Recurrence at Three Months and High-grade Recurrence as Prognostic Factor of Progression in Multivariate Analysis of T1G2 Bladder Tumors

Juan Palou, Federico Rodríguez-Rubio, Félix Millán, Ferran Algaba, Oscar Rodríguez-Faba, Jorge Huguet, and Humberto Villavicencio

OBJECTIVES
To evaluate the risk factors for disease progression in the frequent subgroup of Stage T1G2 (World Health Organization 1973) bladder tumors using an analysis of a large cohort of patients with Stage T1G2 disease.

METHODS
A cohort of 616 patients with Stage T1G2 were treated with transurethral resection and random bladder biopsies. The mean follow-up was 4.2 years. Univariate and multivariate analyses were done using Cox regression analysis. The independent variables were multiplicity, association with carcinoma in situ (CIS), tumor size, tumor recurrence at 3 or 6 months, tumor grade, and association with CIS at first recurrence. The dependent variable was progression to muscle-invasive disease.

RESULTS
Progression to muscle-invasive disease was identified in 28 of the 616 patients (4.5%). On multivariate analysis, when considering recurrence at 3 months, this factor was the principal prognostic factor, with a relative risk of 4.0 (95% confidence interval 1.2-13.3), followed by the presence of high-grade disease or CIS at first recurrence (relative risk 2.8, 95% confidence interval 1.3-5.8) and CIS associated with the primary tumor (relative risk 1.8, 95% confidence interval 1.1-2.9). When considering recurrence at 6 months, more prognostic factors were involved for progression, including as multiple tumors, CIS associated with the primary tumor, recurrence at 6 months, and the presence of high-grade disease or CIS at the first recurrence.

CONCLUSIONS
In primary urothelial T1G2 bladder cancer, recurrence at 3 months was the main prognostic factor related to progression. Additional factors were the association of CIS with the primary tumor and the presence of high-grade disease and/or CIS at first recurrence. UROLOGY 73: 1313–1317, 2009. © 2009 Elsevier Inc.

It is well known that Stage T1 bladder tumors have a less favorable prognosis than Stage Ta tumors, and they have been considered as a "stepping stone" to muscle invasion.1 Much research on Stage T1 tumors of the bladder has been devoted to the identification of risk factors for recurrence and progression.2-11 Heney12 stated that, “in T1 tumors the individual course is difficult to predict, especially in grade 2 (WHO [World Health Organization] 1973) disease.”

Most previous reports have focused on the survival of patients with Stage Ta or T1 tumors, independent of the grade. It has already been emphasized that the presence of grade 3 disease is the main prognostic factor for progression of Ta and T1 urothelial carcinoma of the bladder.11 Our aim in the present study was to provide more information on progression in the frequent subgroup of patients with T1G2 tumors. To address this issue, we analyzed a large cohort of 616 patients with Stage T1G2 disease.

MATERIAL AND METHODS
A total of 1529 patients who underwent treatment of primary superficial transitional cell carcinoma of the bladder from November 1968 to December 1996 were reviewed. The patient characteristics have been previously described.11 From this overall group, we selected a cohort of 616 patients with primary bladder urothelial cell carcinoma classified as Stage T1G2 who had undergone transurethral resection (TUR) and random bladder biopsies. In addition, 106 patients (17.2%) had received...
intravesical chemotherapy and 30 patients (4.9%) had received bacille Calmette-Guérin (BCG).

The tumor size was defined by taking the largest tumor dimension measured using the 1-cm-long resection loop. The tumors were classified into 3 categories: <3 cm, >3 cm, and papillomatosis. Papillomatosis was defined as present when >70% of the bladder surface was covered. Complete TUR of the tumor was performed, and several deep muscle samples were taken using the resection instrument. Sample pathology reports from a uropathologist were used to obtain the cumulative data. All bladder tumors were classified using TNM 200213 and World Health Organization (1973)14 classifications.

Cystoscopy and cytology were performed at 3 months after therapy and, if no recurrence was found, alternate follow-up with cystoscopy/ultrasound and cytology was performed every 4 months for 2 years and every 6 months thereafter. The mean duration of follow-up was 4.2 years. The endpoint of the study was progression, defined as a shift to Stage T2, T3, or T4 disease.

