fewer tumors and no neck or dome involvement. A positive first control cystoscopy is significantly correlated with the size of the largest tumor and the number of

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Table 2 shows how patient characteristics are correlated with each other. For example, primary patients tend to have larger and fewer tumors and no neck or dome involvement. A positive first control cystoscopy is significantly correlated with the size of the largest tumor and the number of
tumors, and also with G grade and site involvement. Neck involvement is significantly associated with dome or posterior wall involvement.

2. Analysis of prognostic factors

2.1. Time to first recurrence

Tumors recurred in 54% of the 576 patients analyzed; in 17% recurrence was already observed at the first cystoscopy. Recurrence occurred at the earliest after 6 wk of follow-up and at the latest after 5 yr. The median time to first recurrence was 1.81 yr. The univariate analysis identified the number of tumors, G grade, prior recurrence rate, time from diagnosis, and involvement of the trigone, right or left wall, posterior wall, dome, and neck as being associated with the time to first recurrence. These factors are highly correlated with each other (Table 2). From the multivariate analysis, only the following factors need to be considered among the above factors: prior recurrence rate, G grade, tumor size, and number of tumors (or wall involvement, posterior wall involvement, dome involvement). The number of tumors becomes a more important factor when one ignores the sites of involvement.

2.2. Recurrence rate per year

The end point recurrence rate per year was likewise analyzed in a multivariate model using logistic regression. Again, the prior recurrence rate, G grade, and number of tumors were the most important prognostic factors ($p < 0.0001$). The most important prognostic factor for the long-term recurrence rate is the presence or absence of recurrence already at 3 mo taking as time zero the first follow-up cystoscopy.

2.3. Time to invasion

Among the 76 patients (13%) who progressed to T2 or worse, 43 (57%) did so during the first year, thus while on treatment. The shortest time to muscle invasion was 12 wk and the longest was 6.6 yr. As for the time to first recurrence, the multivariate analysis identified G grade (not T category, correlated with G grade and tumor size), prior recurrence rate, and recurrence at the first cystoscopy (yes/no) as being associated with future invasion.

2.4. Death due to malignant disease

Among the 576 patients analyzed, 53 died of malignant disease. The factors most associated with death from malignant disease were age, sex, prior recurrence rate, G grade, and tumor size. To determine to what degree invasion was associated with survival, a variable representing invasion was included and updated at 1, 2, and 3 yr using the best model for invasion. Invasion then became, with age, the most significant factor ($p < 0.0001$).

2.5. Risk groups for progression (≥ T2) and death due to malignant disease (Table 3)

Three main factors determined the patient’s prognosis: tumor size, G grade, and prior recurrence rate (grouping primary with a recurrence of less than one in a year). Based on these three factors and their association with invasion and death due to malignant disease, an index was computed reflecting the risk of early invasion and death due to malignant disease. The estimated Cox models are: for invasion: 0.51 recurrence rate per year (RR) + 0.84 grade (G) + 0.48 tumor size (TS); for death: 0.89 RR + 0.73G + 0.44 TS. 

Table 4 shows the observed rate of tumor progression and death due to malignant disease (DMD) by risk group.

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of patients</th>
<th>Progression (%)</th>
<th>DMD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>281</td>
<td>20 (7, 1)</td>
<td>12 (4, 3)</td>
</tr>
<tr>
<td>2</td>
<td>218</td>
<td>38 (17, 4)</td>
<td>28 (12, 8)</td>
</tr>
<tr>
<td>3</td>
<td>36</td>
<td>15 (41, 6)</td>
<td>13 (36, 1)</td>
</tr>
<tr>
<td>Total</td>
<td>535</td>
<td>73 (13, 6)</td>
<td>53 (9, 9)</td>
</tr>
</tbody>
</table>


Fig. 1 – The distribution of time to invasion in each of the three risk groups. Reproduced with permission from Kurth et al. Eur J Cancer 1995;31:1840–6.
and death due to malignant disease according to the risk group as defined in Table 3. Fig. 1 shows the distribution of time to invasion in each risk group.

3. The EORTC risk tables for predicting recurrence and progression in individual patients

Until recently there was no simple scoring system based on universally assessed clinical and pathologic factors that allowed urologists to easily predict an individual patient’s risk of recurrence and progression. After TUR and one immediate instillation of chemotherapy, further treatment could then be adapted according to the patient’s prognosis:

- Intravesical chemotherapy or no further treatment for patients with a low score (good-prognosis patients).
- Patients with a high score (poor-prognosis patients) would be best treated with bacillus Calmette-Guérin (BCG) and a maintenance schedule.
- Patients with an intermediate score would be treated with either intravesical chemotherapy or BCG.

