Construction of Predictive Models for Cancer-specific Survival of Patients with Non-muscle-invasive Bladder Cancer Treated with Bacillus Calmette-Guérin: Results from a Multicenter Retrospective Study

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Objective: The aims of this study were to clarify the prognostic factors and to validate the bacillus Calmette-Guérin failure classification advocated by Nieder et al. in patients with non-muscle-invasive bladder cancer who had intravesical recurrence after bacillus Calmette-Guérin therapy.

Methods: Data from 402 patients who received intravesical bacillus Calmette-Guérin therapy between January 1990 and November 2011 were collected from 10 institutes. Among these patients, 187 with bacillus Calmette-Guérin failure were analyzed for this study.

Results: Twenty-nine patients (15.5%) were diagnosed with progression at the first recurrence after bacillus Calmette-Guérin therapy. Eighteen (62.1%) of them died of bladder cancer. A total of 158 patients were diagnosed with non-muscle-invasive bladder cancer at the first recurrence after bacillus Calmette-Guérin therapy. Of them, 23 (14.6%) underwent radical cystectomy. No patients who underwent radical cystectomy died of bladder cancer during the follow-up. On multivariate analysis of the 135 patients with bladder preservation, the independent prognostic factors for cancer-specific survival were age (≥70 [P = 0.002]), tumor size (≥3 cm [P = 0.015]) and the Nieder classification (bacillus Calmette-Guérin refractory [P < 0.001]). In a subgroup analysis, the estimated 5-year cancer-specific survival rates in the groups with no positive, one positive and two to three positive factors were 100, 93.4 and 56.8%, respectively (P < 0.001).

Conclusions: Patients with stage progression at the first recurrence after bacillus Calmette-Guérin therapy had poor prognoses. Three prognostic factors for predicting survival were identified and used to categorize patients with non-muscle-invasive bladder cancer treated with bacillus Calmette-Guérin into three risk groups based on the number of prognostic factors in each one.

Key words: non-muscle-invasive bladder cancer – bacillus Calmette-Guérin – BCG failure classification
INTRODUCTION

Approximately 70% of bladder tumors are non-muscle-invasive bladder cancer (NMIBC) confined to the mucosal and submucosal layers (Ta, Tis and T1) of the bladder at the time of initial evaluation. Although most TaT1 tumors can be completely resected by transurethral intervention, the intravesical recurrence rate is >50% (1–3). Progression to muscle-invasive bladder cancer (MIBC) is much less frequent than recurrence in NMIBC. However, 30% or more of the patients with high-risk NMIBC develop progressive disease, which is associated with metastasis and cancer death (4–8). Intravesical Bacillus Calmette-Guérin (BCG) therapy is useful for adjuvant treatment of patients with high-risk NMIBC (9, http://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf). Some studies showed that intravesical BCG therapy reduced the risk of recurrence compared with either transurethral resection alone or chemotherapy (10–13). However, there was recurrence in 30–50% of the patients regardless of whether they received maintenance BCG therapy or not (13,14). European Association of Urology (EAU) and National Comprehensive Cancer Network (NCCN) guidelines recommend that patients with failure of intravesical BCG therapy should be offered radical cystectomy (9, http://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf). Those whose disease progresses to muscle-invasive disease at radical cystectomy after BCG therapy have a poor prognosis compared with NMIBC at radical cystectomy (15). To decrease the recurrence rate and improve cause-specific survival, early cystectomy is recommended for high-risk NMIBC (8,16). However, radical cystectomy, despite advances in urinary diversion techniques, has its disadvantages (7). Furthermore, the distribution of patients with unsuccessful treatment with BCG is heterogeneous. Nieder et al. (14) stratified BCG failure into four categories: BCG refractory, BCG resistant, BCG relapse and BCG intolerant. Although a few studies (17,18) revealed the accuracy or adequacy for prognosis of the BCG failure classification by Nieder et al., there are no robust data on prognostic factors for the survival of patients with NMIBC treated with BCG. The aims of this study were to clarify the prognostic factors and to validate the BCG failure classification advocated by Nieder et al. in patients with NMIBC who had intravesical recurrence after BCG therapy.

