Review

Patient Risk Profiles: Prognostic Factors of Recurrence and Progression

Dr. Juan Palou is a urologist in the Urology Department and Chief of Urological Oncology at Fundació Puigvert, Barcelona, Spain. He is an associate professor of urology at Universidad Autónoma de Barcelona, and a member of the Spanish, European, American, and International Urological Associations, and the European Society of Infection in Urology (ESIU). His publications include 15 chapters in medicine and urology books, and he has participated in more than 100 articles in Spanish urologic journals and more than 80 in international journals. His clinical research in oncology focuses on transitional cell carcinomas, specifically, superficial bladder cancer and upper urinary tract tumours.

Juan Palou
Fundació Puigvert, Cap de la Unitat d’Urologia Oncologica, Servei d’Urologia, Cartagena, 340-350, 080255 Barcelona, Spain

Abstract

A vast array of pathologic features has been considered in the outcome of patients with Ta and T1 urothelial carcinoma. The problem, when analysing the factors related to recurrence, is that the published series may present different methodologic bias: short follow-up, small number of patients, different treatments, factors considered, and other. In addition, different clinical factors related to recurrence have been mentioned: multiplicity, size and location of the tumour, response to intravesical instillations, recurrence rate, and anaplasia. Related to progression, factors such as grade, association with carcinoma in situ (CIS), size of the tumour, and early recurrence have been considered. The author’s experience with clinical prognostic factors of recurrence and progression is presented in order to decide on the best therapeutic approach. Experience shows that risk groups for recurrence may differ from those adopted for progression. For patients with low-grade tumors (grade 1 and the majority of grade 2 tumours) multiplicity is the main prognostic factor of recurrence and the main variable to consider when deciding on treatment. Once low-grade tumors become high grade, or in the case of CIS, progression has to be considered, and the tumour should be treated accordingly. In the case of high-grade tumours, although they may recur, progression is the main concern. Clinical prognostic factors may help to decide whether to manage them conservatively (bacillus Calmette-Guérin) or with radical cystectomy.

© 2006 European Association of Urology. Published by Elsevier B.V. All rights reserved.
1. Introduction

A vast array of clinical and pathologic features has been considered in the outcome of patients with urothelial carcinoma. Prognostic factors can be used as a potential means of predicting the course of bladder cancer in individual patients. Risk groups for cancer recurrence and progression can be used to help decide on the best therapeutic approach. Risk group classification adopted for recurrence, however, may differ from risk groups for progression. The challenge, when analysing factors related to recurrence, is that the published series may present different methodologic bias: short follow-up, small number of patients, different treatments, and other issues. In addition, different clinical factors have been mentioned in relation to recurrence: multiplicity, size of the tumour, tumour location, response to intravesical instillations, recurrence rate, and anaplasia. With respect to progression, factors such as grade, association with carcinoma in situ (CIS), size of the tumour, and early recurrence have been considered. Recently, a combined analysis of 2596 patients included in seven European Organization for Research and Treatment of Cancer (EORTC) trials of patients treated with or without intravesical chemotherapy has provided tables to calculate recurrence and progression. This is an important step towards improving the management of patients with Ta and T1. But it has to be considered however, that we do not know the real incidence of CIS (no random biopsies) and very few patients were treated with bacillus Calmette-Guérin (BCG), which may bias the results of intermediate- and high-risk groups [1].

2. Prognostic factors for recurrence

Prognostic factors for recurrence have been investigated by several clinical groups. The most frequent factor related to recurrence, in almost all the series, has been multiplicity. Intravesical instillation has been defined as a protective factor (Table 1).

Kurth et al. [11] reported on factors affecting recurrence and progression from the data of two trials involving 576 patients. The trials considered factors such as tumour size, grade, and recurrence rate per year, and concluded that the most significant prognostic factors for recurrence were multiplicity, recurrence at 3 mo, size of the tumour, and anaplasia.

Based on the prognostic factors investigated by various clinical groups, the following risk groups were developed by the European Association of Urology (EAU) related to recurrence and progression [15]:

- Low-risk tumors: single, Ta, G1, <3 cm diameter
- High-risk tumors: T1, G3, multifocal or highly recurrent, CIS

