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ORIGINAL ARTICLE

The comparison of different BCG strains in the intravesical treatment of non-muscle invasive urothelial carcinoma of urinary bladder-A real-world practice

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Abstract

Background: Bacillus Calmette–Guérin (BCG) has been well recognized as the first-line intravesical therapy for high-risk non-muscle-invasive bladder cancer (NMIBC). Oncotice, the Tice strain of BCG, serves as a viable alternative to the Connaught strain owing to the worldwide shortage of the latter. We retrospectively compared these two strains in terms of efficacy and adverse effects (AE) in patients who underwent at least one maintenance course after induction.

Methods: In this single-institution, retrospective study, patients diagnosed with NMIBC who were administered either Connaught or Tice intravesical therapy were enrolled. Recurrence was defined as the reappearance of urothelial carcinoma. Progression was defined as stage/grade advance, metastasis, or cancer-related death. The primary outcomes were recurrence-free survival (RFS) and progression-free survival (PFS), and the secondary outcome was AE.

Results: A total of 76 and 84 patients receiving Tice and Connaught, respectively were enrolled. The median follow-up periods for the Tice and Connaught groups were 32.0 months (range, 7-69 months) and 81.5 months (range, 9-154 months), respectively. Kaplan–Meier method showed no intergroup difference with regard to 3-year RFS and PFS. On Cox multivariate regression analysis, Tice was a significant predictor for inferior PFS (HR = 5.30; 95% CI, 1.11-25.29; $p = 0.036$). The AE incidence was 38.3% in the Connaught group and 25.0% in the Tice group ($p = 0.079$).

Conclusion: Tice and Connaught were comparable in terms of RFS, PFS, and AE for patients with NMIBC accepting BCG induction and at least one maintenance course in our real-world practice. However, Tice was a predictor of inferior PFS on multivariate analysis.

Keywords: Bacillus Calmette–Guérin; Bladder cancer; Intravesical Instillation; Recurrence

1. INTRODUCTION

Bacillus Calmette–Guérin (BCG) has been well recognized as the first-line intravesical therapy for high-risk non-muscle-invasive bladder cancer (NMIBC).[1-3] More than seven BCG strains have been commercially deployed for intravesical instillation, including ImmuCyst (Connaught strain), Oncotice (Tice strain), Pasteur strain, Immunobladder (Tokyo 172 strain), BCG-Medac (RIVM strain), SII-ONCO-BCG (Moscow strain), and ImmunoBCG (Moreau RdJ strain).[4-6] Meta-analysis by the European Organization for Research and Treatment of Cancer (EORTC) (n = 2596) suggested no major differences in efficacy among various BCG strains used for intravesical instillation.[7,8] However, conflicting results from various studies have made this topic controversial.[9,10]

ImmuCyst, the Connaught strain, had previously been widely accepted worldwide. Oncotice, the Tice strain, was introduced in 2013 in our institute owing to the worldwide shortage of the Connaught strain. There is conflicting evidence regarding the clinical efficacy of the Tice strain in comparison with the Connaught strain. According to a previous meta-analysis of 24 randomized clinical trials, maintenance treatment with BCG could reduce the risk of progression.[7] Hence, it would be interesting to compare the different BCG strains in real-world practice. We retrospectively compared the Connaught and Tice strains in terms of their efficacy and adverse events (AE) in patients who underwent at least one maintenance course after the induction course, that is, nine intravesical instillations.

2. METHODS

In this single-center, retrospective study, patients with stage Ta, T1 NMIBC, or carcinoma in situ (CIS) from 2007 to 2018 after

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diagnostic transurethral resection (TURBT) were given either Connaught or Tice intravesical therapy were enrolled in this study. From June 2007 to August 2012, the patients received Connaught (ImmuCyst 81 mg, 1.8–15.9 × 10^8 colony forming units) as the intravesical agent. From November 2013 to August 2018, Tice (Oncotice 50 mg, 2–8 × 10^8 colony forming units) was used as the alternative to Connaught because of the shortage of the latter. The exclusion criteria were as follows: (1) history of solid organ transplantation (2) previous muscle-invasive bladder cancer (MIBC) history (3) low AUA(American Urological Association)/SUO (Society of Urologic Oncology) risk stratification (4) follow-up period <3 months or missing data and (5) accepting fewer than nine intravesical BCG instillations. This study was ethically approved by the institutional review board (2019-03-010CC).