PATIENTS AND METHODS

PATIENTS’ CHARACTERISTICS

Data from 402 patients who received intravesical BCG therapy between January 1990 and November 2011 were collected from 10 institutes (Sapporo Medical University Urologic Oncology Consortium). Among these patients, 187 with BCG failure were analyzed for this study. The mean follow-up interval from transurethral resection of the bladder tumor (TURBT) before BCG treatment was 68.4 ± 53.0 months (mean ± SD). The patients consisted of 154 men and 33 women aged 69.2 ± 9.6 (mean ± SD) years. Ninety-seven (51.9%) of the patients underwent initial TURBT, and 90 (48.1%) underwent one or more TURBT procedures before BCG therapy. A second resection was performed when the TUR before BCG treatment was incomplete or the specimen did not contain tissues from the muscularis propria. Patients who had muscularis propria tissue in the TUR specimens before BCG therapy were included in this study. If, in carcinoma in situ (CIS) patients, TUR biopsy was performed and the specimen did not contain tissues from the muscularis propria at the location of the mucosal changes, these patients were excluded from this study. The measurement of tumor size and multiplicity were based on the clinical records, which clearly noted the tumor morphology. In CIS cases, measurements were performed based on both the mucosal changes and pathological results in the clinical records. One hundred and sixty-eight (89.9%) patients received intravesical instillation of BCG at a dose of 81 mg (Connaught strain) or 80 mg (Tokyo 172 strain). Two (1.1%) and 17 (9.1%) received intravesical instillation of BCG at doses of 60 and 40 mg, respectively. Four (2.1%) patients received BCG maintenance therapy (Table 1).

We used Nieder’s classification (14) to divide patients with BCG failure into the following categories: (i) BCG refractory, the failure to achieve a disease-free state by 6 months after initial BCG therapy with either maintenance or retreatment at 3 months. It also includes any progression in stage, grade or disease extent by 3 months after the first cycle of BCG. (ii) BCG resistant as recurrence or persistence of disease at 3 months after the induction cycle. It is of lesser degree, stage or grade and no longer present at 6 months after BCG retreatment. (iii) BCG relapse as recurrence of disease after achieving a disease-free status by 6 months. (iv) BCG intolerant if disease recurs after a less than adequate course of therapy is applied because of a serious adverse event or symptomatic intolerance that mandates discontinuation of further BCG.

Patients who had a history of upper urinary tract cancer and MIBC before BCG therapy were excluded; because after the first BCG instillation, the accelerated immunological response is not sufficient at first week (19). For examining the antitumor efficacy of BCG for NMIBC, patients who could continue four or more weekly administrations of induction BCG therapy were included in this study. Progression was defined as muscular invasion and/or development of metastasis during the follow-up period. For all patients, pathological grades were classified as Grade 1 (G1), Grade 2 (G2) or Grade 3 (G3) according to the 1973 WHO system.

The follow-up protocol consisted of cystoscopy and urine cytology every 3 months in the first 3 years and subsequently every 6 months for 10 years. In this follow-up period, if bladder cancer recurrence was suspected based on urine cytology or cystoscopy, TUR was performed to determine whether the patient was disease free or not. Upper tract monitoring was performed yearly with either computed tomography or an intravenous urogram. The starting point of this study was the timing of TURBT for BCG failure and
Endpoints in this study were progression-free survival (PFS) and cancer-specific survival (CSS). This study was approved by the ethics committees of all participating institutions.

**Statistics**

Kaplan–Meier curves were generated for PFS and CSS. PFS and CSS in univariate analysis were compared between the groups using the log-rank test. Multivariate Cox regression models were used for PFS and CSS. Statistical tests were performed with SPSS version 16.0 (SPSS, Chicago, IL, USA). Differences were considered significant if $P < 0.05$.

**Results**

The patients were stratified into groups based on whether they were BCG refractory (77, 41.2%), BCG resistant (4, 2.1%), BCG intolerant (8, 4.3%) or BCG relapsed (98, 52.4%). The pathological diagnoses before initial BCG treatment and at BCG failure are shown in Table 1. Twenty-nine patients (15.5%) were diagnosed with progression at the first recurrence after BCG therapy. Of these patients, 18 (62.1%) died of bladder cancer. The mean interval from TURBT before BCG therapy to progression was 19.8 ± 31.9 months (mean ± SD). The 5-year CSS rate of these 29 patients from progression was 34.6%. Of the 29 patients who had disease progression, 22 (75.9%) underwent radical cystectomy and 5 (17.2%) received radiation treatment. Two (6.9%) patients received best supportive care.

