ORIGINAL ARTICLE

Second transurethral resection and prognosis of high-grade non-muscle invasive bladder cancer in patients not receiving Bacillus Calmette-Guérin

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Abstract

Objective: To define the natural history of T1G3 bladder tumor not receiving intravesical Bacillus Calmette-Guerin (BCG) and to assess the diagnostic and therapeutic value of a second transurethral resection (Re-TUR) in these patients.

Patients and methods: Retrospective study on the natural history of 210 patients treated at two institutions for T1G3 bladder carcinoma without associated CIS. In no case was BCG administered; 79 (37.6%) received TUR alone, and 131 (62.4%) Re-TUR 4–6 weeks later; 23 (12.4%) underwent cystectomy for tumor progression.

Results: Median follow-up was 55 (78 IQR) months, male/female ratio 8/1, and mean age 70.6 ± 11.8 (range 37–93). 19.5% were free of recurrence at 10 years, and 61.9% free of progression. Independent prognostic factors for progression were solid pattern (HR: 2.71; p = .0004), multiplicity (HR: 2.26; p = .0003), and recurrence at 3 months (HR: 3.4; p = .003). Cancer-specific survival was 81.5% at 5 and 69% at 10 years. Independent predictors of survival were: progression during the first year (HR: 17.9; p < .0001), solid pattern (HR: 2.13; p = .02), multiplicity (HR: 2.05; p = .03), and age >65 years (HR: 2.9; p = .03). Re-TUR avoided understaging (7.4%), detected T1G3 residual disease (10.7%), reduced recurrence rate at 3 months (11.4–4.6%; p = .06), and rate of progression on the 1st year (13.9–3.8%; p = .0075). However, in these patients the risk remains and no differences were detected in the long term in terms of recurrence (log-rank, p = .14), progression (p = .91), or cancer death (p = .21) in patients treated with Re-TUR.

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**Introduction**

The majority of primary bladder tumors diagnosed in Spain, one of the countries with the highest incidence of bladder cancer, are high-grade non-muscle-invasive tumors. These tumors, also known as ‘‘T1G3’’ (AJCC/WHO) or ‘‘high-grade papillary carcinoma’’ (USIP) follow an aggressive course due to its high potential for early progression and possibly underestimated risk of distant metastases. For three decades, the use of immunotherapy with Bacillus Calmette-Guerin (BCG) has been considered the standard treatment. At earlier time treatment had been very controversial, usually using transurethral resection (TUR) alone and sometimes radiotherapy. It is not surprising then that the survival of the high-grade non-muscle-invasive disease at that time was very poor (63% at 5 and 56% at 10 years, respectively), probably due to high staging error and late indication for cystectomy. Even in the era of BCG, T1G3 tumors have high propensity to recur and progress, admitting a variable risk of dying from cancer that in different series ranges between 5 and 46%. The therapeutic effect of BCG on these patients has been widely established. Six randomized trials showed a reduction in the risk of recurrence at one year of 51–26%. The meta-analysis published by Sylvester et al. in 2002, that collects information from 24 clinical trials, showed benefit in the progression rate, with risk reduction from 27% to 13.8%. However, in clinical practice patients with T1G3 tumors have frequently been treated with TUR exclusively, either because they are patients from the pre-BCG period, because of fear of complications, poor tolerance, advanced age or poor condition, delay in adjuvant treatment decision making or even shortage of BCG. On the other hand, radical cystectomy has also been advocated. Although there is no direct comparison, it is possible that radical cystectomy provides greater chances of cure and better life expectancy adjusted to the quality of life than other more conservative treatments.

Patients with T1G3 tumors of worse prognosis, and therefore better candidates for aggressive treatment, are those with deep invasion, recurrent, multiple or with associated carcinoma in situ (CIS).

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**Conclusion:** The recurrence in the first 3 months of a T1G3 tumor not receiving BCG is the main risk factor for progression, and progression of this type of tumors within the first year is the main factor of cancer death. The Re-TUR improves both variables but it does not change the long-term prognosis.

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tumors with non-papillary morphology and invasive front and those with vascular-lymphatic invasion also have a worse prognosis and it is really unknown if BCG treatment is effective in them. Therefore, it is assumed that patients that accumulate poor prognostic factors may be better candidates for early cystectomy than deferred cystectomy after failure of an initially conservative treatment.

