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CAN INTRAVESICAL BACILLUS CALMETTE-GUÉRIN REDUCE RECURRENCE IN PATIENTS WITH SUPERFICIAL BLADDER CANCER? A META-ANALYSIS OF RANDOMIZED TRIALS

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ABSTRACT

Objectives. To determine whether intravesical bacillus Calmette-Guérin (BCG) administration reduces recurrence after transurethral resection of superficial bladder cancer using a meta-analysis.

Methods. Published data of randomized clinical trials comparing transurethral resection plus intravesical BCG to either resection alone or resection plus another treatment were analyzed, considering possible confounding factors such as disease type, maintenance therapy, and others. Both the fixed effect model and the randomized effect model were applied, and the odds ratio (OR) with its 95% confidence interval (CI) was used as the effect size estimate.

Results. We searched 176 trials, eliminated 151 of them, and identified 25 trials with recurrence information on 4767 patients. Of 2342 patients undergoing BCG therapy, 949 (40.5%) had tumor recurrence compared with 1205 (49.7%) of 2425 patients in the non-BCG group. In the combined results, a statistically significant difference in the OR for tumor recurrence between the BCG and no BCG-treated groups was found (randomized combined effect OR 0.61, 95% CI 0.46 to 0.80, $P < 0.0001$). Stratified by BCG maintenance and disease type, the combined results of the individual reports showed statistical significance for BCG maintenance (OR 0.47, 95% CI 0.28 to 0.78, $P = 0.004$) and treatment of papillary carcinoma (OR 0.50, 95% CI 0.33 to 0.75, $P = 0.0008$). Chemotherapy and BCG plus chemotherapy/immunotherapy were not better than BCG alone.

Conclusions. Adjuvant intravesical BCG with maintenance treatment is effective for the prophylaxis of tumor recurrence in superficial bladder cancer. For patients with papillary carcinoma, adjuvant intravesical BCG with maintenance therapy should be offered as the treatment of choice. UROLOGY **67:** 1216–1223, 2006.

Of all patients with bladder cancer, 70% to 80% initially present with superficial disease (Stage Ta-T1 or carcinoma in situ). The standard treatment for these patients is transurethral resection (TUR) of all visible tumor. However, despite complete resection, tumor will recur in 50% to 70% within 5 years postoperatively. Recently, adjuvant intravesical instillation against tumor recurrence with chemotherapy and/or immunotherapy has been widely used. However, whether such therapy can delay or prevent recurrence is still the subject of controversy, because some studies have appeared to show its effectiveness but others have not. This discrepancy in results has largely been due to the short follow-up and small number of patients in most of the individual studies.[1] To determine the effect of intravesical instillation on recurrence in patients with superficial bladder cancer, a meta-analysis of the published results of randomized clinical trials was performed to have greater power to detect potential treatment differences and to provide a more precise estimate of the size treatment effect.

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MATERIAL AND METHODS

Selection Criteria

All available published data on the treatment results in patients with histologically confirmed superficial bladder cancer were selected for analysis if the following criteria were met. First, the data on treatment results for patients with histologically confirmed Stage Ta or T1 of any grade or carcinoma in situ bladder carcinoma were selected for analysis provided the data source was randomized trials or controlled observational cohort studies. Second, these trials had to have compared intravesical bacille Calmette-Guérin (BCG) plus TUR to TUR

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alone, or TUR plus intravesical chemotherapy or TUR plus immunotherapy, or, alternatively, intravesical chemotherapy/immunotherapy and BCG. Finally, the odds ratios had to have been provided or could be calculated from the data source. We selected trials from 1997 to 2005 by electronic search of Medline, the OVID database, and the Cochrane Library database. Hand searches of abstracts published in the *Journal of Urology*, the *European Urology* journal, and the *British Journal of Urology* were also performed. Reports of any language were eligible.

The primary endpoint criterion of this meta-analysis was the frequency of tumor recurrence within the follow-up period of the studies. Recurrence was defined as the reappearance of tumor of the same or lower stage and grade as the primary tumor.

Statistical Analysis

The odds ratio (OR) for each trial was calculated from the number of evaluable patients and number of patients with recurrence in each treatment group. For dichotomous outcomes, the ORs with their two-sided 95% confidence intervals (CIs) were used as the confirmatory effect size estimate and test criterion. In the course of data combination (pooling), the heterogeneity was evaluated by the Cochran-Q and Breslow-Day tests. Both the fixed effect model and the random effect model were applied. The hypotheses tests were based on the 95% CIs, and *P* values were used for illustration. To determine the potential risk bias in the overall results owing to including studies that violated some of the eligibility criteria, a sensitivity analysis was performed on the basis of trial quality. Potential confounding effects were investigated by stratified meta-analysis. Two independent reviewers extracted and interpreted the data according to the analysis protocol, input them into the Review Manager software, established the database, and chose the optimal effect model and judged the references quality using the software and standard provided by Lichtenstein *et al.*[2] The Comprehensive Meta-Analysis and Excel 2003 software programs were also used for this analysis.