A total of 158 patients were diagnosed with NMIBC at the first recurrence after BCG therapy. The mean interval from TURBT before BCG therapy to the first recurrence after BCG therapy was 19.1 ± 22.9 months (mean ± SD). Of these patients, 23 (14.6%) underwent radical cystectomy and 135 (85.4%) received bladder preservation therapy at the first recurrence after BCG therapy. The 23 patients who underwent radical cystectomy were stratified into groups based on whether they were BCG refractory (17, 73.9%), BCG resistant (0, 0%), BCG intolerant (1, 4.3%) or BCG relapsed (5, 21.7%). The 135 patients with bladder preservation were also stratified into groups based on whether they were BCG refractory (48, 35.6%), BCG resistant (4, 3.0%), BCG intolerant (6, 4.4%) or BCG relapsed (77, 57.0%) (Fig. 1). The 5-year CSS rates of patients with radical cystectomy and those with bladder preservation at the first recurrence after BCG therapy were 100 and 89.8%, respectively (Fig. 2). CSS did not differ significantly between patients with radical cystectomy and those with bladder preservation ($P = 0.111$).

Of the 135 patients with bladder preservation at the first recurrence after BCG therapy, 52 and 22 patients received intravesical instillation of second BCG and anti-cancer drugs, respectively. On the basis of multiplicity at BCG failure, 74 (54.8%) and 61 (45.2%) of the 135 cases were unifocal and multifocal, respectively. On the basis of tumor configuration at BCG failure, 22 (16.3%) and 113 (83.7%) were papillary.
pedunculated tumors and others, respectively. Of these patients, none were diagnosed with tumors 3 cm at BCG failure. Among the 135 patients, 45 underwent radical cystectomy and 39 had progression during follow-up. On univariate analysis of the patients with bladder preservation at the first recurrence after BCG therapy, the depth of invasion (Ta or Tis versus T1) before initial BCG therapy ($P = 0.046$), concurrent CIS before initial BCG therapy ($P = 0.044$), the grade (G1 or G2 versus G3) at BCG failure ($P = 0.009$) and the Nieder classification (refractory versus others) ($P < 0.001$) were significant predictors of progression. On multivariate analysis of the patients with bladder preservation, the grade (G1 or G2 versus G3) at BCG failure ($P = 0.023$) and the Nieder classification (refractory versus others) ($P = 0.001$) were significant predictors of progression (Table 2). According to the Nieder classification, the 5-year PFS rates of BCG-refractory and BCG-relapse patients were 59.2 and 77.0%, respectively, ($P = 0.001$). According to the grade at BCG failure, the 5-year PFS rates of patients with Grade 3 and Grades 1–2 were 58.3 and 78.0%, respectively, ($P = 0.009$).