Univariate and multivariate analyses were done using the Cox regression model. A descriptive analysis of T1G2 tumors and multivariate analysis using the Cox proportional hazards model with stepwise forward selection were performed. The independent variables were multiplicity, association with CIS, tumor size, tumor recurrence at 3 or 6 months, grade, and association with CIS at first recurrence. The dependent variable was progression to muscle-invasive disease. All P values are 2-sided, and the relative risk (RR) and 95% confidence interval (CI) are reported. All data were analyzed using the Statistical Package for Social Sciences, version 12.0 (SPSS, Chicago, IL) statistical program.

RESULTS

The characteristics of the 616 patients with primary T1G2 bladder tumors (sex, association with CIS, tumor size, multiplicity, time and grade of relapse) are listed in Table 1. T1G2 tumors accounted for 40.3% (616/1529) of our total primary non-muscle invasive transitional cell carcinoma cases and 62.8% (616/981) of all T1 tumors.

Of the 616 patients, 286 (46.4%) developed recurrences, 15.5% grade 1, 66.1% grade 2, and 18.3% grade 3. Eleven patients underwent cystectomy before progression because of high-grade recurrence (5 T1G3, 4 CIS, and 2 unknown).

Progression to muscle-invasive disease was identified in only 28 of the 616 patients (4.5%).

In this series, the primary tumor characteristics that were significantly related to progression on univariate analysis were multiplicity and association with CIS (Table 2). In relation to the first recurrence, univariate analysis identified the presence of CIS, recurrence at 3 and 6 months, and grade 3 as factors that influenced progression (Table 2).

On multivariate analysis, considering recurrence at 6 months, multiple tumors (RR 2.4, 95% CI 1.0-5.4), CIS associated with the primary tumor (RR 2.1, 95% CI 1.3-3.3), recurrence at 6 months (RR 2.7, 95% CI 1.2-6.0), and high-grade disease or CIS at first recurrence (RR 3.3, 95% CI 1.6-6.6) were the main prognostic factors for progression to invasive disease. However, when we considered recurrence at 3 months, that factor became the main factor (RR 4.0, 95% CI 1.2-13.3), followed by high-grade disease or CIS at first recurrence (RR 2.8, 95% CI 1.3-5.8) and CIS associated with the primary tumor (RR 1.8, 95% CI 1.1-2.9).

COMMENT

The clinical outcome of noninvasive bladder tumors is normally assessed on the basis of recurrence and progression. Although the former is managed conservatively, the latter is more life threatening. The risk of progression to muscle-invasive disease increases with increasing grade and depth of subepithelial tissue invasion, ranging from 2% for Stage TaG1 tumors to 48% for Stage T1G3 tumors.12 However, the rates of progression are highly variable, even when comparing patients with a similar clinical stage. The discrepancies in the published progression rates have resulted from a number of factors: accuracy of staging by pathologists, availability of information from multiple random biopsies, tumor grade, definition of progression, quality of TUR of the bladder tumor, amount and type of adjuvant therapy, and duration of follow-up.

In a review of >1000 patients with Stage T1 tumors treated with TUR plus BCG, the progression rate was 13%-48% with a median follow-up of 5 years.15 Rodriguez et al.,16 in a series of 175 patients with T1 bladder tumors, reported a 5- and 12-year progression-free survival rate of 83.1% and 75.6%, respectively. The independent variables for progression were age, multifocality, solid microscopic morphology, p53 expression, and Ki-67 expression. These investigators included grade 1, 2, and 3