RESULTS

Trial and Patient Characteristics

A total of 25[3–27] publications or abstracts, the trials of which met the selection criteria, were identified. The trial publication dates ranged from 1997 to 2005. A wide range of control groups was noted, including TUR alone (9 trials), the use of different immunotherapy agents, including interferon, interleukin-2, and BCG (2 trials), and the use of different chemotherapy regimens, including mitomycin C, thiotepa, doxorubicin, epirubicin, adriamycin, and camptothecin (10 trials), and BCG and chemotherapy/immunotherapy (4 trials). Some form of BCG maintenance was used in 8 trials and no BCG maintenance was used in 10 trials (Table I).

As shown in Table II, in the 25 eligible clinical trials, with a total of 4767 patients, the sample size range of the included trials was 34 to 560 patients. In total, 2342 patients were treated with BCG and compared with 2425 patients treated with no BCG.

Tumor Recurrence in All Studies Combined and BCG Toxicity

Within the follow-up period, 949 (40.5%) of 2342 BCG-treated patients and 1205 (49.7%) of 2425 patients treated without BCG developed tumor recurrence. In the combined analysis, a statistically significant difference in the recurrence rate between the two-treatment group was found. The randomized model combined OR was 0.61 (95% CI 0.46 to 0.80, $P < 0.0001$, Fig. 1). Thus, the overall results of the 25 included studies were consistent with the conclusion of a statistically significant difference between BCG and no BCG efficacy on tumor recurrence in the overall pooled data. Cystitis

TABLE I. *Trial characteristics (n = 25)*

Publication date	
Oldest	1997
Most recent	2005
Disease type	
Papillary	10
CIS	4
Papillary and/or CIS	4
Other (T1G3 and T1)	7
Treatment comparisons	
BCG vs. transurethral resection only	9
BCG vs. BCG and chemotherapy/immunotherapy	4
BCG vs. immunotherapy	2
BCG vs. chemotherapy	10
BCG maintenance	
No	10
Yes	8
BCG strain	
Connaught	4
Tokyo 172	3
Pasteur	4
Tice	2
Danish 1331	1
RIVM	1

Key: CIS = carcinoma in situ; BCG = bacille Calmette-Guérin.

TABLE II. *Patient characteristics*

Characteristic	n (%)
Evaluable	4767
No BCG	2425 (49.7)
BCG	2342 (40.5)
Treatment comparisons	4767
BCG vs. transurethral resection only	1100 (23.1)
BCG vs. BCG and chemotherapy/immunotherapy	764 (16.0)
BCG vs. immunotherapy	1110 (23.3)
BCG vs. chemotherapy[4]	1793 (37.6)
BCG maintenance	3142
No	2072 (65.9)
Yes	1070 (34.1)
BCG strain	3366
Connaught	1350 (40.1)
Tokyo 172	178 (5.3)
Pasteur	496 (14.7)
Other (Tice, Danish 1331, RIVM)	1342 (39.9)

Key: BCG = bacille Calmette-Guérin.