Of the 135 patients with bladder preservation at the first recurrence after BCG therapy, 22 died due to bladder cancer during follow-up. The CSS rate at 5 years for the 135 patients with bladder preservation was 89.8%. On univariate analysis of the patients with bladder preservation, age ($\geq 70$ years) ($P = 0.012$), tumor size ($<3$ cm versus $\geq 3$ cm) before initial BCG therapy ($P = 0.009$), the depth of invasion (Ta or Tis versus T1) before initial BCG therapy ($P = 0.007$), the depth of invasion (Ta or Tis versus T1) at BCG failure ($P = 0.023$) and the Nieder classification (refractory versus others) ($P < 0.001$) were significant predictors of CSS. On multivariate analysis of the patients with bladder preservation, the independent factors for CSS were age ($<70$ years or $\geq 70$ years) ($P = 0.012$), tumor size ($<3$ cm versus $\geq 3$ cm) ($P = 0.015$) and the Nieder classification (refractory versus others) ($P < 0.001$) (Table 3). According to the Nieder classification, the 5-year CSS rates of patients who were BCG refractory and had BCG relapse were 74.2 and 96.9%, respectively, ($P < 0.001$) (Fig. 3a). The 5-year CSS rates of patients aged 70 years or more and $<70$ years were 81.8 and 97.0%, respectively ($P = 0.012$) (Fig. 3b). The 5-year CSS rates of patients with tumor sizes $<3$ cm and tumor sizes $\geq 3$ cm were 90.9%
and not reached, respectively (\(P = 0.009\)) (Fig. 3c). In a subgroup analysis using the prognostic factors (tumor size \(> 3 \text{ cm}, \text{age} \geq 70 \text{ years}\) and BCG refractory) that were independent prognostic factors for CSS in both univariate and multivariate analyses, the estimated 5-year CSS rates in the groups with no positive \((n = 39)\), one positive \((n = 70)\) and two to three positive factors \((n = 26)\) were 100, 93.4 and 56.8%, respectively \((P < 0.001)\) (Fig. 4). There were significant differences in CSS between patients with no positive and one positive factor \((P = 0.030)\), between no positive factor and two to three positive factors \((P < 0.001)\) and between one positive factor and two to three positive factors \((P < 0.001)\).

**DISCUSSION**

For the patients with bladder preservation at the first recurrence after BCG therapy, the Nieder classification was a significant predictor of progression and CSS. The patients who were BCG refractory had a poor prognosis compared with the other BCG failure groups. Shirakawa et al. investigated whether the Nieder classification of BCG failure could identify patients with higher malignant potential. Univariate and multivariate analyses revealed that being BCG refractory were independent predictors of progression. In addition, BCG refractory patients were significantly more likely to die than those in other BCG failure groups \((17)\). Considering the interval from BCG therapy to failure, Andius and Holmang \((20)\) reported that patients with a tumor at the first cystoscopy had a much higher risk of progression than those who were tumor free. Lerner et al. \((21)\) found that failure to achieve a complete response (CR) after induction BCG therapy was associated with a 67% higher risk of death. These results indicated that being BCG refractory or failure to achieve a CR for induction BCG therapy could be a prognostic factor for progression and cancer death.

**Table 2.** Univariate analysis and multivariate Cox analysis predicting tumor progression in the patients with bladder preservation at the first recurrence after BCG therapy \((n = 135)\)

| Variables                                      | Univariate | Multivariate |
|------------------------------------------------|------------|--------------|
| Recurrent tumor (yes versus no)                | 0.547      |              |
| Age (<70 versus \(\geq 70\))                  | 0.074      |              |
| Tumor size (<3 cm versus \(\geq 3\) cm)       | 0.356      |              |
| Tumor configuration (papillary, pedunculated versus non-papillary and/or non-pedunculated) | 0.136      |              |
| Grade (G1 or G2 versus G3)                     | 0.109      |              |
| Depth of invasion (Ta or Tis versus T1)        | 0.046      |              |
| Concurrent CIS (yes versus no)                 | 0.044      |              |
| BCG failure groups (refractory versus others)  | <0.0001    | 2.802 (1.49−5.29) |

**Table 3.** Univariate analysis and multivariate Cox analysis predicting cancer-specific survival of the patients with bladder preservation at the first recurrence after BCG therapy \((n = 135)\)

| Variables                                      | Univariate | Multivariate |
|------------------------------------------------|------------|--------------|
| Recurrent tumor (yes versus no)                | 0.947      |              |
| Age (<70 versus \(\geq 70\))                  | 0.012      | 4.253 (1.67−10.80) |
| Tumor size (<3 cm versus \(\geq 3\) cm)       | 0.009      | 7.577 (1.48−38.80) |
| Tumor configuration (papillary, pedunculated versus non-papillary and/or non-pedunculated) | 0.343      |              |
| Grade (G1 or G2 versus G3)                     | 0.179      |              |
| Depth of invasion (Ta or Tis versus T1)        | 0.007      |              |
| Concurrent CIS (yes versus no)                 | 0.16       |              |
| BCG failure groups (refractory versus others)  | <0.0001    | 5.969 (2.43−14.67) |

HR, hazards ratio; CI, confidence interval; CIS, carcinoma in situ.