In 2006, Sylvester and coworkers published a method to predict recurrence and progression in individual patients that enabled clinicians to determine the most appropriate adjuvant treatment for their patients after TUR [16]. Updated data from 2596 patients with category Ta, T1, or Tis tumors from seven EORTC trials were used to develop a prognostic index [2–8]. Variables that represented the prior recurrence rate, number of tumors, tumor size, T category, grade, and carcinoma in situ (CIS) were included in the final multivariate models for time to first recurrence and time to progression. Based on the coefficients of these variables in the multivariate model, a score for each patient was calculated. For time to first recurrence the score varied from 0 (best prognosis) to 17 (worst prognosis) and for progression from 0 (best prognosis) to 23 (worst prognosis). Patients were then divided into four groups according to their score. The probabilities of recurrence at 1 yr and 5 yr and their 95% confidence intervals according to the patient’s score are shown in Table 5.

<table>
<thead>
<tr>
<th>Recurrence score</th>
<th>Prob. recurrence 1 yr (95%CI)</th>
<th>Prob. recurrence 5 yr (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>15% (10%, 19%)</td>
<td>31% (24%, 37%)</td>
</tr>
<tr>
<td>1–4</td>
<td>24% (21%, 26%)</td>
<td>46% (42%, 49%)</td>
</tr>
<tr>
<td>5–9</td>
<td>38% (35%, 41%)</td>
<td>62% (58%, 65%)</td>
</tr>
<tr>
<td>10–17</td>
<td>61% (55%, 67%)</td>
<td>78% (73%, 84%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Progression score</th>
<th>Prob. recurrence 1 yr (95%CI)</th>
<th>Prob. recurrence 5 yr (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.2% (0%, 0.7%)</td>
<td>0.8% (0%, 1.7%)</td>
</tr>
<tr>
<td>2–6</td>
<td>1.0% (0.4%, 1.6%)</td>
<td>6% (5%, 8%)</td>
</tr>
<tr>
<td>7–13</td>
<td>5% (4%, 7%)</td>
<td>17% (14%, 20%)</td>
</tr>
<tr>
<td>14–23</td>
<td>17% (10%, 24%)</td>
<td>45% (35%, 55%)</td>
</tr>
</tbody>
</table>


Fig. 2 presents the time to first recurrence for four different groups based on their prognostic score. Fig. 3 presents time to progression curves by progression score. As one may expect the prognosis becomes worse as the score increases. The probability of progression ranges from <1% to 17% at 1 yr and from <1% to 45% at 5 yr.

The most important prognostic factor in patients with T1G3 tumors is the presence of concomitant CIS. In T1G3 patients without CIS the probability of progression is 10% at 1 yr and 29% at 5 yr. In T1G3 patients with CIS, the corresponding figures are 29% and 74%, respectively (in only one of the seven trials were patients initially treated with BCG, but without maintenance). The EORTC-GU Group will analyze in the same way as reported here those patients recruited in controlled studies for intravesical adjuvant treatment with BCG followed by maintenance BCG.

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.

Fig. 2 – Time to first recurrence by recurrence score. O = Observed number of recurrences, N = Number of patients. Reproduced with permission from Sylvester et al. Eur Urol 2006;49:466–75.
The presence of a recurrence at the first follow-up cystoscopy was in a multivariate model of similar importance as the two most important prognostic factors for progression, the presence of CIS and the presence of grade 3 tumors. Without a recurrence at the first cystoscopy, 8.7% (181 of 2070 patients) progressed during follow-up to T2 compared to 25.6% (80 of 313 patients) with a recurrence at 3 mo. A high risk of progression may be a strong argument to convince a patient that an early cystectomy should be performed.

Pathologic factors not assessed in this analysis may be of importance for the decision of early cystectomy in non-invasive urothelial cancer (UC). Vascular invasion is rare in non–muscle-invasive bladder tumors, and when present, it should be another strong argument for not delaying cystectomy. Micropapillary bladder cancer Ta/T1, a rare variant of UC, has been shown to be associated with a poor prognosis. Optimal treatment strategy for non–muscle invasive micropapillary UC is radical cystectomy performed before progression [17].