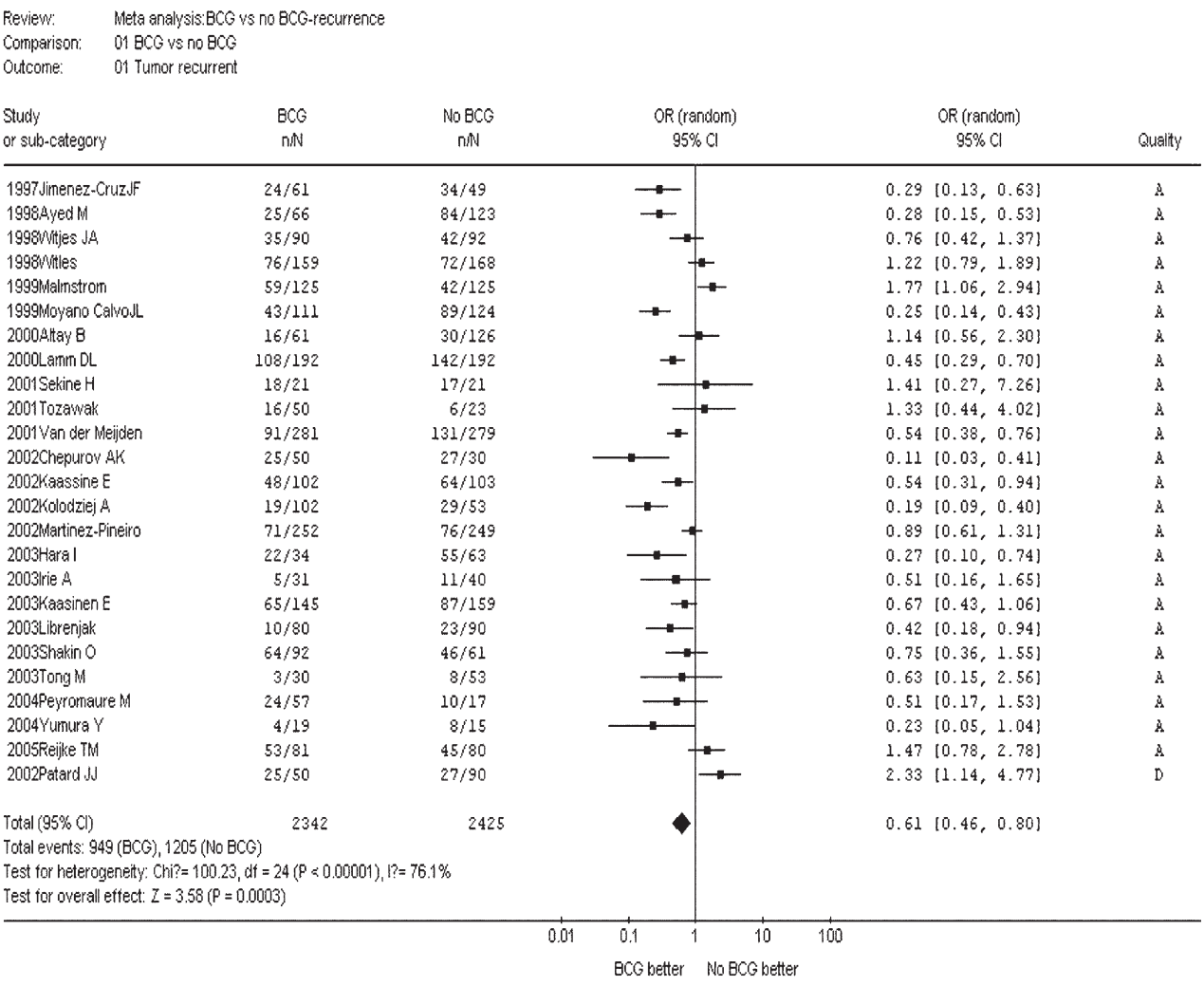

FIGURE 1. *Recurrence in studies with BCG compared with no BCG treatment.*

and allergy were common side effects of intravesical treatment. Drug-induced cystitis, dysuria, frequency/urgency, and systemic side effects such as chills, fever, malaise, and nausea were significantly more frequent in the BCG group than in the chemotherapy and immunotherapy group. Overall, about 30% of those patients receiving mitomycin C developed local toxicity compared with 44% of those receiving BCG.

Stratification by BCG Maintenance Therapy

In this meta-analysis, BCG maintenance therapy was defined as a 6-week induction course of BCG and then three weekly BCG instillations at 3 and 6 months and every 6 months thereafter for 3 years. Patients who only received a 6-week (or less than) induction course of BCG were included in the no-BCG maintenance group. A total of 1070 patients received BCG maintenance therapy for at least 1 year. In 10 studies with a total of 2072 patients, no maintenance therapy was given. In the BCG maintenance subgroup, the combined random effect OR was 0.47 (95% CI 0.28 to 0.78, $P = 0.004$, Fig. 2). The results indicated a statistical significance of BCG versus no BCG efficacy on tumor recurrence in the BCG maintenance subgroup. The no BCG maintenance subgroup showed a combined random effect model OR of 0.90 (95% CI 0.52 to 1.56, $P = 0.71$, Fig. 3).

Stratification by BCG Versus TUR Alone/Chemotherapy/Immunotherapy and BCG Plus Chemotherapy/Immunotherapy Versus BCG Alone

A total of 230 (36.1%) of 638 BCG-treated patients and 268 (58.0%) of 462 TUR alone-treated patients had tumor recurrence. When stratifying BCG versus TUR alone, the combined random effect OR was 0.35 (95% CI 0.20 to 0.59, $P < 0.001$, Fig. 4). In the BCG versus chemotherapy subgroup, which means patients who received BCG versus patients who only received chemotherapy without immunotherapy or BCG, the combined random effect OR was 0.88 (95% CI 0.58 to 1.35, $P = 0.0005$, Fig. 5). At the same time, in the BCG plus chemotherapy/immunotherapy ver-

