Is T1G3 Bladder Cancer Having a Definite Muscle Layer in TUR Specimens a Highly Progressive Disease?

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Objective: Patients with T1G3 bladder cancer are at high risk of progression to muscle-invasive cancer, and early cystectomy is considered as a treatment option in this particular situation. On the other hand, understaging of T1G3 bladder cancer has been gradually proven as second or repeat transurethral resection (TUR) has been widely applied. To evaluate the real rate of progression, we investigated the prognosis of T1G3 bladder cancer in which a muscle layer was histologically confirmed in the TUR specimens.

Methods: We retrospectively reviewed 48 patients with primary T1G3 bladder cancer in which a muscle layer in the TUR specimens was confirmed between 1990 and 2006 in our institute. We investigated recurrence and progression in 45 patients, excluding 3 who were immediately treated with radical cystectomy. Fifteen and 12 patients received intravesical treatment with bacillus Calmette–Guérin (BCG) and anticancer agents just after TUR, respectively. The remaining 18 did not have any such treatment.

Results: Recurrence and progression were observed in 21 (47%) and 3 patients (6.7%), respectively, during a median follow-up period of 42.1 months. The 3-year recurrence-free and progression-free survival rates were 54% and 91%, respectively. No significant differences were observed in the rates between the patients with and without BCG treatment in the study.

Conclusions: There is a possibility that the progression rate in patients with T1G3 bladder cancer is not as high as previously reported when only patients whose muscle layer was histologically confirmed were analyzed. An adequate technique for TUR that unmistakably collects the muscle layer may be important to predict the outcome accurately.

Key words: T1G3 – bladder cancer – progression – understaging – muscle layer

INTRODUCTION

Approximately 70% of bladder tumors are diagnosed as superficial cancer without invasion to the muscle layer at initial presentation (1). Although the prognosis of superficial bladder cancer is generally favorable, it is known that T1G3 bladder cancer is a distinct clinical entity from the remaining superficial cancer since it has been reported that the disease eventually progresses in approximately half of the patients with T1G3 cancer during follow-up (2,3). Because of its high risk for progression, early radical cystectomy is sometimes considered as an initial treatment, although it is controversial (4).

As second or repeat transurethral resection (TUR) for T1 bladder cancer is becoming widely used, it is known that understaging of T1 cancer frequently occurs (5). Although T1 cancer is defined as a tumor with invasion to the lamina propria but no invasion to the detrusor muscle, it seems to be clinically composed of two types. One is genuine T1 cancer in which cancer cells really exist up to the lamina propria. The other is T2 or higher cancer misdiagnosed as T1 cancer because the detrusor muscle is not included in the TUR specimens.

As previously noted, it has been believed that patients with T1G3 cancer have a high progression rate. If there is contamination by T2 or higher cancer, the prognosis of T1G3 cancer must be worse than the true one. However, only a few reports analyzing the prognosis of T1G3 cancer demonstrate whether the TUR specimens included the...
detrusor muscle (6). In the present study, we retrospectively evaluated recurrence and progression in patients with T1G3 bladder cancer whose detrusor muscle was histologically confirmed.

PATIENTS AND METHODS

In our institute, TUR of bladder cancer was done in the standard manner. Once all visible tumors were resected, the base of the main tumor was resected again until the perivesical fat tissue became visible. Care had to be taken not to extensively penetrate the bladder wall. Between 1990 and 2006, we treated 48 patients with initially diagnosed T1G3 bladder cancer in our institute. It was histologically confirmed that TUR specimens derived from all patients included enough of the muscle layer to adequately determine the T stage. On the other hand, there were another 11 patients diagnosed with T1G3 bladder cancer at the same period in our institute who had no evaluable muscle layer in the TUR specimens. Patients who had findings suggestive of muscle-invasive bladder cancer on radiographic studies and a history of upper urinary tract cancer were excluded. In addition, patients who did not receive regular cystoscopic examination every 3 months after TUR were excluded.