4. Biologic prognostic markers

Molecular markers (Table 6) for prognostication may make their way from the research laboratory to the clinic with the expectation to improve patient care and outcome. However they have not been sufficiently validated to be used in day-to-day practice at this time [18]. p53, a marker with some promise, has been recently prospectively evaluated as a prognostic marker in T1 UC of the bladder. Tissue typing by immunohistochemistry was not clinically useful as a prognostic marker in a contemporary series of T1 tumors [19]. Expression of the antiapoptotic protein survivin is hardly detectable or even absent in many differentiated adult tissues but is up-regulated in most types of cancer. Survivin nuclear labeling index (BIRC5-N index) has been reported to be a superior prognostic marker for Ta/T1 UC of the bladder [20]. N-cadherin expression was an independent prognostic marker for pT1 tumor progression in one study [21]. In a multivariate analysis, the expression level of prostate stem cell antigen (PSCA) was an independent predictor of disease recurrence in NMIBC [22]. In several recent reviews the authors have agreed that none of the markers have been proven to be sensitive and specific enough to replace cystoscopy [23–27].

Bladder tumors of different grades and stages possess unique and specific genotypic and phenotypic characteristics. Although recognition of several of these molecular alterations is possible by analyzing tumor tissue, urine, and serum samples, few if any of these “molecular markers” for bladder cancer are widely used in clinical practice. There are several candidate markers for assessing prognosis or response to chemotherapy, but studies of large patient populations are lacking. Further studies involving larger numbers of patients are required to determine their accuracy and widespread applicability in guiding the treatment of bladder cancer. The full clinical utility of the existing molecular markers will not be determined until more multi-center prospective trials are conducted to assess their efficacy, safety, and predictive value in the monitoring of patients with NMIBC.

In addition to markers that use conventional technologies such as enzyme-linked immunosorbent assay, point-of-care devices, reverse transcriptase polymerase chain reaction, fluorescent in situ hybridization, and immunocytochemistry, proteomic and gene profiling approaches are being used to find new biomarkers to assist in the molecular profiling of bladder cancer [26].

Using gene expression microarrays, it has been possible to identify signatures that predict various properties of bladder cancer such as stage, grade, progression, and likelihood of metastases. Using arrays for genomic instability, similar properties have been examined, but the effectiveness seems to be less than that of gene expression [27].

In addition, whether any of these factors and others listed in Table 6 will in the future become part of the clinical armamentarium for better judging as described above the individual risk of a patient to recur or to progress to ≥ T2 will probably not only

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**Fig. 3 – Time to progression by progression score.**

O = Observed number of progressions, N = Number of patients. Reprinted with permission from Sylvester et al. Eur Urol 2006;49:466–75.
### Table 6 – Biologic markers of superficial urothelial cell (UC) bladder tumors related to recurrence and/or progression

