Original article

Maintenance bacillus Calmette–Guérin therapy prolongs recurrence-free survival in non-muscle-invasive bladder cancer: A real-world experience

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ABSTRACT

Objective: We studied the benefit of bacillus Calmette–Guérin (BCG) maintenance therapy to determine the ideal maintenance therapy schedule.
Methods: We retrospectively reviewed non-muscle-invasive bladder cancer patients who underwent transurethral resection of bladder tumors and BCG instillation treatment at Chang-Gung Memorial Hospital, Linkou, Taiwan, from January 1997 to December 2009. All patients in the study had non-muscle-invasive urothelial carcinoma of the bladder or carcinoma *in situ*. We compared the recurrence-free rate of patients who received induction alone and with maintenance BCG therapy sessions. In addition, we analyzed the best number of maintenance therapy sessions that gave the lowest cancer recurrence.
Results: This study included 427 patients with a mean age of 64 years. The median number of BCG treatments was 11, and the ratio of male to female was 3:1. Receiving an induction dose alone was a significant factor for tumor recurrence with a hazard ratio of 3.77. The recurrent risk rate of patient who received BCG therapy 13–15 times had lower recurrence rate than other groups.
Conclusion: A maintenance dose gave patients a significant benefit over those who just received induction therapy. BCG maintenance therapy worked best if given 13–15 times in our study.
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1. Introduction

Approximately 75–85% of patients with bladder cancer present with the disease confined to the mucosa[1] or submucosa (stage T1).[2] Transurethral resection (TUR) of bladder tumors, with or without intravesical adjuvant therapy, is still the primary treatment for non-muscle-invasive bladder tumor. According to many published results of randomized trials, it has become clear that intravesical bacillus Calmette–Guérin (BCG) is a better therapeutic choice for high risk Ta, T1 papillary carcinomas as well as for carcinoma *in situ* (CIS)[3] compared with TUR alone[4,5] or chemotherapy.[6,7] For optimal efficacy, an induction course followed by maintenance BCG is recommended. Lamm et al[8] reported in the Southwest Oncology

Group study that 3-year BCG maintenance therapy markedly prolonged the recurrence-free survival and time to disease progression in comparison with conventional induction therapy. The maintenance therapy significantly prolonged the post-TUR recurrence-free survival compared with BCG induction therapy alone.[9]

However, patients may not complete the entire BCG maintenance regimen due to several reasons. Some adverse events may occur after treatment and present as the most frequent conditions for therapy withdrawal. The longer the instillations are given, the more likely a severe toxicity will develop in the patients.[8] Some studies reported decreased recurrence and progression with maintenance therapy. Herr et al[10] reported that BCG treatment without maintenance in patients with high-risk non–muscle-invasive bladder cancer compared favorably with trials in which comparable patients received maintenance BCG.

Most practice guidelines recommend maintenance BCG for 1–3 years.[2,8,11] However, only few studies commented on the duration of dose of maintenance BCG used. Among them, the largest study was reported by Lamm et al that 3-year BCG maintenance therapy

may prolong the recurrent free survival.[8] The aim of our study was to prove that BCG maintenance therapy is more beneficial than induction only and to investigate the optimal duration for maintenance therapy.

2. Patients and methods

A retrospective cohort study was performed, with 427 consecutive patients with bladder cancer were evaluated from 1997 to 2009. They underwent TUR and were found to have non-muscle-invasive bladder cancer (Ta, T1, and/or Tis). Subsequently, they received six weekly instillations of Connaught strain (81 mg) BCG therapy as induction therapy and were evaluated for response after 3 months by cystoscopy, urine cytology, and TUR biopsy. Patients then received three weekly maintenance therapies every 3—6 months and up to 21 times if possible. The total therapy course was nearly 2 years. Patients were also followed every 3—6 months with cystoscopy, repeated TUR as needed, and urine cytology if possible. After finishing the BCG intravesical instillation therapy, there was no other intravesical chemotherapy during follow-up duration. Patients with previous bladder cancer histories will receive the intravesical chemotherapy, such as mitomycin C or epirubincin. We excluded patients who had previously received BCG intravesical instillation therapy. Each patient's data were entered into a database, and clinical information was recorded from charts. Patients upstaged to muscle invasion (T2) at the beginning of TUR, undergoing immediate cystectomy without receiving BCG, receiving incomplete induction BCG therapy, or missing follow-up within 1 month were all excluded from this analysis.