<table>
<thead>
<tr>
<th>Author and year</th>
<th>Study type</th>
<th>Tumor status</th>
<th>No. of cases</th>
<th>Grade</th>
<th>T stage</th>
<th>Associated CIS</th>
<th>Multiplicity</th>
<th>Tumour size</th>
<th>Intravesical instillations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loening 1980 [2]</td>
<td>Retrospective</td>
<td>Primary recurrent</td>
<td>178</td>
<td>No</td>
<td>Yes</td>
<td>–</td>
<td>No</td>
<td>No</td>
<td>–</td>
</tr>
<tr>
<td>Narayana 1983 [3]</td>
<td>Prospective</td>
<td>Primary</td>
<td>468</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>–</td>
</tr>
<tr>
<td>Dalesio 1983 [4]</td>
<td>Prospective</td>
<td>Primary recurrent</td>
<td>308</td>
<td>No</td>
<td>–</td>
<td>–</td>
<td>Yes</td>
<td>Yes</td>
<td>–</td>
</tr>
<tr>
<td>Parmar 1989 [5]</td>
<td>Prospective</td>
<td>Primary</td>
<td>305</td>
<td>No</td>
<td>No</td>
<td>–</td>
<td>Yes</td>
<td>No</td>
<td>–</td>
</tr>
<tr>
<td>Witjes 1992 [6]</td>
<td>Prospective</td>
<td>Primary</td>
<td>1026</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>–</td>
<td>Yes</td>
</tr>
<tr>
<td>Kiemeney 1993 [7]</td>
<td>Prospective</td>
<td>Primary</td>
<td>1674</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>–</td>
<td>Yes</td>
</tr>
<tr>
<td>Kiemeney 1994 [8]</td>
<td>Prospective</td>
<td>Primary</td>
<td>1674</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>–</td>
<td>–</td>
<td>Yes</td>
</tr>
<tr>
<td>Witjes 1994 [9]</td>
<td>Prospective</td>
<td>Primary recurrent</td>
<td>469</td>
<td>No</td>
<td>No</td>
<td>–</td>
<td>Yes</td>
<td>No</td>
<td>–</td>
</tr>
<tr>
<td>Mulders 1994 [10]</td>
<td>Prospective</td>
<td>Primary recurrent</td>
<td>371</td>
<td>No</td>
<td>No</td>
<td>–</td>
<td>Yes</td>
<td>No</td>
<td>–</td>
</tr>
<tr>
<td>Pawinski 1996 [12]</td>
<td>Meta-analysis</td>
<td>Primary recurrent</td>
<td>2535</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Yes</td>
</tr>
<tr>
<td>Shinka 1997 [13]</td>
<td>Prospective</td>
<td>Primary</td>
<td>141</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>–</td>
</tr>
<tr>
<td>Millán 2000 [14]</td>
<td>Retrospective</td>
<td>Primary</td>
<td>1529</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

CIS = carcinoma in situ.
Intermediate-risk tumors: all other tumors, Ta-1, G1-2, multifocal, >3 cm diameter

Fitzpatrick et al. [16] found that a patient with a negative cystoscopy at 3 mo had a 79% chance of being free of disease for 10 yr; conversely, 90% of patients with tumour at first cystoscopy had a recurrence.

Parmar et al. [17] considered multiplicity and recurrence at 3 mo as the main prognostic factors in recurrence. These two parameters provided the most predictive information related to recurrence, and they were independent of the stage. The following risk groups were proposed:

- Good risk (60% of the cases): solitary tumour at presentation and no new occurrence at first cystoscopy. Recurrence rate of 20% at 1 yr.
- Medium risk (30% of the cases): patients who had either multiple transitional cell carcinoma of the bladder (TCCB) at diagnosis, and who were tumour free at first cystoscopy, or had solitary TCCB with new occurrence at first cystoscopy. Recurrence risk of 40% at 1 yr and 60% at 2 yr.
- Poor risk (10% of the cases): patients having multiple TCCB at presentation and new occurrence at first cystoscopy. Recurrence rate of 50% at 6 mo and 90% by 1–2 yr.

Although the above Medical Research Council classification is useful to predict the risk of recurrence, it is not useful from the viewpoint of progression. Hall et al. [18] considered T1G3 TCCB of particularly poor prognosis, because 29% progressed, and they suggested that these tumours would have to be considered as a different group in the classification scheme of Parmar et al. [17].

When considering all these classifications, it becomes clear that in low-grade tumours, multiplicity and recurrence at 3 mo allow us to establish groups of risk related to recurrence [15,19,20]. In high-grade tumours, recurrence at 3 mo is a significant risk factor, but for progression [21]. Establishing prognostic factors for progression, however, is more problematic. Another point to consider for the establishment and management of risks groups is the introduction of the World Health Organization/International Society of Urologic Pathology (WHO/ISUP) 2003 classification for grading of bladder tumours in papilloma, and papillary urothelial tumours of low malignant potential, low and high grade tumours. Under the new classification [22], tumours that were classified as grade 1 based on the 1973 WHO/ISUP classification are now named papillary urothelial neoplasm of low malignant potential (PUNLMP), grade 2 tumours are now classified mostly as low-grade tumours, with a few of them classified as high grade, and grade 3 tumours are now all classified as high-grade carcinoma (Table 2). This new classification will have to be considered in future studies and results when establishing risks groups related to recurrence and progression.

### 3. Prognostic factors for progression

Grade, associated CIS, and stage are factors globally related to progression in the series that have investigated prognostic factors (Table 3).