We analyze predictors of progression in a series of patients with T1G3 urothelial carcinoma without accompanying CIS treated with bladder TUR alone, intending to define whether the predictors differ from those the literature reveals when patients receive intravesical BCG instillations. On the other hand, we investigate the intrinsic therapeutic value of Re-TUR in these lesions.

Materials and methods

Patients and methods

We retrospectively reviewed 425 patients with high-grade non-muscle-invasive carcinoma (T1G3) from the historical files of Fundació Puigvert in Barcelona (255 cases treated in the period 1981-1996) and Hospital Universitario de Getafe in Madrid (170 cases treated during 1991-2006) according to institution board approved protocols. A total of 209 cases were T1G3 bladder carcinoma without accompanying CIS treated exclusively with TUR. That is to say, they did not receive any dose of intravesical BCG therapy or other chemotherapeutic agents. Patients from Barcelona (n=78) received complete TUR of the bladder lesion including muscle in the specimen, multiple random bladder biopsies and biopsy of prostatic urethra in males. All patients in Madrid (n=131) received complete TUR of the bladder tumor including smooth muscle in the specimen, bladder biopsies of suspicious areas to rule out CIS and Re-TUR 4–6 weeks after the first TUR to reduce the risk of understaging. Follow-up at both centers based on cystoscopy and cytology every 3 months for the first 2 years, every 6 months up to 5 years and then once yearly.

We evaluated time till the first recurrence, time progression till muscle-invasive (>T2) or metastatic disease, and time till death from bladder cancer. For each event we analyzed the following variables: age, gender (male or female), multiplicity (single or multiple), and growth pattern (papillary or solid). Cases with CIS and/or CIS of prostatic urethra had been previously excluded for the analysis. Data on T1 subtyping, according to relative invasion to the level of the musculare mucosae, and tumor size were not properly recorded in all the patients and were excluded from the analysis as well. In patients experiencing tumor recurrence during follow-up instillation of intravesical agents was performed according to patient characteristics, and when disease progression occurred radical cystectomy was proposed, also in line with individual condition and patient’s age and comorbidity.

Statistical analysis

We carried out a comparison between the casuistry from both centers to establish the possible differences in the composition of the sample. We estimated the risk till the first recurrence, progression, or death from urothelial carcinoma by univariate analysis, evaluating survival function according to the Kaplan–Meier method and log-rank test, and multivariate analysis by means of the Cox proportional hazards regression model. Estimated hazard ratios (HR) with their respective 95% confidence intervals (CI) were defined for each variable analyzed.

Results

The characteristics of the patients and tumors object of this work are presented in Table 1. No differences were detected between the composition of the sample from each center regarding focality of the lesion ($\chi^2; p=0.1$), growth pattern ($p=0.4$), or topographic distribution ($p=0.3$). There were no differences concerning the sex ratio ($p=0.12$) either. However, differences were found indeed with regard to the age of the patients (67.4±12.5 vs. 75.8±8.3 years; $p<0.001$) and mean follow-up (59.5±41.6 vs. 88.7±44.8 years) of each institutional series. Globally, with a mean follow-up of 5.9 years and a maximum follow-up of 21.5 years, a total of 149 patients (71%) experienced recurrence of the disease, 58 (27.6%) progression, and 44 (21%) death from urothelial carcinoma.

Analysis of prognostic factors

The probability of being free of recurrence was 29.8% (95%CI 20.2–36.4) at 5 years and 19.5% (95%CI 12.8–26.2) at 10 years (Fig. 1). Multiplicity (log-rank; $p=0.0003$) and non-papillary growth pattern ($p=0.03$) increased the recurrence rate, but no differences were detected with regard to sex or age of the patients (both $p=0.5$), or the topography of the lesions ($p=0.6$). The rate of recurrence was not detected different either in patients treated with or without Re-TUR ($p=0.14$).