The end point was defined as local recurrence or progression. Tumor recurrence was defined as any tumor on biopsy or positive urine cytology during follow-up examinations. Progression was defined as a muscle-invasive tumor or metastasis. Pathological staging was based on the TNM classification and tumor grade was determined in accordance with the WHO classification. Patients who died from other causes were defined as censored data. Follow-up duration was calculated by the subtraction of local recurrence or progression date (expired date, the last clinics follow-up date) and the last date of BCG therapy.

Statistical analysis was performed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA). Baseline characteristics were represented as mean ± standard deviation for continuous data and n (%) for categorical data (Table 1). Originally, we divided patients into two groups, the induction group (with 6 BCG treatments) and the maintained group (>6 BCG treatment). Chi-square test was used to compare categorical variables, and two-sample independent t test for continuous variable. Recurrence-free plot was based on the Kaplan—Meier method with the log rank test. Furthermore, we divided patients into several groups according to the numbers of BCG treatment. The first group completed six BCG treatments, followed by maintenance groups from one to three treatments, from four to six treatments, from seven to nine treatments, and ≥10 treatments. Cox proportional hazard model was used to estimate the hazard ratios of recurrence. A p value <0.05 was considered significant.

3. Results

From January 1997 to December 2009, 427 patients were evaluated. Among them, 312 were males and 115 females. There were 106 patients with recurrent and 321 patients without recurrent tumor. Mean age was 64.4 years and mean follow-up time was 31.7 months. Median number of treatments was 11. There were 280 (65.6%) patients with history of bladder tumor. Most patients had urothelial carcinoma and only 31 patients (7.3%) were concomitant

Table 1
Clinicodemographic characteristics.

Baseline characteristics	Statistics
Age at BCG treatment (y)	64.4 ± 12.0
Sex	
Male	312 (73.1)
Female	115 (26.9)
BCG treatments	
6 (induction)	137 (32.1)
>6 (maintenance)	290 (67.9)
Multiplicity	
1	230 (55.0)
≥2	188 (45.0)
Category	
Urothelial carcinoma	391 (92.7)
Concomitant carcinoma *in situ*	31 (7.3)
Grade	
Low	179 (43.9)
High	229 (56.1)
Stage	
Ta	136 (46.7)
T1	155 (53.3)
Bladder cancer history	280 (65.6)
Had received intravesical therapy	62 (14.5)
Mean follow-up (mo)	43.10
Median follow-up (mo)	31.7 (0.23—160.46)
Treatment times	10.8 ± 4.5

Data are presented as n (%) or mean ± SD.
BCG = bacillus Calmette—Guérin.

with CIS. Of the 427 patients, 290 entered maintenance therapy and 137 patients received induction therapy only. Main characteristics of the patients are given in Table 1.

Table 2 shows the characteristics of the patients with induction therapy only and those who entered maintenance therapy. More patients in the maintenance group had high grade, advanced stage,

Table 2
Comparison of bacillus Calmette-Guérin (BCG) induction therapy and maintenance therapy.

	BCG induction ($n = 137$)	BCG maintenance ($n = 290$)	p
Age at BCG instillation (y)[a],*	67.15 ± 11.47	63.17 ± 12.03	0.001
Sex[b]			0.981
Male	100 (73.0)	212 (73.1)	
Female	37 (27.0)	78 (26.9)	
History of bladder tumor[b]	88 (64.2)	192 (66.2)	0.689
Smoking[b]	49 (36.6)	100 (35.3)	0.806
Exposure to dying agents[b]	8 (7.1)	17 (7.4)	0.917
Multiplicity[b]			0.421
1 piece	71 (52.2)	159 (56.4)	
≥2 pieces	65 (47.8)	123 (43.6)	
Unknown cases	1	8	
Size (the biggest diameter, cm)[a]	2.17 ± 1.58	1.93 ± 1.16	0.139
Category[b]			0.232
UC	129 (94.9)	262 (91.6)	
UC concomitant CIS	7 (5.1)	24 (8.4)	
Unknown cases	1	4	
Grade[b]			0.288
Low	62 (47.7)	117 (42.1)	
High	68 (52.3)	161 (57.9)	
Unknown cases	10	12	
Stage[b]			0.823
Ta	42 (47.7)	94 (46.3)	
T1	46 (52.3)	109 (53.7)	
Unknown cases	49	87	
Previous intravesical chemotherapy[b]	27 (19.7)	35 (12.1)	0.036
Median follow-up (mo)*	20.240	37.850	<0.001