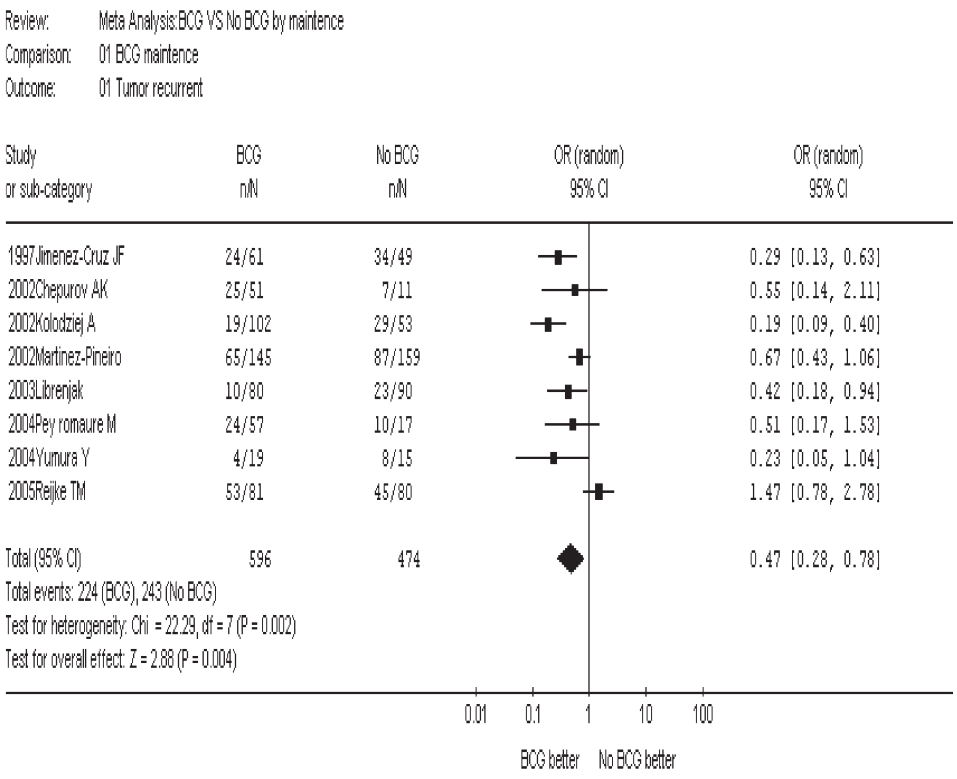

FIGURE 2. *Recurrence in studies with BCG maintenance compared with no BCG treatment.*

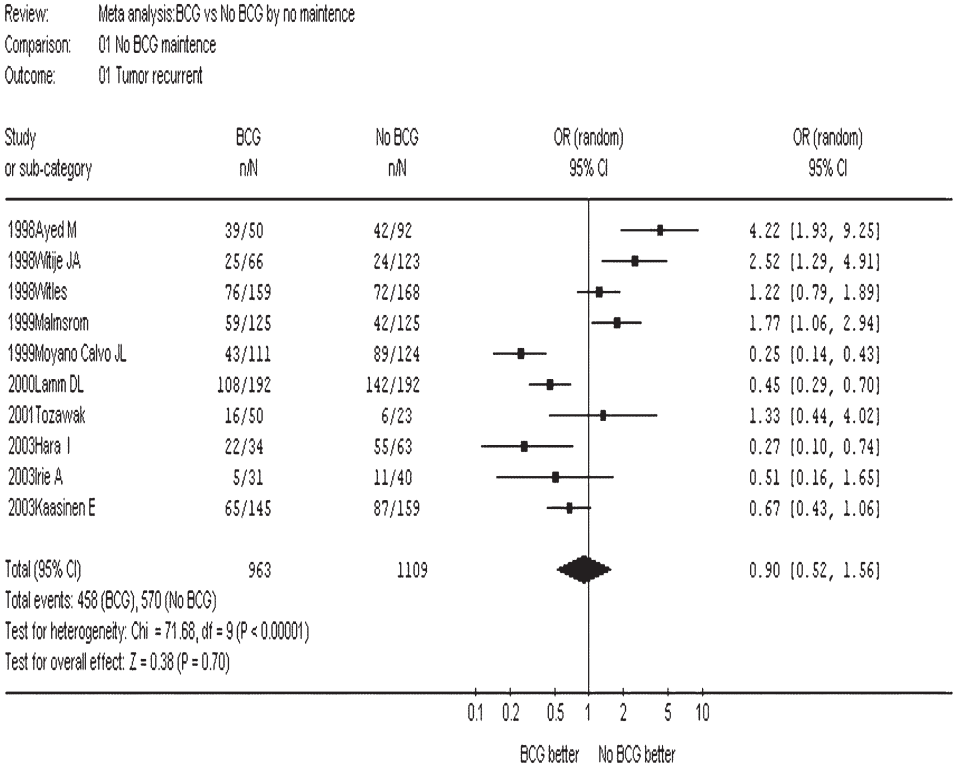

FIGURE 3. *Recurrence in studies with no BCG maintenance compared with no BCG treatment.*

