



Original article

Upper tract urothelial carcinoma following intravesical bacillus Calmette-Guérin therapy for nonmuscle-invasive bladder cancer: Results from a multi-institutional retrospective study

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Abstract

Objectives: The aim of this study was to clarify the prognostic indicators for upper tract urothelial carcinoma (UTUC) following intravesical bacillus Calmette-Guérin (BCG) therapy for nonmuscle-invasive bladder cancer (NMIBC).

Methods: Data from 402 patients who received intravesical BCG therapy between January 1990 and November 2011 were collected from 10 institutes. The median follow-up interval from transurethral resection of the bladder tumor (TURBT) followed by BCG treatment was 50.0 months (IQR: 31.8–77.0). Of these patients, 186 (46.3%) had intravesical recurrence during the follow-up period after BCG therapy.

Results: Thirty patients (7.5%) were diagnosed with UTUC after BCG therapy. The 10-year recurrence-free survival rates for UTUC (RFS-UTUC) was 87.5%. In univariate and multivariate analyses, the independent predicting factors for UTUC were intravesical recurrence ($P = 0.016$) and tumor morphology at TURBT before BCG ($P = 0.045$). The 10-year RFS-UTUC of patients with intravesical recurrence and others, were 80.6% and 95.0%, respectively. The 10-year RFS-UTUC of patients with papillary pedunculated tumors and nonpapillary or nonpedunculated were 96.1% and 84.6%, respectively.

Conclusions: The frequency of UTUC in patients with NMIBC after BCG therapy is not negligible. Two independent predicting factors (intravesical recurrence and nonpapillary nonpedunculated at TURBT before BCG) were identified for UTUC. These results might be useful to predict UTUC after BCG therapy for NMIBC. © 2018 Elsevier Inc. All rights reserved.

Keywords: Nonmuscle-invasive bladder cancer; Bacillus Calmette-Guérin; Upper tract urothelial carcinoma

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1. Introduction

Although most nonmuscle-invasive bladder cancer (NMIBC) can be completely resected by transurethral

intervention, the intravesical recurrence rate is higher than 50% [1–3]. Intravesical bacillus Calmette-Guérin (BCG) therapy is the most successfully employed adjuvant treatment for patients with high-risk NMIBC. The European Association of Urology (EAU) and National Comprehensive Cancer Network (NCCN) guidelines recommend that patients with high-risk NMIBC should be offered BCG therapy [4,5]. However, there is intravesical recurrence in from 30%–50% of the patients regardless of whether they receive maintenance BCG therapy or not [6,7].

Urothelial carcinoma is often multifocal throughout the urinary tract. It includes the urothelia of the upper tract urothelial carcinoma (UTUC), bladder, and urethra [8]. The incidence of intravesical recurrence after treatment of UTUC ranges from 15%–50% [9]. On the other hand, the development of UTUC following diagnosis of primary bladder cancer is relatively rare. The incidence of UTUC following diagnosis of primary bladder cancer is from 1%–9% [10–16]. However, 25% of patients with high-risk NMIBC who were monitored for 15 years developed urothelial carcinomas in the UTUC [17].

Although some studies [18,19] revealed that patients with intravesical progression at the recurrence after BCG had poor prognoses, there are no robust data on prognostic factors for UTUC and the prognosis for the survival of patients with UTUC treated with BCG. The aims of this study were to clarify the prognostic indicators for UTUC following BCG therapy for NMIBC and prognosis for the survival of patients with UTUC treated with BCG.

2. Patients and methods

2.1. 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: SUOC) (Table 1). The median follow-up interval from transurethral resection of the bladder tumor (TURBT) followed by BCG treatment was 50.0 months (IQR: 31.8–77.0). The patients consisted of 340 (84.6%) men and 62 (15.4%) women aged 71.0 (IQR: 64.0–76.3) years. Of these patients, 261 (64.9%) were diagnosed with primary NMIBC at TURBT before BCG and 141 (35.1%) had intravesical recurrence of NMIBC before BCG therapy.

The measurement of tumor size and multiplicity were based on the clinical records, which clearly noted the tumor morphology. In carcinoma in situ cases, measurements were performed based on both the mucosal changes and pathological results in the clinical records. Patients who had a history of UTUC and MIBC before BCG therapy were excluded. Because the accelerated immunological response is not sufficient for examining the antitumor efficacy of BCG at 1 week after the first BCG instillation [20], patients

who could continue 4 or more weekly administrations of induction BCG therapy were included in this study. Fourteen (3.5%) patients received BCG maintenance therapy. For all patients, pathological grades were classed as Grade 1 (G1), Grade 2 (G2), or Grade 3 (G3) according to the 1973 WHO system. UTUC was defined as any documented radiographic, endoscopic or pathologically proven urothelial carcinoma in the upper urinary tract according to the clinical records.

2.2. Follow-up schedule

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. Upper tract monitoring was performed yearly with either computed tomography (CT) or an intravenous urography. If UTUC was suspected based on CT, intravenous urography and positive urine cytology without intravesical recurrence, these patients underwent enhanced CT, retrograde pyelography, and urine cytology from the ureter or upper urinary tract endoscopy. Finally, UTUC was proven by ureteral biopsy, urine cytology from the ureter or enhanced CT. All of the patients who underwent cystectomy during the follow-up period underwent intraoperative pathological diagnosis of the marginal ureter for UTUC at cystectomy.

The endpoints in this study were recurrence-free survival from UTUC (RFS-UTUC) and cancer-specific survival (CSS).

The study was approved by the ethics committees of all participating institutions.

2.3. Statistics

Kaplan-Meier curves were calculated for RFS-UTUC and CSS. RFS-UTUC in univariate analysis was compared between the groups using the log-rank test and Cox regression models. Multivariate Cox regression models were used for RFS-UTUC. Statistical tests were performed with SPSS version 24.0 (SPSS, Chicago, IL). Differences were considered significant if $P < 0.05$.

3. Results

The patients' characteristics are shown in Table 1. On the basis of the macroscopic organization at the time of the TURBT before BCG therapy, 107 (26.6%) and 295 (73.4%) patients had papillary pedunculated tumors and nonpapillary or nonpedunculated, respectively. Of these patients, 186 (46.3%) had intravesical recurrence during the follow-up period from BCG therapy to UTUC.

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