Data are presented as n (%) or mean ± SD.
*$p < 0.05$, significant.
CIS = carcinoma *in situ*; UC = urothelial carcinoma.
[a] Two-sample independent t test, mean ± standard deviation.
[b] Chi-square test, n (%).

Table 3
Cumulative recurrence-free rate of bacillus Calmette–Guérin (BCG) treatment times.[a]

Cumulative recurrence-free rate	n	Follow-up after BCG treatment (%)		
		1 y	5 y	10 y
Overall	427	81.7	72.9	70.0
6 BCG treatment times (induction)	137	64.6	52.1	48.9
>6 BCG treatment times (maintenance)	290	89.6	82.6	80.0

[a] Log-rank test for recurrence-free rate between the induction and maintenance therapies is $p < 0.001$.
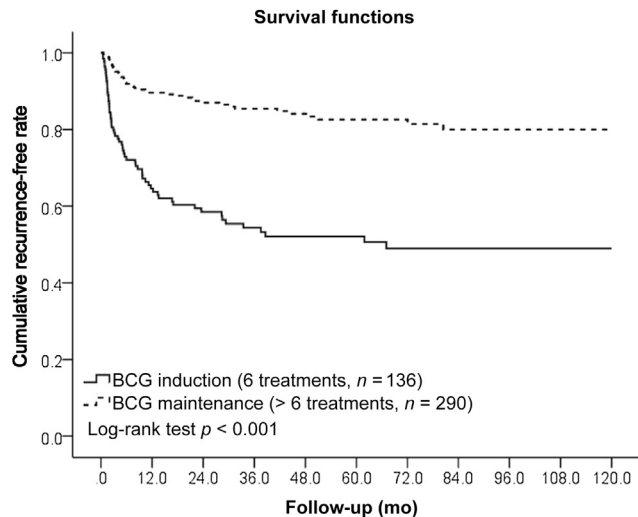

Fig. 1. Recurrence-free rate between bacillus Calmette–Guérin (BCG) induction and maintenance therapy. Patients on maintenance BCG therapy had higher recurrence-free rate than those who just received induction therapy.

and multiplicity than the induction group. Also, the maintenance group had better recurrence-free rates than the induction group. The recurrent free rates were 64.6% versus 89.6%, 52.1% versus 82.6%, 48.9 versus 80.0% in 1 year, 3 years, and 10 years respectively (Table 3).

Fig. 1 shows the significantly lower recurrent free rate in patients who received induction therapy only by Kaplan–Meier test.

The characteristic of each group is shown in Table 4. Table 5 reveals the significantly lower recurrence rates for each of the further classified subgroups of maintenance therapy compared with the patients of the induction group, whereas the group with BCG maintenance therapy from seven to nine times had the lowest hazard ratio (Fig. 2). The recurrence-risk for patients who received BCG maintenance therapy from seven to nine times was 84% lower compared with the patients who only received induction BCG therapy. The other groups were lower by 67%, 71%, and 83% after BCG maintenance therapy from one to three times, from four to six times, and ≥10 times respectively. The group with BCG maintenance therapy from seven to nine times had the lowest recurrence-risk rate.