The probability for a patient to be free of progression was 72% (65.1–78.9) at 5 years and 61.9% (53.2–70.6) at 10 years (Fig. 1). Tumor recurrence within the first 3mo of follow-up was a predictor of progression ($p=0.004$). Non-papillary growth pattern ($p=0.002$) and multiplicity

| Table 1 Characteristics of the patients and the tumors. |
|---------------------------------|-----|-----|
| Patients (n=) | Cases (%) |
| Male/Female | 210* | 100 |
| Age, years, mean (range) | 70.6±11.8 (37–93) | – |
| Without Re-TUR/with Re-TUR | 79/131 | 37.6/62.4 |
| Single/multiple | 123/87 | 58.6/41.4 |
| Papillary/non papillary | 159/51 | 75.7/24.3 |
| Trigone/rest | 47/163 | 22.4/77.6 |

* They were all tumors without CIS and treated without BCG.
increased progression rate \( p = 0.03 \). No differences were detected in terms of progression regarding sex \( p = 0.8 \) or age of the patients \( p = 0.13 \), topography of the lesions \( p = 0.14 \) or having received Re-TUR \( p = 0.9 \). In multivariate analysis, recurrence at 3 months \( p = 0.003 \), non-papillary growth pattern \( p = 0.0004 \), and multiplicity \( p = 0.003 \) were independent predictors of progression (Table 2).

Cancer-specific survival rate was 81.5\% (75.3–87.6) at 5 years and 69\% (60.5–77.5) at 10 years (Fig. 1). Tumor recurrence within the first 3 months of follow-up was a predictor of survival \( p = 0.0001 \) and so was progression within the first 12 months \( p < 0.0001 \). Advanced age of the patient at the time of diagnosis \( p = 0.006 \), non-papillary growth pattern \( p = 0.04 \) and multiplicity also involved worse survival \( p = 0.02 \). No differences were found regarding sex \( p = 0.6 \), topography of the lesion \( p = 0.38 \) or having received Re-TUR \( p = 0.24 \). There is association between recurrence at 3 months and progression at 12 months (Fisher test; \( p = 0.0002 \)); so, in order to avoid the problem of multicollinearity, the variable recurrence at 3 months was removed from the multivariate analysis. Thereof, progression during 1 year \( p = 0.0001 \), non-papillary growth pattern \( p = 0.02 \), age >65 years \( p = 0.03 \) and multiplicity of the lesions \( p = 0.03 \) were independent predictors of cancer-specific death (Table 2).

### The role of Re-TUR

A total of 162 patients (38.1\%) of the 425 that make up the original series of T1G3 bladder cancer reviewed were treated with Re-TUR 4–6 weeks after the initial TUR. The rate of complications related to Re-TUR was 9.3\%; 6.8\% minor (4 cases (2.5\%) perforation, 5 (3.1\%) hematuria, 2(1.2\%) febrile UTI) and 2.5\% major complications (1 case (0.6\%) ureteral stenosis, 2(1.2\%) urethral stenosis, 1 (0.6\% sepsis and admission to ICU).

Nineteen cases (11.7\%) had CIS or TaG3 in the second TUR, so they received BCG and were therefore excluded from the analysis. Another 12 (7.4\%) showed residual tumor with muscle infiltration (T2) that had been under-staged in the first assessment. These patients received early cystectomy and, therefore, do not appear in the analysis either. Finally, of the remaining 131 patients that constitute the group of genuine T1G3 tumors without CIS treated with Re-TUR, 14 (10.7\%) showed persistence of high-grade invasive urothelial carcinoma without involvement of the muscular layer (T1). These data reveal the value of Re-TUR to avoid the staging error (7.4\%) and to detect tumor persistence of any kind (27.8\%). The probability of recurrence of a T1G3 tumor derived from residual persistence of a TUR wrongly considered complete is 10.7\% in our experience.

When the outcome of patients treated with TUR alone versus patients treated with TUR and Re-TUR is compared no statistically significant differences were found with respect to recurrence \( p = 0.14 \), progression \( p = 0.91 \), or death from bladder cancer \( p = 0.21 \) (Fig. 2). Exclusion of patients with CIS and absence of BCG instillations, both factors that modify disease progression, is of particular interest in this model. Curiously, long-term recurrence was higher in the group receiving Re-TUR, although it did not reach statistical significance.

The decline in the first portion of progression and cancer death curves in patients receiving Re-TUR is equivalent to the reduction of understaging and tumor persistence due to inadvertently incomplete TUR. Thus, the recurrence rate at 3mo decreases significantly in patients receiving Re-TUR (4.6\% vs. 11.4\%; \( p = 0.06 \)) and also progression rate within the first 12 months (3.8\% vs. 13.9\%; \( p = 0.0075 \)). The association between recurrence at 3 months and progression within the first year in this series [Fisher test, \( p = 0.0002 \); OR 12.3 (3.7–41.5)] is lost in patients receiving Re-TUR [Fisher test, \( p = 1 \); OR 1.68 (0.08–33.9)] while it is maintained in patients treated with TUR alone [Fisher test, \( p = 0.0002 \); OR 26 (4.9–136.4)]. When Odds Ratios are compared in each group, we confirm that not having received Re-TUR is a factor that influences the relationship between early recurrence and disease progression (Breslow-Day test, \( p = 0.05 \)).