The demographic data, including sex, age, smoking, hypertension, diabetes mellitus, chronic kidney disease, and hemodialysis status, were documented. Furthermore, the intravesical therapy courses and the following factors within the AUA/SUO Guideline Risk Stratification System were reviewed: (1) prior recurrence status (2) number of tumors (3) tumor size (4) tumor stage (5) tumor diameter (6) tumor grade, and (7) concurrent/primary CIS.[11] However, immediate intravesical chemotherapy was recorded. Immediate intravesical chemotherapy with mitomycin-C as the intravesical chemotherapeutic agent was given within 24 hours following the initial TURBT.

The Southwest Oncology Group protocol was deployed for intravesical instillation (3-4 weeks after TURBT; 6-week induction, followed by three weekly maintenance instillations at 3, 6, 12, 18, 24, 30, and 36 months).[12] Recurrence was defined as any urothelial carcinoma (UC) reappearance within the urinary bladder after the initial TURBT; however, an interval <3 months was regarded as a residual tumor. Progression was defined as stage or grade advance (such as pathology report of Ta to T1-4 or T1 to T2-4), metastasis, or death caused by UC of the urinary bladder.[13]

The primary outcomes were 3-year recurrence-free survival (RFS) and progression-free survival (PFS), which were defined as the time from the date of surgery (TURBT) to the biopsy/surgery-proven event. The secondary outcome was AE, whose severity was recorded and categorized as grade 1 to 3 according to the Cleveland Clinic Approach of BCG Toxicity (Supplementary Table 1, http://links.lww.com/JCMA/A155).[14]

2.1. Statistical analysis

All nominal variables were reported in a number (percentage) fashion, and continuous variables were presented as mean (standard deviation). Pearson's χ^2 test was used for comparative analysis, such as AE, and Fisher's exact test was utilized for nonparametric analysis. Mann–Whitney U test was performed after the normality test for the continuous variables. For survival analysis, Kaplan–Meier estimates with a log-rank test were used. Furthermore, the possible covariates were examined for each survival, and Cox proportional hazard model (discussed below) was developed. The results were expressed in terms of hazard ratios (HR) with a 95% confidence interval (CI) and *p*-values. Statistical tests were performed using the SAS software, V9.2 (SAS Institute, NC, USA).

2.2. Selection of variables in the Cox multivariate models

In due consideration of the retrospective nature of the study, crucial factors mentioned in large trials were included in our Cox multivariate models.[15,16] Tumor size and tumor grade were eliminated owing to imbalanced distribution in our cohort. However, multivariate analysis with or without these two covariates resulted in the same conclusion.

For analyzing the T1 high-grade (T1HG) subgroup, which is considered a high-risk subset of NMIBC, we adopted previously reported prognostic factors derived from a large EORTC cohort as a covariate.[17] Tumor number and size were used for RFS analysis. Age, concurrent CIS, and tumor size were applied for PFS regression.

3. RESULTS

From June 2007 to August 2018, 181 patients received Oncotice (Tice group) and 228 received ImmuCyst (Connaught group) intravesical instillations. Those who did not complete at least one maintenance course (i.e. received less than nine instillations, which comprised 85 [47%] in the Tice group and 130 [57%] in the Connaught group) were excluded (Fig. 1). Those who had undergone transplant surgery or had a history of MIBC were also excluded. Furthermore, those who were categorized as low risk according to the AUA/SUO guidelines and for whom data were missing were excluded. Finally, 76 patients were included in the Tice group and 84 in the Connaught group. The median follow-up duration was 32.0 months (range 7-69) for Tice and 81.5 months (range 9-154) for Connaught.