4. Discussion

Herr et al[12] reported that maintenance BCG does not appear superior to initial BCG treatments in preventing or delaying tumor progression. Herr et al[10] also revealed that BCG treatment without maintenance for patients with high-risk non–muscle-invasive bladder cancer compared favorably with trials in which comparable patients received maintenance BCG.[10]

Nevertheless, many studies have found BCG therapy to be effective in reducing the risk of disease progression only when maintenance schedules were applied.[3] Hinotsu et al[9] demonstrated that BCG intravesical instillation maintenance therapy was able to prolong post-TUR recurrence-free survival significantly in patients with recurrent or multiple, stage Ta or T1, bladder cancer. Also, a number of reports have shown that BCG must be given in a maintenance schedule for optimal efficacy.[2]

Our study revealed that patients who received maintenance BCG therapy had significantly higher recurrence-free rate. Two-year recurrence-free rates of approximately 80% and 60% were estimated for the maintenance group and the nonmaintenance group, respectively in the study by Lamm et al.[8] In addition, Saint et al[13] carried out a clinical study that administered the BCG Connaught strain according to a 3-year maintenance schedule, and they reported a 2-year recurrence-free rate of 84.9%. Furthermore, van der Meijden et al[14] reported an estimated 2-year recurrence-free

Table 4
Clinicodemographic characteristics of each group.

	BCG induction	BCG maintenance: 1–3 ($n = 76$)	BCG maintenance: 4–6 ($n = 79$)	BCG maintenance: 7–9 ($n = 84$)	BCG maintenance: ≥ 10 ($n = 51$)
Age at BCG instillation (y)	67 ± 11	65 ± 13	64 ± 12	62 ± 12	61 ± 12
Sex					
Male	100 (73.0)	56 (73.7)	58 (73.4)	63 (75.0)	35 (68.6)
Female	37 (27.0)	20 (26.3)	21 (26.6)	21 (25.0)	16 (31.4)
History of bladder tumor	88 (64.2)	52 (68.4)	45 (57.0)	63 (75.0)	32 (62.7)
Smoking	49 (36.6)	22 (29.7)	27 (35.1)	29 (34.9)	22 (44.9)
Multiplicity					
1 piece	71 (52.2)	44 (58.7)	45 (59.2)	42 (50.6)	28 (58.3)
≥2 pieces	65 (47.8)	31 (41.3)	31 (40.8)	41 (49.4)	20 (41.7)
Size (cm)	2 ± 2	2 ± 1	2 ± 1	2 ± 1	2 ± 1
Category					
UC concomitant CIS	3 (02.2)	3 (03.9)	2 (02.5)	3 (03.7)	2 (04.0)
UC	129 (94.9)	69 (90.8)	71 (89.9)	76 (93.8)	46 (92.0)
Grade					
Low	62 (47.7)	29 (40.3)	30 (39.0)	33 (41.3)	25 (51.0)
High	68 (52.3)	43 (59.7)	47 (61.0)	47 (58.8)	24 (49.0)
Stage					
Ta	42 (47.7)	30 (54.5)	22 (38.6)	30 (50.8)	12 (37.5)
T1	46 (52.3)	25 (45.5)	35 (61.4)	29 (49.2)	20 (62.5)
Previous intravesical chemotherapy	27 (19.7)	15 (19.7)	14 (17.7)	5 (06.0)	1 (02.0)

Data are presented as n (%) or mean ± SD.
BCG = bacillus Calmette–Guérin; CIS = carcinoma in situ; UC = urothelial carcinoma.

Table 5
Estimated hazard ratio (HR) for numbers of maintenance bacillus Calmette—Guérin therapy sessions.

BCG treatment group	Model I		Model II[a]	
	Estimated HR (95% CI)	p	Estimated HR (95% CI)	p
Group 1	1		1	
Group 2 vs. Group 1	0.33 (0.19—0.58)	>0.001	0.26 (0.13—0.54)	>0.001
Group 3 vs. Group 1	0.29 (0.16—0.52)	>0.001	0.28 (0.14—0.56)	>0.001
Group 4 vs. Group 1	0.16 (0.08—0.33)	>0.001	0.12 (0.05—0.32)	>0.001
Group 5 vs. Group 1	0.17 (0.07—0.39)	>0.001	0.10 (0.02—0.41)	0.001
Sex			1.47 (0.86—2.52)	0.156
Age			1.00 (0.98—1.02)	0.932
Grade			1.45 (0.83—2.52)	0.193
Stage			1.14 (0.68—1.93)	0.616
Mutiplicity (≥2 vs. 1)	—		2.27 (1.36—3.79)	0.002
Chemotherapy	—		1.94 (1.09—3.45)	0.025