Of the 48 patients, 3 patients underwent immediate radical cystectomy because of the patients’ decisions, based on concomitant localized prostate cancer, severe hematuria and storage symptoms caused by bladder cancer. In the remaining 45 patients with T1G3 cancer, the bladder was preserved. Eighteen patients did not have any bladder instillation therapy after TUR. Of the remaining 27 patients, 15 and 12 received intravesical treatment with bacillus Calmette–Guérin (BCG, 80 mg of Tokyo strain for 8 patients and 81 mg of Connaught strain for 7 patients) and an anticancer agent (anthracyclines for 8 patients and mitomycin C for 4 patients), respectively. BCG was intravesically instilled every week for 6–8 weeks as one course and every patient received at least one course of BCG. None received maintenance BCG therapy. Because of the retrospective nature of the present study, indications for additional therapy and criteria for drug selection were not uniform. However, patients who had carcinoma in situ or persistent positive urine cytology after TUR were exclusively treated with BCG (Table 1).

The patients were followed by cystoscopic examination and urine cytology every 3 months. If necessary for suspicious symptoms and findings of metastatic development, radiographic examination using computed tomography and chest X-rays was conducted. When bladder tumors were found on cystoscopic examination, TUR was performed to pathologically confirm recurrence. Invasion of the muscle layer, as well as development of distant metastasis, was defined as progression.

The Kaplan–Meier method and log-rank test were used for statistical analysis of recurrence and progression. A value of $P < 0.05$ was defined as statistically significant.

### Table 1. Backgrounds of patients treated with BCG and an anticancer agent

<table>
<thead>
<tr>
<th></th>
<th>BCG ($n = 15$)</th>
<th>Non-BCG ($n = 30$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoma in situ</td>
<td>3 (20.0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Positive cytology* (after TUR)</td>
<td>2 (13.3%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Tumor size (mm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$&lt; 10$</td>
<td>6 (40.0%)</td>
<td>4 (13.3%)</td>
</tr>
<tr>
<td>$\geq 10$</td>
<td>9 (60.0%)</td>
<td>26 (86.7%)</td>
</tr>
<tr>
<td>Tumor number</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solitary</td>
<td>3 (20.0%)</td>
<td>9 (30.0%)</td>
</tr>
<tr>
<td>Multiple</td>
<td>12 (80.0%)</td>
<td>21 (70.0%)</td>
</tr>
<tr>
<td>Repeat TUR</td>
<td>1 (6.7%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

BCG, bacillus Calmette–Guérin; TUR, transurethral resection.

*Patients who represented positive urine cytology after TUR were different from patients who had carcinoma in situ.

RESULTS

The median age of the 45 patients (42 men and 3 women) at initial TUR was 68 years, ranging from 29 to 97. The median follow-up period was 42.1 months (range, 9.5–131.4).

Recurrence was observed in 21 (47%) patients. The recurrence-free survival rates at 2 and 3 years were 57% and 54%, respectively (Fig. 1). Most recurrences occurred within 2 years after TUR. The recurrence-free survival rate in the 15 patients treated with BCG was 73% at 2 and 3 years (Fig. 2). Although the 50% 2-year and 44% 3-year recurrence-free survival rates in 30 patients without BCG were lower than those with BCG, there was no significant difference in recurrence-free survival between them ($P = 0.097$, log-rank test). The 3-year progression-free survival rate of the 45 patients was 91% (Fig. 3).

Progression was observed in three patients (6.7%). None of the three patients received BCG therapy or had distant metastasis at the initial presentation of progression. After progression, two patients (4.4%) eventually died of bladder cancer.

Pathological comparison between the TUR and cystectomy specimens in the three patients treated with immediate radical cystectomy revealed understaging for one patient (pT3pN0). The patient developed distant metastasis 19 months after surgery and finally died of bladder cancer in spite of treatment by several courses of systemic chemotherapy.

Of the 11 patients without a muscle layer in the TUR specimens, 6 (54.5%) and 3 (27.3%) patients showed recurrence and progression, respectively. Eventually, two patients died of bladder cancer.

DISCUSSION

One of the biggest problems of T1G3 bladder cancer is progression to muscle-invasive cancer. Since it is obvious that
the prognosis of muscle-invasive cancer is not promising, to accurately predict the probability of progression in patients with T1G3 cancer is clinically important to make treatment decisions, especially considering whether immediate radical cystectomy should be offered as the initial treatment.

Previous studies have demonstrated that the recurrence and progression rates in patients with T1G3 cancer vary widely from 27% to 70% and 4% to 33%, respectively (Table 2) (3,6,13,14). Such variation may indicate that T1G3 cancer is composed of heterogeneous groups. Since it is known that understaging of T1 cancers frequently occurs (4), the degree of contamination by muscle-invasive cancer in T1G3 cancer may be related to the differences in progression rates among the reports.