sus BCG alone subgroup, 4 trials included 389 patients who received BCG alone and 375 patients who received BCG plus chemotherapy/immunotherapy. The combined randomized model OR was 1.27 (95% CI 0.96 to 1.70, $P = 0.10$; data not shown). These results did not show any statistically significant differences in their efficacy in preventing tumor recurrence (ie, compared with BCG, chemotherapy and BCG plus chemotherapy/immunotherapy were not significantly better than BCG).

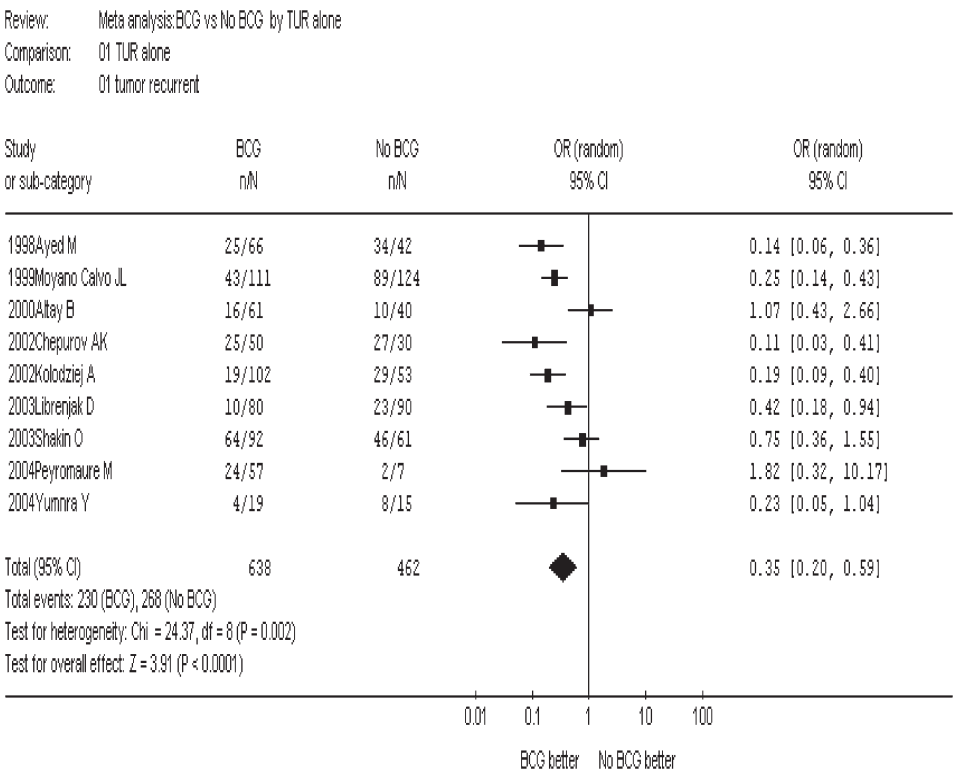

FIGURE 4. *Recurrence in studies with BCG compared with TUR alone treatment.*

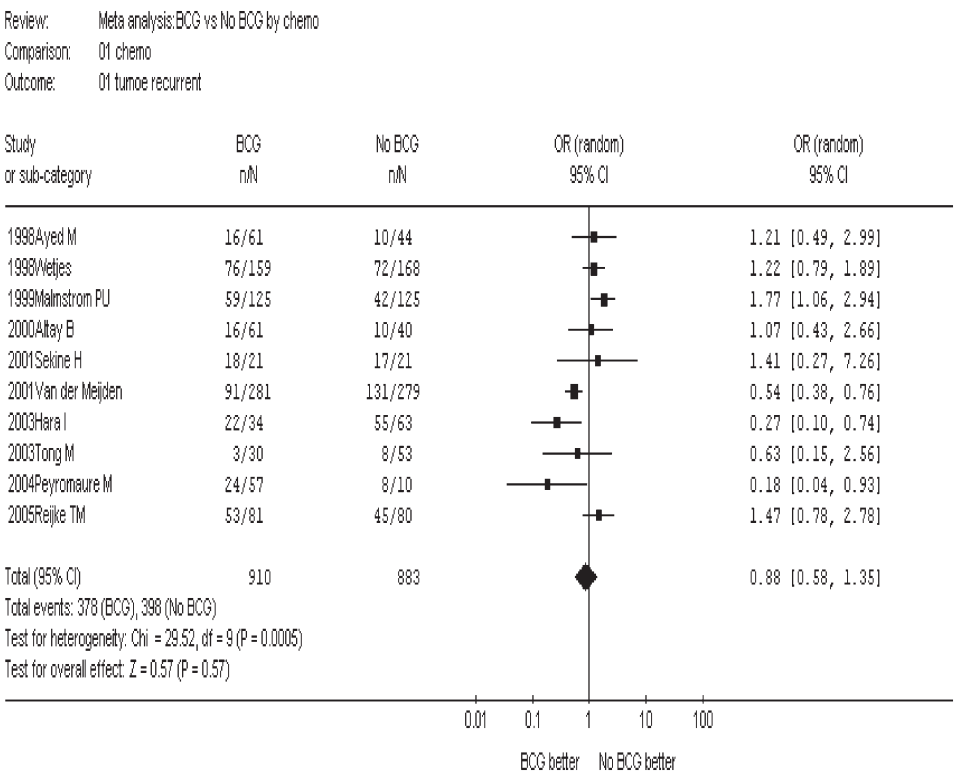

FIGURE 5. *Recurrence in studies with BCG compared with chemotherapy treatment.*

Potential Confounding Effect on Treatment Efficacy Against Tumor Recurrence

In our study, several strains of BCG were used, including Connaught, Tokyo 172, Pasteur, Tice, Danish, and RIVM. The stratified meta-analysis did not show any statistically significant confounding effects on