3.1. Patient characteristics

The demographic data of patients are displayed in Table 1. No significant differences were found between the two groups in terms of sex, age, smoking, hypertension, diabetes mellitus, chronic kidney disease, or hemodialysis status. The Tice group is more likely to be multifocal ($p = 0.014$) and have a smaller tumor size ($p = 0.018$) and more Ta disease ($p = 0.002$) than the Connaught group. No significant differences were noted in the percentage of primary disease, tumor grade, or the presence of any CIS. The BCG instillation sessions in the Tice group were more than those in the Connaught group (mean 13.9 vs. 12.1 times, $p < 0.001$). Moreover, immediate intravesical chemotherapy was performed more frequently in the Tice group than in the Connaught group (56.8%, $p = 0.004$).

3.2. Primary outcomes

In the Tice group, recurrence occurred in 17 of the 76 patients (22.4%) during the whole follow-up period, and the Kaplan–Meier estimate for 3-year RFS was 80.6% (95% CI, 75.7-85.5) (Table 2). In this group, six patients (7.9%) experienced progression, and the 3-year PFS was 95.3% (95% CI, 92.6-98.0). In the Connaught group, recurrence occurred in 26 of the 84 patients (31.0%) and progression in 13 patients (15.5%) until the end of the study. In this group, the 3-year RFS was 78.5% (95% CI, 73.9-83.1) and the 3-year PFS was 94.7% (95% CI, 92.1-97.3).

Kaplan–Meier estimate with log-rank test (Fig. 2) showed no significant differences in the 3-year RFS ($p = 0.912$) and PFS ($p = 0.647$). Univariate regression did not identify any predictors for RFS and PFS (Table 3). On multivariate adjustment, TICE was not a significant predictor for RFS but a significant predictor for inferior PFS (HR = 5.30; 95% CI, 1.11-25.29; $p = 0.036$). In addition, prior recurrence status was an independent predictive factor of RFS.

3.3. Subgroup analysis

Although the AUA/SUO low-risk NMIBC patients were excluded, heterogeneity was still noted when the goodness-of-fit for the model was assessed. The imbalance of the tumor stage (Ta/T1) may lead to a huge impact. Hence, we repeated the analysis in a subgroup of 93 patients (56 in Connaught and 37 in the Tice group) with a T1HG pathological diagnosis. Tice was not a significant factor of RFS (HR = 0.90; 95% CI, 0.39-2.08; $p = 0.803$)