At Fundació Puigvert, based on 1529 patients with primary superficial bladder cancer, three risk groups were developed. The trial used recurrence prognostic factors such as multiplicity, tumour size, and CIS and progression prognostic factors such as grade, CIS, and multiplicity. The risk groups developed, however, were more useful in evaluating progression than recurrence [14]:

- Low risk: solitary G1 Ta-T1 without CIS. Risk of recurrence of 37% and progression of 0%.
- Medium risk: multiple G1T1, G2Ta, solitary G2T1 without CIS. Risk of recurrence of 45% and progression of 1.8%.
- High risk: multiple G2T1, G3 Ta-T1, primary CIS, or any tumour associated to CIS. Risk of recurrence of 54% and progression of 15%.

The presence of mucosal abnormalities, such as CIS, has been associated with progression [24,25]. Clearly, high grade is related to progression [14], and this is the main concern in the conservative (BCG) management of superficial bladder cancer. It should be noted that Murphy [26] advocated avoiding talking about “superficial disease” because in some patients this “apparently low risk disease” may end as a life-threatening invasive and metastatic cancer.

| WHO = World Health Organization; ISUP = International Society of Urologic Pathology; TCC = transitional cell carcinoma; PUNLMP = papillary urothelial neoplasm of low malignant potential; UNLMP = urothelial neoplasm of low malignant potential. |
4. Progression in G2T1

Grade 2 T1 tumours, even though they invade the submucosa, do not behave as aggressively as G3T1 tumours. In our experience at Fundació Puigvert with 565 patients with primary G2T1 bladder tumours, only 5.2% progressed. With the introduction of the new classification grading system (low and high grade), a lower proportion will progress, because disease in some of the G2 patients will be classified as high grade. Very seldom does a patient with a G2T1 tumour, without CIS, progress to invasive disease, without any previous high-grade superficial recurrence. In our study only one patient who had an initial G2T1 tumour developed an invasive bladder carcinoma in the first recurrence. Therefore, in G2T1 tumours initially we have to worry more about recurrence than progression. Patients with multiple G2T1 tumours, however, may be at a higher risk of progression and, indeed, in the EAU guidelines they are considered a high-risk group. Furthermore, an increase in grade or presence of CIS in the first recurrence also increases risk; from 30% to 40% will progress with a relative risk of 12.9 (95% confidence interval, 1.4–118.7) [27].

5. Progression in G3T1

And what about G3T1? Multiple articles have mentioned risk factors [25,28] but since the introduction of better resection and staging of disease in these patients, and endovesical treatment with BCG, the global results have improved [29].

Some variables have been used to analyse progression: association with CIS [14,24], multiplicity [14], morphology (papillary or solid), tumour size (< or >3 cm) [11], early or late recurrence (3/6 months) [30], sex and age (< or >65 yr), CIS of the prostatic urethra [23], and substaging [31]. We analysed a series of 243 Fundació Puigvert patients diagnosed with primary T1G3 bladder carcinoma, 146 of whom were treated with BCG, and with a median follow-up of 86 mo. Because there was a clear difference in recurrence and progression [25] of patients with T1G3 bladder carcinoma based on treatment, we analysed only the group of patients treated with BCG to determine clinical prognostic factors to decide on the best therapeutic approach.

The analysis showed that when we consider patients with T1G3 (treated with BCG) and factors such as association with CIS, tumour size, or multiplicity, progression varies from 11% to 19%. That means that almost 80% of patients will not progress and, therefore, it may not be correct to decide on an aggressive treatment based on these factors alone, even though all of them have to be considered high-risk group patients [15]. The most recent series in T1G3 bladder tumours treated with BCG confirm these results, with a global decrease of progression [32]. One prognostic factor that has established a clear difference in progression is recurrence at 3 mo [30]. CIS in the prostatic urethra is also being considered as a parameter to take into account in the final decision of whether to proceed with conservative or aggressive treatment [33]. Consideration of the association of factors, as in Sylvester et al. [1], may be a better approach for predicting the progression of disease. But with the changing patterns of recurrence and progression with endovesical BCG, only those treated with BCG have to be considered in the decision tables in Ta, T1 high-grade urothelial carcinoma of the bladder. For example, in our experience with BCG, for a patient with a papillary tumour, <3 cm, and no CIS, the probability to progress is <5%, and for a patient with CIS in the prostatic urethra and recurrence at 3 mo the probability is almost 100% (Fig. 1). Future validation of these results will allow for a more appropriate management of these patients.
6. Conclusion

For patients with low-grade tumours (grade 1 and the majority of grade 2 tumours) multiplicity is the main prognostic factor of recurrence and one of the main variables to consider when deciding on treatment. Once low-grade tumours become high grade, or in the case of CIS, progression has to be considered, and the tumour should be treated accordingly. High-grade tumours may recur, but progression is the main concern. Clinical prognostic factors may help to decide whether to manage them conservatively (BCG) or with radical cystectomy. The evaluation of the response at 3 mo is an important step as a prognostic factor in recurrence and progression in the management of patients with Ta, T1, and CIS.

References