the results when stratified by BCG strain. However, a statistically significant difference was found between BCG and no BCG on tumor recurrence in the papillary subgroup, with a combined

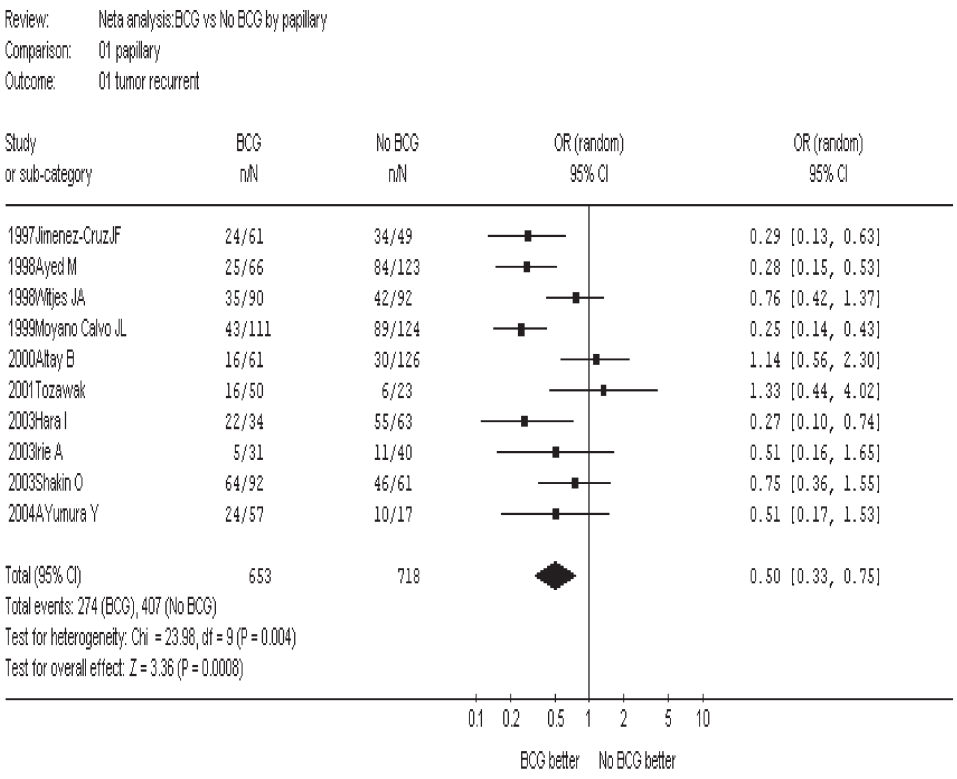

FIGURE 6. *Recurrence in studies with BCG compared with no BCG treatment in the subgroup of papillary tumors.*

random effect OR of 0.50 (95% CI 0.33 to 0.75, $P = 0.0008$, Fig. 6). The combined random effect OR for carcinoma in situ was 0.90 (95% CI 0.63 to 1.28, $P = 0.55$; data not shown) and for papillary and/or carcinoma in situ was 0.19 (95% CI 0.02 to 1.56, $P = 0.12$; data not shown). Thus, BCG maintenance therapy and a papillary disease type were associated with statistical significance for BCG versus no BCG against tumor recurrence. However, for Stage T1G3 disease, the random effect OR was 0.55 (95% CI 0.21 to 1.42, $P < 0.0001$). This indicates that BCG therapy had no statistical significance compared with no BCG therapy against T1G3 tumor recurrence.