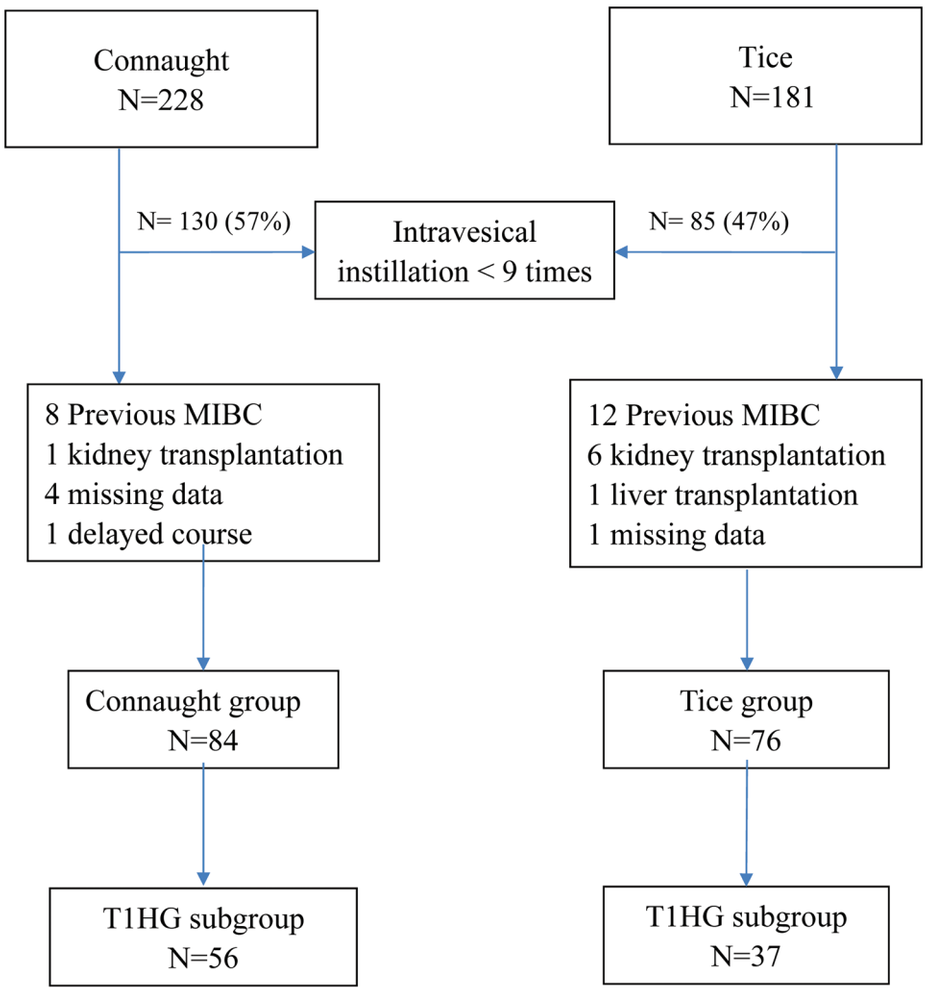

Fig. 1 Exclusion flowchart of the Patients.

or PFS (HR = 4.73; 95% CI, 0.81-27.68; $p = 0.085$) after multivariate analysis in this subgroup (Table 4).

3.4. Secondary outcome: adverse events

The occurrence of AE was 31 (38.3%) in the Connaught and 18 (25.0%) in the Tice group, without significant differences ($p = 0.079$) (Table 2). No differences existed between the two groups even for severe or serious (Grade 2 and 3) AE, such as persistent hematuria, fever, and prostatitis, ($p = 0.231$).

4. DISCUSSION

One prospective randomized trial has compared the outcomes of Connaught and Tice intravesical instillations in treating NMIBC. Rentsch et al.[9] reported a superior 5-year RFS ($p = 0.011$) for Connaught over Tice (n = 142 among pTis, Ta, and T1). The researchers further conducted *in vivo* experiments and established that Connaught is a stronger immunomodulator (favorable type 1 T-helper responses, priming of BCG-specific $CD8^+$ T cells, and T-cell recruitment in mice) than Tice. Both phase III trials reported comparable side effects (28%-42%) for the two drugs. Nevertheless, only induction therapy (six instillations) was administered in both studies, which may lead to concerns of inadequate treatment.

A large (n = 2099) retrospective study comparing the efficacy of Tice and Connaught in T1 high-grade NMIBC patients had showed conflicting results in those with and without maintenance instillations.[10] In the absence of maintenance instillations, Connaught was more effective than Tice in terms of the time to first recurrence (HR = 1.48; 95% CI, 1.20-1.82; $p < 0.001$). On the contrary, with maintenance, Tice was more effective than Connaught in terms of the time to first recurrence (HR = 0.66; 95% CI, 0.47-0.93; $p = 0.019$) and cancer specific survival (CSS) (HR = 0.36; 95% CI, 0.14-0.92; $p = 0.033$). A recent study on intermediate-/high-risk patients reported that BGC, TICE, and RIVM provided longer RFS than Connaught (HR_{TICE}: 0.58; 95% CI, 0.39-0.86), but PFS was not superior over CSS between strains.[18]