*a Cox proportional hazards model.
Our results also revealed that age and tumor size were prognostic factors for predicting survival. The 5-year CSS rates of patients aged 70 years or older and those younger than 70 years were 81.8 and 97.0%, respectively. Fernandez-Gomez et al. showed that age was a significant predictive factor for progression. Univariate analysis showed that age older than 70 years had a significant effect on survival compared with age 60 years or less (hazards ratio 1.863, \( P = 0.0151 \)) (22). Herr et al. evaluated the influence of age on the response to BCG therapy. The median cancer-free survival time among patients younger than 70 years was 20 months versus 16 months in patients older than 70 years (\( P = 0.005 \)) (23). Joudi et al. reported the influence of age on the response to intravesical immunotherapy in NMIBC. Aging appears to be associated with a decreased response to intravesical immunotherapy, which is particularly apparent in very elderly patients (24).

Cystectomy is the main option recommended in the NCCN guidelines for patients with recurrence of high-grade T1 disease after induction BCG therapy. However, non-surgical candidates might consider concurrent chemoradiation within the context of a clinical trial (http://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf). The EAU guidelines provide recommendations for recurrence and failure after BCG therapy. In these guidelines, all of the treatment recommendations for BCG failure include radical cystectomy and bladder preservation therapy (9). However, it is unclear which patients should undergo radical cystectomy and bladder preservation therapy.

This study showed that patients with stage progression at the first recurrence after BCG therapy had poor prognoses. However, no patients who underwent radical cystectomy diagnosed with NMIBC at the first recurrence after BCG therapy died of bladder cancer during the follow-up. Soloway et al. reported that patients whose disease progressed to T2 or a higher stage had significantly lower survival. The 5-year CSS rates for patients who received BCG therapy before radical cystectomy with \( <T2 \), \( T2 \) and \( T3/T4 \) were 86, 48 and 26%, respectively (15). Herr reported 15-year outcome data for high-grade T1 bladder tumors. In their study, 81% of the patients received BCG therapy at some time during their follow-up. Of these patients, 52% progressed first to muscle invasion or metastasis and 31% died of the disease (25). The 3-year bladder cancer-specific survival was 67% for patients initially presenting with muscle-invasive disease, but only 37% in patients after BCG treatment. When cystectomy was performed before progression to muscle-invasive disease, CSS was >90% (10,26).
Thomas et al. reported the long-term outcome of treated high-risk NMIBC. Of their patients, 63% received immunotherapy. In multivariate analysis, CSS was associated with advanced age, progression to muscle invasion, disease stage and dysplastic urothelium (27). In the present analysis, we found that the BCG failure classification advocated by Nieder et al. predicted subsequent progression and CSS. Furthermore, three prognostic factors for predicting survival were identified and used to categorize patients with NMIBC treated with BCG into three risk groups based on the number of prognostic factors in each one. Although this study and others showed that patients with recurrence or unsuccessful treatment of BCG had heterogeneity with respect to progression and CSS, our risk groups might be useful in clinical trial design and interpretation, as well as in the management of patients.

There are some limitations in this study. This was a retrospective study with a small patient population and without a central pathologist. Moreover, not all of the patients underwent a second TUR. Because the specimens did not contain tissues from the muscularis propria at the location of the mucosal changes, these patients were excluded from this study. And not all of the patients underwent maintenance BCG instillation. Disease-free status was diagnosed based on cystoscopy and urine cytology. Not all of the patients underwent TUR biopsy after BCG instillation for diagnosing the persistence of bladder tumors. In addition, there is no consensus about the definition of BCG failure, and Nieder’s classification has never been recognized as a gold standard. Several definitions have emerged from the recent literature (9,28), and validation of which classification system is the most suitable for NMIBC is needed. Finally, external validation of our risk groups and a prospective study with larger BCG failure cohorts are needed before this prognostic classification can be used for treatment management.

CONCLUSIONS

Patients with stage progression at the first recurrence after BCG therapy had poor prognoses. Three prognostic factors for predicting survival were identified and used to categorize patients with NMIBC treated with BCG into three risk groups based on the number of prognostic factors in each one. However, external validation of our risk groups and a prospective study using larger BCG failure cohorts are still needed.

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Conflict of interest statement

None declared.

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