Sensitivity Analysis and Publication Bias

As shown in Figure 1, the quality of publications or abstracts were "A" (24 trials) and "D" (1 trial) as judged by the Review Manager. After deleting the data of the D trial and reanalyzing the data of the other 24 trials, the randomized combined effect OR was 0.57 (95% CI 0.44 to 0.75, $P < 0.0001$), very similar to the OR of 0.61 (95% CI 0.46 to 0.80, $P < 0.0001$). This indicates that our meta-analysis was little influenced by publication bias. However, we only searched Medline, the OVID database, and the Cochrane Library database in this study, and data with statistical significance are easier to get published, which influenced the validity of our study to some extent.

COMMENT

Many individual trials have only a low power to detect medically plausible differences between two treatment regimens, especially if both regimens have valid efficacy. One possible way to overcome this problem is to perform a combined analysis of the available material using a meta-analysis. A meta-analysis is a formal statistical method used to combine the results of separate, but similar, studies in a quantitative manner, so that the statistical power of the tests used to compare treatments is increased by using all the evidence from a larger number of controlled trials rather than only one.[28]

Meta-analytical techniques were also used to draw conclusions on the benefits of different therapeutic options for the adjuvant treatment of superficial bladder cancer. Our meta-analysis has shown that intravesical BCG after TUR reduces the risk of recurrence, especially in papillary tumors when maintenance BCG is used. At present, chemotherapy and immunotherapy are widely used to reduce the incidence of tumor recurrence. Sylvester *et al.*[29] reported that BCG was superior to mitomycin C in trials with maintenance BCG (OR 0.57, $P = 0.04$) and intravesical BCG significantly reduced the risk of short-term and long-term treatment failure compared with intravesical chemotherapy in their meta-analysis. Our meta-analysis has confirmed that compared with BCG, BCG plus chemotherapy/im-

munotherapy is not better than BCG alone and that BCG, especially regimens including maintenance BCG, was more effective in the subgroup of patients with papillary tumors than other agents.

In our study, the results indicated the statistical significance of BCG efficacy on tumor recurrence in the BCG maintenance subgroup. Grade 3 tumors are likely to progress, and treatment for them is still the subject of controversy. In our study, the results indicated that BCG had no statistical significance against T1G3 tumors. Chemotherapy or immunotherapy agents can be instilled into the bladder directly by catheter, thereby avoiding the morbidity of systemic administration in most cases. In our study, mitomycin C, thiotepa, doxorubicin, epirubicin, adriamycin, camptothecin, interferon, interleukin-2, and BCG were included. However, our results did not show any statistically significant differences regarding their efficacy in preventing tumor recurrence.

Although BCG has been used for 25 years, the optimal dose and instillation schedule remain unclear. In our meta-analysis, many different maintenance schedules were used. Despite this heterogeneity, a reduction in the risk of recurrence was only observed in patients receiving maintenance BCG. Recently, many different strains of BCG have been reported in published studies, although few comparative studies of the different strains have been performed. However, our meta-analysis suggested no large difference in the efficacy among the different strains.

CONCLUSIONS

The evidence from this formal meta-analysis suggests that adjuvant intravesical BCG with maintenance treatment is significantly effective for the prophylaxis of tumor recurrence in patients with superficial bladder cancer. For patients with papillary bladder cancer, adjuvant intravesical BCG therapy with maintenance should be offered as the treatment of choice.

REFERENCES

1. Richard J, Adrian PM, Donald L: 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 **168:** 1964–1970, 2002.

2. Lichtenstein MJ, Mulrow CD, and Elwood PC: Guidelines for reading case control studies. J Chron Dis **40:** 893–903, 1987.

3. de Reijke TM, Kurth KH, Sylvester RJ, *et al:* Bacillus Calmette-Guérin versus epirubicin for primary, secondary or concurrent carcinoma in situ of the bladder: results of a European Organization for the Research and Treatment of Cancer–Genito-Urinary Group Phase III Trial. J Urol **173:** 405–409, 2005.

4. Yumura Y, Oogo Y, Takase K, *et al:* Results of adjuvant intravesical bacillus Calmette-Guérin therapy for grade 3 superficial bladder cancer. Hinyokika Kiyo **50:** 767–771, 2004.