A meta-analysis had investigated the impact of maintenance BCG on RFS (RR = 1.33; 95% CI, 1.17-1.50).[19] Different BCG strains (Tice, Connaught, and RIVM) were compared, and a probably worse recurrence outcome (RR = 1.29; 95% CI, 1.01-1.64) was noted in patients receiving Tice with induction therapy only. A Spaniard-based analysis had also addressed the importance of the maintenance course regardless of the strain used.[20]

The aforementioned reports implied that maintenance instillations are important for Tice to achieve an efficacy that is comparable to that of Connaught. One hypothesis is that the

Table 1

Patient baseline and pathological characteristics

Connaught		Tice	
	(n = 84)	(n = 76)	*p*
Baseline			
Age, mean ± SD (range), year	72 ± 11.0 (49-95)	69 ± 11.4 (45-92)	0.06[a]
≥65 years, No. (%)	56 (66.7)	37 (51.3)	0.05
≥70 years, No. (%)	52 (61.9)	28 (36.8)	0.002
Sex, male No. (%)	68 (81.0)	60 (78.9)	0.75
Smoking, No. (%)	28 (33.3)	25 (32.9)	0.95
HTN, No. (%)	49 (58.3)	37 (48.7)	0.22
DM, No. (%)	23 (27.4)	15 (19.7)	0.26
CKD, No. (%)	7 (8.3)	8 (10.5)	0.64
Hemodialysis, No. (%)	1 (1.2)	3 (3.9)	0.35[b]
Pathologic feature			
Primary tumor, No. (%)	54 (64.3)	39 (50.8)	0.097
Number of tumors			0.014
Single, No. (%)	39 (46.4)	21 (27.6)	
Multifocal, No. (%)	45 (53.6)	61 (72.4)	
T category			0.002
Ta, No. (%)	12 (14.3)	26 (34.2)	
T1, No. (%)	58 (69.0)	37 (48.7)	
T1HG, No. (%)	56 (66.7)	37 (48.7)	
CIS			
Pure, No. (%)	11 (13.6)	13 (17.1)	0.48
Concurrent, No. (%)	13 (15.7)	19 (25.0)	0.13
Any CIS [c], No. (%)	24 (28.6)	32 (42.1)	0.07
Unknown, No. (%)	3 (3.6)	0 (0)	
Tumor diameter			0.018
<3 cm, No. (%)	67 (80.7)	71 (93.4)	
≥3 cm, No. (%)	16 (19.3)	5 (7.9)	
Unknown, No. (%)	1 (1.2)	0	
Tumor grade, No. (%)			
Low grade	3 (3.6)	0	
High grade	81 (96.4)	75 (98.7)	0.62[b]
History of UTUC			
Previous treated UTUC	7 (8.3)	5 (6.5)	
Concurrent UTUC	1 (1.2)	2 (2.6)	
BCG treatment sessions			
Intravesical instillation courses, mean ± SD (range)	12.12 ± 3.21 (9-27)	13.86 ± 3.11 (9-27)	<0.001[a]
≥15 times of instillation (%)	23 (27.4)	41 (53.9)	0.001[a]
Immediate MMC instillation	22 (26.2)	42 (56.8)	0.004

CIS = carcinoma *in situ*; CKD = Chronic kidney disease; DM = Diabetes mellitus; HTN = Hypertension; MMC = Mitomycin-C; PUNLMP = papillary urothelial neoplasm of low malignant potential; UTUC = upper tract urothelial cancer.

[a]Mann-Whitney U test.

[b]Fisher's Exact Test.

[c]Pure and Concurrent CIS.

immune response invoked by Tice in the urothelium is weaker than that invoked by Connaught, leading to the requirement of more instillations. On the other hand, AE might be less frequent in Tice than in Connaught, which has been reported in some articles.[20,21] Furthermore, a suitable instillation protocol tailored for Tice, such as eight or more weekly inductions or a more intensive maintenance course, should be taken into consideration based on current evidence.