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>545 (88.5)</td>
</tr>
<tr>
<td>Women</td>
<td>71 (11.5)</td>
</tr>
<tr>
<td>Associated CIS</td>
<td></td>
</tr>
<tr>
<td>At diagnosis</td>
<td>53 (8.5)</td>
</tr>
<tr>
<td>At first relapse</td>
<td>23 (3.8)</td>
</tr>
<tr>
<td>Tumor size (cm)</td>
<td></td>
</tr>
<tr>
<td>&lt;3</td>
<td>324 (52.6)</td>
</tr>
<tr>
<td>&gt;3</td>
<td>84 (13.6)</td>
</tr>
<tr>
<td>Papillomatosis</td>
<td>17 (2.8)</td>
</tr>
<tr>
<td>Unknown</td>
<td>191 (31)</td>
</tr>
<tr>
<td>Multiplicity</td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>428 (69.5)</td>
</tr>
<tr>
<td>Multiple</td>
<td>188 (30.5)</td>
</tr>
<tr>
<td>Relapse at 3 mo</td>
<td></td>
</tr>
<tr>
<td>3 mo</td>
<td>41 (6.7)</td>
</tr>
<tr>
<td>&gt;3 mo</td>
<td>245 (39.8)</td>
</tr>
<tr>
<td>Relapse at 6 mo</td>
<td></td>
</tr>
<tr>
<td>6 mo</td>
<td>100 (16.2)</td>
</tr>
<tr>
<td>&gt;6 mo</td>
<td>186 (30.2)</td>
</tr>
<tr>
<td>Tumor grade at first relapse</td>
<td></td>
</tr>
<tr>
<td>G1</td>
<td>39 (3.4)</td>
</tr>
<tr>
<td>G2</td>
<td>166 (18.9)</td>
</tr>
<tr>
<td>G3</td>
<td>46 (6.6)</td>
</tr>
</tbody>
</table>

CIS, carcinoma in situ.
tumors in their study cohort. Zieger et al. studied 70 T1 bladder carcinomas of varying grade (1-4; Bergkvist classification) and found that 39% of the patients had disease progression. The significant risk factors were positive CIS-preselected site biopsies, size >3 cm, and early recurrence. Multivariate analysis from other studies has identified several risk factors for poor prognosis for Stage pTa-pT1 bladder cancer, including stage, grade, tumor multiplicity, tumor size, association with CIS, previous recurrence, and results of the 3-month cystoscopy. These studies have also shown that lamina propria invasion is 1 of the most important prognostic indicators. All these studies have presented global information on patients with non-muscle invasive bladder cancer: both Ta and T1 tumors were included, and the tumor grades ranged from 1 to 3. Consequently, it is difficult to analyze the risk of progression specifically for those with T1G2 tumors.

To our knowledge, the present series is the largest addressing the specific scenario of primary T1G2 bladder tumors. Some previous studies on T1 tumors have been published, but these have included low-, moderate-, and high-grade bladder cancer. T1G2 tumors are a very frequent category, accounting for approximately 70% of Stage T1 bladder cancer cases. In the present study, Stage T1G2 tumors represented 40.3% of the total of 1529 primary superficial transitional cell carcinoma and 62.8% of all T1 tumors.

The natural history of T1G2 tumors is not well known. Anderstrom et al. reported 99 patients with tumors infiltrating the lamina propria and found a 5-year survival rate of 83% in those patients with grade 2 tumors. However, such tumors infiltrating the lamina propria underwent TUR or cystectomy. In 1983, Heney et al. showed progression in 4% of Stage Ta and 30% of Stage T1 tumors, with the progression-free interval significantly shorter for those with Stage T1 than for those with Stage Ta tumors (P < .001). These investigators also analyzed progression by grade within stage and showed that progression occurred in 21% of T1G2 tumors. The investigators stated that, “our findings also underscore strongly the difference in prognosis between tumors that are confined to the mucosa and those that have already invaded the lamina propria” and observed that such invasion is associated with a decrease in 5-year survival. Holmang et al. provided follow-up results obtained from 176 patients with primary Ta or T1 tumor. They were treated by TUR and followed up for 20 years or until death. A subset of 41 patients with Stage T1G2 were studied, with 32% showing tumor progression and 22% dying of the disease. Using the European Organization for Research and Treatment of Cancer risk tables reported by Sylvester et al., which allow the calculation of short- and long-term risk of recurrence and progression in patients with Stage Ta-T1 bladder cancer, a patient with a primary solitary or multiple T1G2 bladder tumor has a probability of progression at 5 years ranging of 6%-17%.