<table>
<thead>
<tr>
<th>Prognostic marker</th>
<th>Year</th>
<th>The potential value of the marker and reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytogenetic analysis</td>
<td>1976</td>
<td>Triad of tetraploidy, abnormal chromosomes and submucosal invasion carry lethal prognosis. Falor et al [32]</td>
</tr>
<tr>
<td>Chromosomal analysis</td>
<td>1976</td>
<td>Marker chromosomes had a high accurate prognostic aid. Falor and Ward [33]</td>
</tr>
<tr>
<td>Blood group antigen</td>
<td>1979</td>
<td>The absence of blood group cell surface antigen on a low-grade, non-invasive transitional cell carcinoma of the bladder has predicting value for future recurrence with muscle invasion. Young et al [34] An allelic loss and hypermethylation in the promoter region of the ABO gene showed significant correlation with reduction of A antigen expression in UC. Chihara et al [35]</td>
</tr>
<tr>
<td>Urinary polyamines</td>
<td>1981</td>
<td>Putrescine and spermidine correlate with mitotic activity. Pastorini et al [36]</td>
</tr>
<tr>
<td>Flow cytophotometry (FCM; DNA analysis)</td>
<td>1982</td>
<td>FCM determines the proliferation rate of tumors and the relative number of aneuploid cells in each tumor cell sample. Gustafson et al [37]</td>
</tr>
<tr>
<td>Mixed lymphocyte reactivity (MLR)</td>
<td>1983</td>
<td>Measurement of depressed MLR offered a useful adjunct in the evaluation of the biologic potential of low-grade tumor. Herr [38]</td>
</tr>
<tr>
<td>Cell surface antigen (not ABO)</td>
<td>1984</td>
<td>Diversity in surface phenotype of tumor cells reflects diversity in surface antigen of normal cell undergoing progression through stages of differentiation. Fradet et al [39]</td>
</tr>
<tr>
<td>Retinoic acid receptor (RAR)</td>
<td>1985</td>
<td>Higher grade and stage are more associated with RAR^+^ tumors. They appear to recur more likely and to become invasive. de Bolla et al [40]</td>
</tr>
<tr>
<td>Transferrin (TF) receptor expression</td>
<td>1990</td>
<td>TF^+^ receptor expression was highly significant predictive of further recurrence. Smith et al [41] Severe atypia and carcinoma in situ are consistently associated with strong TF receptor activity, markedly elevated proliferation indices, and depressed blood group antigen. Limas et al [42]</td>
</tr>
<tr>
<td>Argyrophilic nuclear organizer region (AgNOR)</td>
<td>1991</td>
<td>AgNORs have independent predictive value for progression and recurrence in superficial UC. Lipponen et al [43] AgNOR count is significantly higher in patients with recurrence. Tomobe et al [44] The combination of AgNOR quantity and oncogene expression (p53, c-erbB-2) may stratify patients into different risk groups. Pich et al [45] Discriminates grade 2 tumors with favorable and unfavorable prognosis. Mulder et al [46]</td>
</tr>
<tr>
<td>Ki 67: cell proliferation marker</td>
<td>1992</td>
<td>Recurrent tumor had higher activity of proliferation. Stavropoulos et al [47] Strong correlations between the BrdUrd labeling index (LI) and both the Ki67 LI and proliferating cell nuclear antigen LI. Cohen et al [48] Parameters determined by DNA image cytometry are valuable in predicting progression-free survival. Next to classic parameters (stage and grade) they are useful especially in superficial UC. Schapers et al [49]</td>
</tr>
<tr>
<td>Static cytometric DNA analysis</td>
<td>1993</td>
<td>Stage, grade, and nuclear DNA content are the most useful prognostic parameters for predicting the biologic behavior of TCC of the bladder. Cai et al [50]</td>
</tr>
<tr>
<td>p53 cell cycle regulator</td>
<td>1994</td>
<td>p53 nuclear overexpression is an early event in bladder cancer, occurring in 48% of cases of carcinoma in situ of the bladder. Sarkis et al [51] Pretreatment p53 nuclear overexpression in superficial bladder tumors is associated with a high risk of disease recurrence, progression, and cancer death after BCG therapy. Saint et al [52] The prognostic value of a p53 mutation is insufficient for individual policy making. Moonen et al [53] p53, prospectively evaluated in T1 UC of the bladder, was not clinically useful as a prognostic marker in a contemporary series. Dalbagni et al [19]</td>
</tr>
<tr>
<td>Vessel density</td>
<td>1995</td>
<td>A majority of studies assessing the prognostic value of measuring tumor angiogenesis (ie, measurement of tumor microvessel densities) have found a positive association between increasing microvessel densities and worsening prognosis. Bochner et al [54]</td>
</tr>
<tr>
<td>VEGF (vascular endothelial growth factor, a peptide growth factor)</td>
<td>2001</td>
<td>Creatinine-corrected concentration of urinary VEGF levels were significantly higher in recurrent vs. non-recurrent patients. Jeon et al [55] VEGF is not useful for predicting recurrence or progression in superficial bladder cancer. Stavropoulos et al [56]</td>
</tr>
</tbody>
</table>
depend on feasibility and availability but also on whether this can be defended economically.

In his comment on the risk tables as published [16], Grossman stated: “As newer forms of therapy and validated biomarkers become incorporated into clinical practice, these prognostic tables will need to be revised.” It is not difficult to predict that this will happen when BCG immunotherapy (yes or no) is added to the prognostic index as a risk factor [9–13,28–30].

5. Conclusion

Six clinicopathologic factors significantly affecting the prognosis of NMIBC were identified in a multivariate analysis and used to develop a scoring system. This system allows one to predict the probability of recurrence and progression in an individual patient. Although for a patient with a low probability of recurrence a single intravesical instillation of chemotherapy immediately after transurethral bladder tumor resection may be sufficient, patients with a higher score may be candidates for intravesical BCG with maintenance or even cystectomy.

The impact of the surgeon on the final outcome was not reassessed although this has been shown to be an important variable [31].

Host factors (eg, Th 1 cytokine secretion, acetylation, smoking) were not addressed in this review; however, they may also affect the prognosis.
Biologic markers appear promising; however, divergent results of different trials suggest that none of them are ready for routine clinical use. Problems to solve include the retrospective design, study size, antigen retrieval, antibodies used, means of assessment (automatic device, scoring system), and standardization of marker research.

Conflicts of interest

The authors have nothing to disclose.

References