In our cohort, immediate intravesical chemotherapy was performed more frequently in the Tice group than in the Connaught group (56.8% vs. 26.2%; $p = 0.004$). According to the European Association of Urology and National Comprehensive Cancer Network guidelines, immediate intravesical chemotherapy reduces the recurrence rate in selected, relatively low-risk patients.[8,22] Instead, our patients are on the other side of the risk spectrum, which is less likely to be influenced by immediate intravesical chemotherapy. This corresponds to the finding from the large cohort we adopted for Cox multivariate models.[15,16]

Our real-world experiences showed that the estimated 3-year RFS was 80.6% for Tice and 78.5% for Connaught. The 3-year PFS was 95.3% for Tice and 94.7% for Connaught. Both RFS and PFS did not exhibit any significant differences between Tice and Connaught. The mean number of BCG instillation sessions was 13.9 in the Tice group vs. 12.1 in the Connaught group. These findings imply that after adequate BCG instillations, the efficacy of Tice might not be inferior to that of Connaught in terms of RFS and PFS, which is consistent with previous reports. Furthermore, in spite of the Kaplan–Meier analysis showing a lack of differences between Tice and Connaught with regard to the survival outcomes, Tice exhibited worse PFS than the Connaught group (HR = 5.30) in multivariate analysis when considering the important factors affecting the survival outcomes.

Table 2

Survival and adverse events analyses

Outcomes	Connaught (n = 84)	Tice (n = 76)	p
Median follow-up, months (range)	81.5 (9-154)	32.0 (7-69)	
Recurrence, No. (%)[a]	26 (31.0)	17 (22.4)	
% 3-year RFS, 95% CI	78.5 (73.9-83.1)	80.6 (75.7-85.5)	0.91[b]
Progression, No. (%)[a]	13 (15.5)	6 (7.9)	
% 3-year PFS, 95% CI	94.7 (92.1-97.3)	95.3 (92.6-98.0)	0.65[b]
Progression status			
Stage/grade advance	8	4	
Metastasis	2	2	
Death due to UC	3	0	
All-cause mortality, No. (%)	22 (26.2)	5 (6.6)	0.85[b]
Cancer-specific mortality, No. (%)	7 (8.3)	1(1.3)	0.99[b]
Adverse events (AE, %)	31 (38.3)	18 (25.0)	0.08
Grade 2&3 AE (%)	6 (7.1)	1 (1.3)	0.23[c]

RFS = recurrence-free survival; PFS = progression-free survival; UC = urothelial cancer.
[a]Any occurrence during the whole follow-up period.
[b]Log-rank test.
[c]Fisher's Exact Test.

The Spanish Urological Club for Oncological Treatment (CUETO) scoring model and EORTC risk table are well-known stratification systems of NMIBC to predict recurrence and progression.[15,16] Many of the covariates within the models are important predicting factors and have been adopted in the AUA/SUO Guideline Risk Stratification System, which was employed in this study for multivariate regression. We excluded low-risk patients in consideration of homogeneity. The patients who had undergone transplantation are considered to be immunosuppressed and were excluded as well owing to the possibility of interference with immune induction in the intravesical therapy. We found that Kaplan–Meier method and univariate analysis showed comparable outcomes for Connaught and Tice. After adjustment for covariates, Connaught had a better PFS than Tice. Further adjustment for ≥15 intravesical instillations (i.e., more the 1 year or not) yielded the same results. However, intergroup heterogeneity was noticed in the pathological characteristic of tumor stage: two out of six progression events in the Tice group and none (out of 13) in the Connaught group were stage Ta. Therefore, we performed a subset analysis on T1HG patients and discovered comparable efficacies in terms of PFS and RFS between these two BCG strains.