CI = confidence interval; Group 1 = BCG induction; Group 2 = BCG maintenance from one to three times; Group 3 = BCG maintenance from four to six times; Group 4 = BCG maintenance from seven to nine times; Group 5 = BCG maintenance ≥10 times.
[a] Model II adjusted by sex, age, grade, stage, multiplicity, and chemotherapy.

rate of 70% with maintenance therapy that employed the BCG Tice strain. Hinotsu et al[9] also reported a 2-year recurrent free rate of 92.7%. In our study, the 2-year recurrent free rates were 88.3% and 63.5% for the maintenance group and the nonmaintenance group, respectively, demonstrating findings similar to the results of the previous studies.

Although maintenance dose can reduce the recurrence rate, no large-scaled studies have shown the optimal times of standard maintenance dose. European Association of Urology guidelines still suggest that BCG should be given on a maintenance schedule in recent reports.[15—18] In addition, Bohle and Bock[18] reported that administration of BCG maintenance therapy for at least 1 year resulted in significantly superior suppression on the risk of disease progression. Moreover, Sylvester et al[17] reported that the BCG group showed statistically significant suppression of disease progression and, for patients who received some form of BCG maintenance therapy for at least 1 year, striking efficacy was demonstrated. In our study, patients who received BCG maintenance therapy from seven to nine times had the lowest recurrence rate in patients with non-muscle-invasive bladder tumor. However, this trend was not seen after adjusting by sex, age, tumor grade, tumor stage, and tumor number.
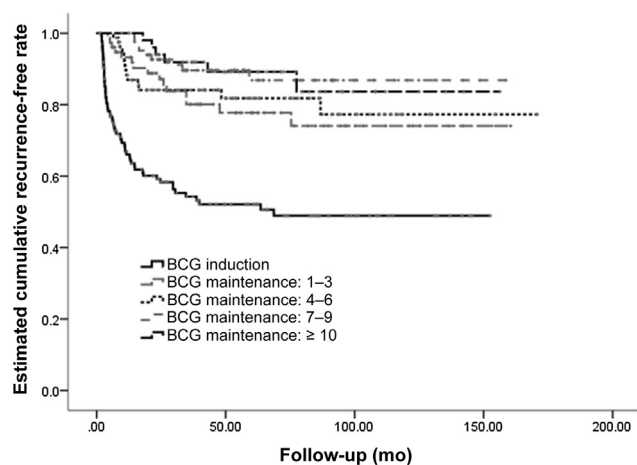

Fig. 2. Recurrence-free rate between different maintenance therapy courses. The group given bacillus Calmette—Guérin (BCG) maintenance from seven to nine times had a higher recurrence-free rate than the other groups.

The major limitation of our study was the small amount of patients included, although nearly 500, as compared with other studies. Patient classification bias was also another limitation in our study due to retrospective study. It needed to have large number patients and a prospective study to confirm our result.

In conclusion, this study demonstrated that BCG intravesical instillation maintenance therapy may significantly increase post-TUR recurrence free rate in patients with bladder cancer. The duration of maintenance BCG therapy is important in preventing the recurrent of non—muscle-invasive bladder cancer. However, the optimal duration of maintenance therapy needs further refinement and validation.

Conflicts of interest

All contributing authors declare no conflicts of interest.