Dutta et al. (7) performed radical cystectomy for 63 patients who were diagnosed as having T1 bladder cancer. The muscle layer was confirmed in the TUR specimens from 37 patients, whereas it was not included for 26 patients. Pathological evaluation of cystectomy specimens indicated that 30% and 62% of the patients with and without the muscle layer in the TUR specimens showed pT2 or higher diseases, respectively.

Herr (5) reported a similar result. They performed repeat TUR for 58 patients who were considered to have T1 bladder cancer in the initial TUR. Repeat TUR found muscle invasion in 5 patients (14%) with the muscle layer and in 11 patients (49%) without the muscle layer in the initial TUR. Thus, it is apparent that understaging of T1 cancer is likely to occur if the muscle layer is not included in the TUR specimen.

In the present study, the progression rate of T1G3 bladder cancer during 42 months of follow-up was 6.7% when only
patients with a histologically confirmed muscle layer in the TUR specimens were analyzed. The 3-year progression-free survival rate was 91%. On the other hand, the 27.3% of the progression rate in the patients without a muscle layer was much higher, although it is hard to compare the rates of the two groups because of the small number of the patients. Gohji et al. (6) reported the lowest progression rate to our knowledge (Table 2). Their study consisted of 45 patients with T1G3 cancer whose TUR specimens included a definite muscle layer. Thus, the progression rate in patients with T1G3 cancer was not so high if we analyzed only patients whose muscle layer was histologically confirmed, which suggests less possibility of contamination by muscle-invasive bladder cancer. In the present study, of the three patients treated with immediate radical cystectomy, one was proven to be understaged because muscle invasion was found in the cystectomy specimen. If this patient is followed without immediate radical cystectomy, progression should be observed. However, even though we assume the patient to be a subject with progression, the progression rate, 8.7% (4 of the 46 patients), was still lower than those in the previous reports, although it is hard to draw a solid conclusion because of the small sample size in this study.

The second clinical problem of T1G3 cancer is its high recurrence rate. Similar to the previous reports, recurrence was observed in 47% in the present study (Table 2). Recurrence occurred within 2 years in most patients. To prevent early recurrence in T1G3 cancer, BCG or anticancer agents are indicated (8,9). Although there was no significant difference in the recurrence-free survival rate between patients with and without BCG therapy in our study, the lack of uniform criteria for intravesical therapy and small sample size may have influenced the result. There was a 29% difference at 3 years after TUR between the two groups and no recurrence was observed after 1 year in the BCG group. Several large studies have indicated that intravesical BCG therapy makes a contribution to prevent recurrence for patients with superficial bladder cancer superior to those of intravesical anticancer agents (10–12).

As previously discussed, it is likely that understaging is more frequent in T1G3 bladder cancer in which the muscle layer is not included. On the other hand, understaging was sometimes observed even in patients whose muscle layer was sufficiently collected in the TUR specimens. In the present study, one of the three patients with muscle-layer-confirmed T1G3 who underwent immediate cystectomy had pT3 bladder cancer. Herr (5) reported that repeat TUR for 35 patients with T1 bladder cancer having a definite muscle layer in the initial TUR showed residual cancer in 26 (74%) and muscle-invasive cancer in 5 (14%). A recent randomized study done by Divrik et al. (15) indicated that T1 patients with repeat TUR plus intravesical mitomycin C had significantly lower recurrence (26%) than those with only initial TUR plus intravesical mitomycin C (63%). In addition, the progression rate was lower in patients with repeat TUR (4%) than in those without it (12%), although the difference did not reach statistical significance ($P = 0.097$). Thus, repeat TUR may contribute to not only more accurate diagnosis and a more precise prognosis but also an improved outcome for patients with T1G3 cancer whose muscle layer is confirmed in the initial TUR specimen.

In conclusion, there is a possibility that the progression rate in patients with T1G3 bladder cancer is not as high as previously reported when only patients whose muscle layer was histologically confirmed were analyzed. An adequate technique for TUR that clearly collects the muscle layer may be important to predict the outcome accurately.

Conflicts of interest statement
None declared.

References