Previous reports have found that AE occurred in a similar proportion of patients between Tice and Connaught, with an incidence of 13.5% to 42%. A prospective, multicenter study showed that the majority of (92.7%) AEs were grade 1, and no statistical significance was observed between different strains.[23] Our study also yielded similar results, with an incidence of 38.3% for Connaught and 25.0% for Tice. However, we excluded patients accepting fewer than nine BCG instillations. Most patients suffering from severe AE are likely to withdraw at the very beginning (less than six times) of the intravesical instillations, which may underestimate the incidence of AE.

Our real-world experiences were consistent with the findings of previous reports. However, there are some limitations in this study. First, the patient numbers of both the Connaught and Tice group were small, and the follow-up period was unequal. The strength of our study is that we excluded patients with fewer than nine intravesical BCG instillations, which accounted for more than half of the patients. Despite the smaller patient cohort after the exclusion, we were able to derive solid conclusions from patients accepting adequate intravesical BCG treatment. Second, even though the incidence of recurrence and progression in our Connaught group (31.0% and 15.5%, respectively) was comparable to that found in other studies (33%-43% for recurrence and 14%-17% for progression), it was lower in the Tice group (22.4% and 7.9%, respectively). This discrepancy could be attributed to the shorter follow-up period of the latter group. The introduction of Tice in our institute was related to the worldwide shortage of Connaught. The shorter follow-up period of Tice was reasonable in such a clinical situation. However, the median follow-up period of Tice was 32.0 months, which should be sufficiently long to observe recurrence and progression in patients with high-risk bladder cancer. Third, aside from the comparison between different strains, the different dosage between Connaught and Tice may also result in different efficacy and adverse effects. It is an important issue worth to be discussed, yet there is no relevant study. However, a large-scale trial comparing dosage in the same BCG strain

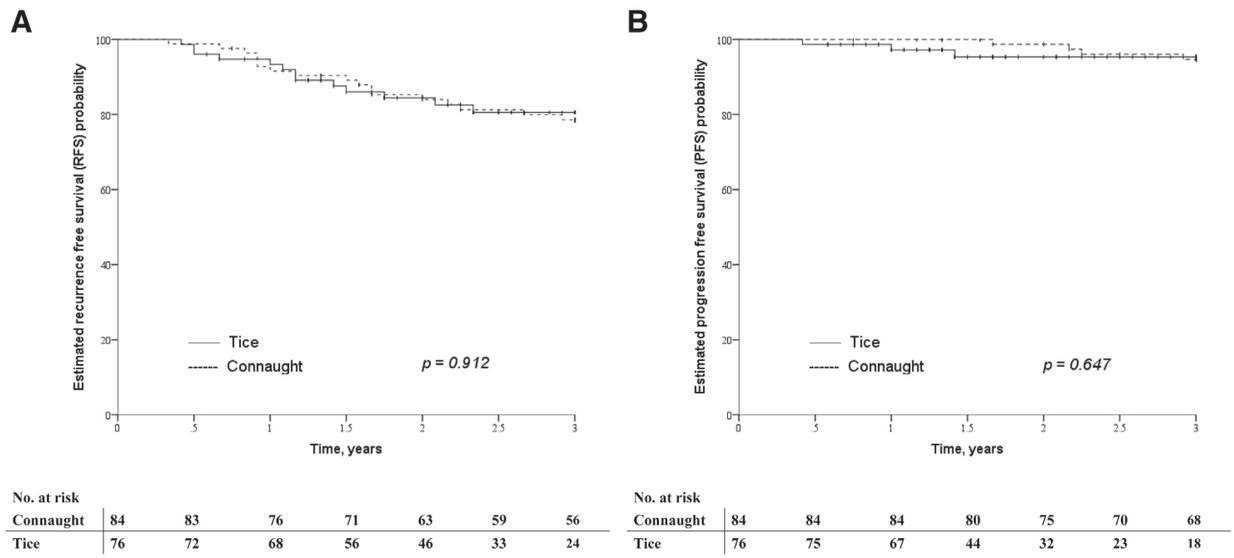

Fig. 2 Kaplan–Meier survival curve of 3-year (A) recurrence-free survival, (B) progression-free survival, for Tice (solid line) and Connaught (dashed line).