References

1. Abraham WT. Cardiac resynchronization therapy for the management of chronic heart failure. *Am Heart Hosp J* 2003;**1**:55—61.
2. Babjuk M, Oosterlinck W, Sylvester R, Kaasinen E, Böhle A, Palou-Redorta J, et al. EAU guidelines on non—muscle-invasive urothelial carcinoma of the bladder. *Eur Urol* 2008;**54**:303—14.
3. van der Meijden AP, Sylvester RJ, Oosterlinck W, Hoeltl W, Bono AV, EORTC Genito-Urinary Tract Cancer Group. Maintenance Bacillus Calmette—Guérin for Ta T1 bladder tumors is not associated with increased toxicity: results from a European Organisation for Research and Treatment of Cancer Genito-Urinary Group Phase III Trial. *Eur Urol* 2003;**44**:429—34.
4. Lamm DL, Thor DE, Harris SC, Reyna JA, Stogdill VD, Radwin HM. Bacillus Calmette—Guérin immunotherapy of superficial bladder cancer. *J Urol* 1980;**124**:38—43.
5. Herr HW, Pinsky CM, Whitmore Jr WF, Oettgen HF, Melamed MR. Effect of intravesical bacillus Calmette-Guérin (BCG) on carcinoma *in situ* of the bladder. *Cancer* 1983;**51**:1323—6.
6. Malmström PU, Wijkström H, Lundholm C, Wester K, Busch C, Norlén BJ. 5-year follow-up of randomized prospective study comparing mitomycin C and BCG in patients with superficial bladder carcinoma. *J Urol* 1999;**161**:1124—7.
7. Lamm DL, Blumenstein BA, Crawford ED, Montie JE, Scardino P, Grossman HB, et al. A randomized trial of intravesical doxorubicin and immunotherapy with bacille Calmette—Guérin for transitional cell carcinoma of the bladder. *N Engl J Med* 1991;**325**:1205—9.
8. Lamm DL, Blumenstein BA, Crissman JD, Montie JE, Gottesman JE, Lowe BA, et al. Maintenance bacillus Calmette—Guérin immunotherapy for recurrent TA, T1 and carcinoma *in situ* transitional cell carcinoma of the bladder: a randomized Southwest Oncology Group Study. *J Urol* 2000;**163**:1124—9.
9. Hinotsu S, Akaza H, Naito S, Ozono S, Sumiyoshi Y, Noguchi S, et al. Maintenance therapy with bacillus Calmette—Guérin Connaught strain clearly prolongs recurrence-free survival following transurethral resection of bladder tumour for non-muscle-invasive bladder cancer. *Br J Urol International* 2010;**108**:187—95.
10. Herr HW, Dalbagni G, Donat SM. Bacillus Calmette—Guérin without maintenance therapy for high-risk non—muscle-invasive bladder cancer. *Eur Urol* 2011;**60**:32—6.
11. Hall MC, Chang SS, Dalbagni G, Pruthi RS, Seigne JD, Skinner EC, et al. Guideline for the management of nonmuscle invasive bladder cancer (stages Ta,T1 and Tis): 2007 update. *J Urol* 2007;**178**:2314—30.
12. Herr HW. Is maintenance bacillus Calmette—Guérin really necessary? *Eur Urol* 2008;**54**:971—3.
13. Saint F, Patard JJ, Irani J, Salomon L, Hoznek A, Legrand P, et al. Leukocyturia as a predictor of tolerance and efficacy of intravesical BCG maintenance therapy for superficial bladder cancer. *Urology* 2001;**57**:617—21. discussion 621—2.
14. van der Meijden AP, Brausi M, Zambon V, Kirkels W, de Balincourt C, Sylvester R, et al. Intravesical instillation of epirubicin, bacillus Calmette—Guérin and bacillus Calmette—Guérin plus isoniazid for intermediate and high risk Ta, T1 papillary carcinoma of the bladder: a European Organization

for Research and Treatment of Cancer genito-urinary group randomized phase III trial. *J Urol* 2001;**166**:476—81.

15. Bohle A, Jocham D, Bock PR. Intravesical bacillus Calmette—Guérin versus mitomycin C for superficial bladder cancer: a formal meta-analysis of comparative studies on recurrence and toxicity. *J Urol* 2003;**169**:90—5.

16. Malmström PU, Sylvester RJ, Crawford DE, Friedrich M, Krege S, Rintala E, et al. An individual patient data meta-analysis of the long-term outcome of randomised studies comparing intravesical mitomycin C versus bacillus Calmette—Guérin for non—muscle-invasive bladder cancer. *Eur Urol* 2009;**56**:247—56.

17. Sylvester RJ, van der Meijden AP, Lamm DL. Intravesical bacillus Calmette—Guérin reduces the risk of progression in patients with superficial bladder cancer: a meta-analysis of the published results of randomized clinical trials. *J Urol* 2002;**168**:1964—70.

18. Bohle A, Bock P. Intravesical bacillus Calmette-Guerin versus mitomycin C in superficial bladder cancer: formal meta-analysis of comparative studies on tumor progression. *Urology* 2004;**63**:682—7.