In the present study, progression to muscle-invasive disease was identified in only 4.5% of patients. The reported progression rates have varied according to the definition of progression. For example, if the criteria for worsening of disease outlined by Lamm et al. were used, the 11 patients who underwent cystectomy because of high-grade disease or CIS would be included among those with recurrence, and the progression rate would have been 6.5%. Our view, however, is that the term “progression” should be limited to the development of muscle-invasive disease rather than encompassing an increase in grade. With longer follow-up, we would expect a greater...
ter rate of progression to muscle-invasive disease. In our large series, certain factors were identified as being associated with a greater rate of progression. On multivariate analysis, we obtained different results, depending on whether recurrence at 3 or at 6 months was considered (Table 2). With recurrence at 3 months, we obtained a greater relative risk of progression than for recurrence at 6 months, and fewer variables were significantly related to progression (CIS associated with the primary tumor and high-grade disease or CIS at first recurrence). It is also important that the information of the risk of progression was obtained 3 months earlier.

Tumor multiplicity has been found to be a risk factor for progression in global non-muscle invasive bladder cancer studies. In our study, multiplicity was related to progression on univariate analysis and when we considered recurrence at 6 months, but not when we considered recurrence at 3 months. Although recurrence does not imply progression, some investigators have emphasized the importance of the data relating to recurrence. Holmang et al. demonstrated that patients with ≥10 recurrences had a high risk of metastatic bladder cancer and a significant risk of dying of this disease, even if the initial diagnosis had been Stage TaG1. These data on recurrence have confirmed an earlier observation reported by Parmar et al. for the British Medical Research Council subgroup on non-muscle invasive bladder cancer. Our results have indicated that in patients with G2 tumors, progression is related to recurrence, but this is especially true if high-grade disease or CIS at first recurrence is present.

In the National Bladder Cancer Collaborative Study, the interval between diagnosis and the first recurrence was a prognostic factor independent of the number of recurrences. Herr reported on 221 patients with superficial bladder tumor (Stage Ta, Tis, and T1) treated by TUR and a 6-week course of intravesical BCG. Of these patients, 195 were evaluated after 3 months for local response. Of the 195 patients, 17 (8.7%) had a Stage T1 tumor, of whom, 14 (82%) subsequently developed muscle invasion, uncontrolled local disease, or metastasis. Herr suggested that patients with Stage T1 tumor 3 months after BCG therapy require additional therapy other than simple tumor resection and meticulous follow-up. Solsona et al. reported that patients with T1G3 or CIS or prostatic involvement at 3 months had a 72.4% risk of progression compared with a risk of only 35% for patients with Stage Ta or G1-G2 residual tumor. Chopin and Gattegno reported, in a review, that the early presence of different factors such as positive cytology findings, tumor recurrence, or CIS is associated with progression. In patients with T1G2 tumors of the bladder, no data are available on the evaluation of response at 3 months and 6 months in relation to progression to ascertain which is the best time to decide on more aggressive management. Related to recurrence at 3 months and residual disease, we know that some patients will have residual disease, but in our experience, the rate is also low with T1G3 tumors: 10% recurrence and 5% progression from 3 to 6 months. Repeat TUR was not done in this group of patients. This study was retrospective, and, on the basis of our results, we cannot recommend that repeat TUR should be performed.

It is well known that the presence of concomitant CIS is an important prognostic factor for progression in patients with T1G3 urothelial tumors. The probability of progression at 5 years in T1G3 patients with and without CIS is 74% and 29%, respectively; however, in patients with T1G2 and CIS, the risk is about 17%. In the present study, the incidence of CIS in patients with T1G2 tumors was 8.5%, and the rate of progression was 3.4% in those without concomitant CIS compared with 13.2% in those with it (P = 0.001).

It is important to remember that when applying the new classification of the World Health Organization/International Society of Urological Pathology 2004, most G2 tumors will be classified as low-grade tumors, but some will be classified as high grade. It is probable that some of the G2 tumors classified as high-grade tumors with the new classification will be those tumors that later progress. However, even with these changes, progression will have to be considered whenever a low-grade tumor becomes high grade or recurs with CIS.

**CONCLUSIONS**

The results of this study have provided new insights into the specific scenario of primary T1G2 bladder tumors. The progression rate (4.5%) is much lower than the data published previously. When the T stage and grade are similar, other factors appear to influence the prognosis. Among patients with primary urothelial T1G2 disease, those with a solitary tumor and a low grade at first recurrence have a very low potential for progression. Recurrence at 3 months was the main prognostic factor related to progression, and it was related to the association of CIS with the primary tumor or the presence of high-grade disease and/or CIS at first recurrence.

**References**