### Discussion

Most data on the natural history of high-grade non-muscle invasive bladder cancer come from studies involving intravesical instillation of BCG after the TUR of the lesion. Early

### Table 2 Multivariate analysis of factors involved in progression and cancer death.

<table>
<thead>
<tr>
<th>Factor</th>
<th>( \beta ) coefficient</th>
<th>Standard error</th>
<th>( \chi^2 )</th>
<th>HR (95% CI, range)</th>
<th>( \text{p-Value} )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Progression</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-papillary morphology</td>
<td>0.99</td>
<td>0.28</td>
<td>12.61</td>
<td>2.71 (1.56–4.69)</td>
<td>( p = 0.0004 )</td>
</tr>
<tr>
<td>Multiple lesion</td>
<td>0.82</td>
<td>0.27</td>
<td>8.93</td>
<td>2.26 (1.32–3.86)</td>
<td>( p = 0.0028 )</td>
</tr>
<tr>
<td>Relapse at 3 months</td>
<td>1.22</td>
<td>0.41</td>
<td>8.93</td>
<td>0.29 (0.13–0.66)</td>
<td>( p = 0.0028 )</td>
</tr>
<tr>
<td><strong>Cancer-specific survival</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progression during the 1st year</td>
<td>2.88</td>
<td>0.43</td>
<td>44.52</td>
<td>0.06 (0.02–0.13)</td>
<td>( p &lt; 0.0001 )</td>
</tr>
<tr>
<td>Non-papillary morphology</td>
<td>0.76</td>
<td>0.33</td>
<td>5.23</td>
<td>2.13 (1.11–4.07)</td>
<td>( p = 0.0222 )</td>
</tr>
<tr>
<td>Age &gt; 65 years</td>
<td>1.06</td>
<td>0.49</td>
<td>4.77</td>
<td>2.89 (1.12–7.51)</td>
<td>( p = 0.0288 )</td>
</tr>
<tr>
<td>Multiple lesion</td>
<td>0.72</td>
<td>0.33</td>
<td>4.69</td>
<td>2.05 (1.07–3.94)</td>
<td>( p = 0.0302 )</td>
</tr>
</tbody>
</table>
Figure 1  Kaplan–Meier recurrence-free (A), progression-free (B) and disease specific (C) survivals for the entire group of patients with T1G3 disease without carcinoma in situ and treated exclusively with TUR.

Figure 2  Kaplan–Meier recurrence-free (A), progression-free (B) and disease specific (C) survivals for the two arms: patients receiving complete TUR alone (red) and patients receiving complete TUR and Re-TUR 4–6 weeks later (blue).
recurrence after TUR, the presence of concomitant CIS, the involvement of the prostatic urethra and deep invasion of the lamina propria\textsuperscript{6,17} are the patients who need an initially more aggressive approach. However, it is really unknown whether these variables remain critical when Re-TUR and/or maintenance with BCG are performed systematically for at least one year.\textsuperscript{19} That is, most of the studies in which these variables have been recognized have not considered these treatment conditions, which are, on the other hand, advocated in the Guidelines of the European Association of Urology.\textsuperscript{19} In addition, there is no real consensus on what should be the optimal duration of maintenance. To complicate this issue even more, both the risk tables of the EORTC and the scoring system of the Cueto Group overestimate the risk of recurrence and progression in patients treated with BCG.\textsuperscript{20,21}

The BCG market has recently undergone some noticeable changes, dictated by the unavailability generated by the contamination of the European factory of the Connaught strain.\textsuperscript{9} Perhaps the relative shortage of BCG has led to reconsider the possibility of practicing early cystectomy in some patients. Therefore, we believe that getting to know the predictors of prognosis in classical series of patients with T1G3 tumors who have not received BCG still makes sense. In addition, the changes that the administration of BCG entails in the natural history of the disease are not fully known. Overall, BCG treatment improves the results obtained both in the short and long term,\textsuperscript{5–7,22} but the patients with T1G3 disease remain at risk for life, which makes in part that the protective factor of BCG vanishes in time.\textsuperscript{23}