Table 3

Univariate and multivariate analyses of recurrence-free survival and progression-free survival.

Univariate				Multivariate		
Variable	**HR**	**95% CI**	***p***	**HR**	**95% CI**	***p***
(A) Univariate and multivariate analyses for recurrence-free survival						
Tice	1.23	0.64-2.35	0.541	1.05	0.49-2.24	0.91
Age ≥ 70 years	1.37	0.75-2.51	0.304	1.03	1-1.06	0.09
Sex	1.44	0.64-3.25	0.378	0.84	0.36-2	0.698
T category	1.39	0.63-3.05	0.410	1.17	0.49–2.8	0.72
Recurrence status	1.62	0.89–2.96	0.115	1.98	1.01–3.88	0.046
Multifocal	1.88	0.95-3.75	0.071	2.32	0.92-5.87	0.07
Any CIS	1.35	0.74-–2.49	0.330	1.51	0.74-3.08	0.26
(B) Univariate and multivariate analyses for progression-free survival						
Tice	2.89	0.92-9.11	0.070	5.30	1.11-25.29	0.036
Age ≥70 years	1.04	0.42-2.56	0.933	1.28	0.44-3.7	0.65
Sex	1.37	0.4-4.7	0.619	0.91	0.25-3.32	0.88
T category	1.89	0.43-8.42	0.402	2.52	0.5-12.64	0.26
Recurrence status	1.03	0.4-2.62	0.953	0.75	0.23-2.41	0.63
Multifocal	1.55	0.59-4.1	0.372	1.74	0.43-6.96	0.44
Any CIS	2.07	0.84-5.11	0.113	1.39	0.44-4.39	0.58

HR = hazard ratio; CI = confidence interval; CIS = carcinoma *in situ*

Table 4

Cox regression analysis of recurrence- and progression-free survival of the T1HG subgroup. The variable selection is adapted from the prognostic factor analysis of T1HG patients from the EORTC trials

(A) Univariate and multivariate analysis for recurrence-free survival in the T1HG subgroup						
Univariate				**Multivariate**		
Variable	**HR**	**95% CI**	***p***	**HR**	**95% CI**	***p***
Tice	1.04	0.46-2.37	0.93	0.90	0.39-2.08	0.80
Multifocal	1.92	0.73-5.08	0.19	1.89	0.68-5.24	0.22
Tumor size	0.69	0.24-2.01	0.499	0.82	0.28-2.46	0.73
(B) Univariate and multivariate analysis for progression-free survival in the T1HG subgroup						
Tice	4.02	0.78-20.820	0.097	4.73	0.81-27.68	0.08
Age ≥ 70 years	1.45	0.47-4.44	0.52	1.57	0.49-5.06	0.45
Tumor size	2.03	0.62-6.66	0.24	2.93	0.8-10.67	0.10
Concurrent CIS	1.84	0.6-5.62	0.29	1.97	0.57-6.84	0.28

HR = hazard ratio; CI = confidence interval; CIS = carcinoma *in situ*

exists, reporting no overall difference in the efficacy and adverse effects compared one-third dose to full-dose BCG.[8] Fourth, the Kaplan–Meier survival (p = 0.65) and univariate analysis (p = 0.07) for PFS showed no significant difference between the two groups, while multivariate analysis showed PFS to be significant (p = 0.036). Besides, we use different covariates in the T1HG subgroup analysis according to a previous large-scale study.[16] Care should be taken to interpret these results, as there could be bias resulted from a variable selection.

In conclusion, in patients with NMIBC accepting BCG induction and at least one maintenance course, the 3-year RFS, PFS, and AE were comparable for Tice and Connaught in our real-world practice. Tice was a predictor for inferior PFS after multivariate adjustment, which we must interpret with care. Further, no significant predictors were identified in the subgroup analysis of T1HG disease in RFS and PFS.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://links.lww.com/JCMA/A155.

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