But the most recent discussion in T1G3 tumors focuses on correctly evaluating the role of a second TUR, intending to improve the classification of the disease and to get to fill the gap between delayed and early cystectomy, since the first one entails a worse prognosis\textsuperscript{5,23} and the second one may not be necessary in many cases.\textsuperscript{7,17} Today the European Guidelines also recommend performing a second bladder TUR (Re-TUR) in all cases of T1 tumor and/or high-grade non-muscle invasive tumor,\textsuperscript{19} although not all the centers systematically perform it.\textsuperscript{13,24}

There is no doubt that the crucial step in the diagnosis and treatment of any bladder cancer is TUR. Brausi et al. demonstrated that it is possible to increase the rate of muscularis propria present in the specimen and also to reduce the rate of early recurrence by improving the quality of TUR of the bladder.\textsuperscript{25} Re-TUR (second TUR) is defined as that performed after a complete TUR. Still though, the rate of residual tumor shown by a Re-TUR is 20–78\% and the rate of understaging 1.7–29\%.\textsuperscript{26–28} In our experience the numbers are 27.8\% and 7.4\%, respectively. Re-TUR decreases the rate of progression and improves cancer-specific survival because it significantly reduces the rate of recurrence at 3 months and the rate of progression at 12 months; the latter being the most decisive predictor in the multivariate analysis. Therefore, although we cannot prove that Re-TUR is a prognostic factor in itself, we should consider it so as it favorably affects the recurrence and progression rates of T1 tumors, and this effect seems even more evident for the high-grade disease.\textsuperscript{26,27}

Early recurrence at 3 months of primary TUR is considered a first-order predictor in patients in whom BCG fails to control the disease.\textsuperscript{16,17} However, early recurrence in patients without any adjuvant treatment, and herein lies the value of studying patients who do not receive BCG, presupposes that this is a residual disease and not a disease refractory to treatment. The second TUR properly magnifies the risks of residual disease and underestimation of muscle-invasion, but its role has not been properly assessed in the long term in patients without BCG and without early adjuvant chemotherapy. Furthermore, the trial by Divrik et al.\textsuperscript{27,28} have numerous biases.\textsuperscript{29} Possibly, therefore, there are critics who believe it is not necessary to perform re-TUR in all cases of T1 disease and/or highgrade in clinical practice.\textsuperscript{13,24}

Our work has important limitations, as expected from a retrospective study. However, we believe that the T1G3 disease without CIS and treated without BCG is a good model to establish the therapeutic value of Re-TUR in a real clinical setting. We do not know why the patients receiving second TUR in our study have greater long-term risk of recurrence than those receiving a single TUR, although without reaching statistical significance. This can be explained maybe because of the absence of random multiple biopsies in one of the centers, i.e. the group receiving Re-TUR, that may have underestimated the probability of unadverted CIS and, therefore, of long-term recurrence. However, we cannot rule out the possibility raised by El-Abbady et al. that Re-TUR might alter the biological behavior of the tumor in the long-term facilitating deep implantation of neoplastic cells in areas of denuded epithelium.\textsuperscript{30} In terms of progression and survival, the Re-TUR improves staging of the disease and obtains a beneficial effect by decreasing the recurrence at 3 months and, hence, progression during the first year (the main predictor of cancer-specific survival). However, it surely does not affect other factors involved such as non-papillary morphology, multiplicity or age. Old age could limit the possibility of rescue by failing to propose deferred cystectomy in all cases it is necessary.

In conclusion, in patients with T1G3 tumors without CIS not receiving BCG, the progression to muscle-invasive or metastatic disease in the first year, the non-papillary morphology of lesions, age >65 years, and the multiplicity of the lesions appear as independent predictors of death from cancer. In our experience, the Re-TUR prevents understaging in 7.4\% of these cases and persistence of T1G3 lesions in 10.7\%, respectively. This fact not only helps to reduce the probability of recurrence at 3 months, but it also decreases the probability of progression 26 times within the first year compared to patients receiving a single TUR. Nevertheless, no long-term benefit is shown in progression or survival because the other factors involved also carry great weight in this model. The advantages of performing Re-TUR are evident, with an acceptable complication rate, but they do not correct the lifetime risk of progression or death in these patients.

**Conflict of interest**

The authors declare that they have no conflict of interest.
Acknowledgements

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