5. Peyromaure M, and Zerbib M: T1G3 transitional cell carcinoma of the bladder: recurrence, progression and survival. BJU Int **93:** 60–63, 2004.

6. Kaasinen E, Wijkstrom H, Malmstrom PU, *et al:* Alternating mitomycin C and BCG instillations versus BCG alone in treatment of carcinoma in situ of the urinary bladder: a Nordic study. Eur Urol **43:** 637–645, 2003.

7. Librenjak D, Situm M, Eterovic D, *et al:* Immunoprophylactic intravesical application of bacillus Calmette-Guérin after transurethral resection of superficial bladder cancer. Croat Med J **44:** 187–192, 2003.

8. Irie A, Uchida T, Yamashita H, *et al:* Sufficient prophylactic efficacy with minor adverse effects by intravesical instillation of low-dose bacillus Calmette-Guérin for superficial bladder cancer recurrence. Int J Urol **10:** 183–189, 2003.

9. Tong M, Yu LZ, Ding Y, *et al:* Prevention of postoperative recurrence of human bladder carcinoma by intravesical instillation of immunotoxin, a clinical study. Zhonghua Yi Xue Za Zhi **83:** 201–203, 2003.

10. Hara I, Miyake H, Takechi Y, *et al:* Clinical outcome of conservative therapy for stage T1, grade 3 transitional cell carcinoma of the bladder. Int J Urol **10:** 19–24, 2003.

11. Shahin O, Thalmann GN, Rentsch C, *et al:* A retrospective analysis of 153 patients treated with or without intravesical bacillus Calmette-Guérin for primary stage T1 grade 3 bladder cancer: recurrence, progression and survival. J Urol **169:** 96–100, 2003.

12. Kaasinen E, Rintala E, Hellstrom P, *et al:* Factors explaining recurrence in patients undergoing chemoimmunotherapy regimens for frequently recurring superficial bladder carcinoma. Eur Urol **42:** 167–174, 2002.

13. Patard JJ, Rodriguez A, Leray E, *et al:* Intravesical bacillus Calmette-Guérin treatment improves patient survival in T1G3 bladder tumours. Eur Urol **41:** 635–641, 2002.

14. Martinez-Pineiro JA, Flores N, Isorna S, *et al:* Long-term follow-up of a randomized prospective trial comparing a standard 81 mg dose of intravesical bacille Calmette-Guérin with a reduced dose of 27 mg in superficial bladder cancer. BJU Int **89:** 671–680, 2002.

15. Kolodziej A, Dembowski J, Zdrojowy R, *et al:* Treatment of high-risk superficial bladder cancer with maintenance bacille Calmette-Guérin therapy: preliminary results. BJU Int **89:** 620–622, 2002.

16. Chepurov AK, Murshudli EC, and Mazo EB: Features of BCG-therapy in treating patients with superficial bladder cancer. Ter Arkh **74:** 70–72, 2002.

17. Sekine H, Ohya K, Kojima SI, *et al:* Equivalent efficacy of mitomycin C plus doxorubicin instillation to bacillus Calmette-Guérin therapy for carcinoma in situ of the bladder. Int J Urol **8:** 483–486, 2001.

18. van der Meijden AP, Brausi M, Zambon V, *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 **166:** 476–481, 2001.

19. Tozawa K, Okamura T, Sasaki S, *et al:* Intravesical combined chemoimmunotherapy with epirubicin and bacillus Calmette-Guérin is not indicated for superficial bladder cancer. Urol Int **67:** 289–292, 2001.

20. Lamm DL, Blumenstein BA, Crissman JD, *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 **163:** 1124–1129, 2000.

21. Altay B, Girgin C, Kefi A, *et al:* The best management of superficial bladder tumours: comparing TUR alone versus TUR combined with intravesical chemotherapy modalities? Int Urol Nephrol **32:** 53–58, 2000.

22. Moyano Calvo JL, Ortiz Gamiz A, Romero Diaz A, *et al:* The prevention of stage-T1 superficial bladder tumors with 27 mg. of BCG weekly over 6 weeks. Arch Esp Urol **52:** 760–768, 1999.

23. Malmstrom PU, Wijkstrom H, Lundholm C, *et al,* for the Swedish-Norwegian Bladder Cancer Study Group: 5-Year followup of a randomized prospective study comparing mitomycin C and bacillus Calmette-Guérin in patients with superficial bladder carcinoma. J Urol **161:** 1124–1127, 1999.

24. Witjes JA, Caris CT, Mungan NA, *et al:* Results of a randomized phase III trial of sequential intravesical therapy with mitomycin C and bacillus Calmette-Guérin versus mitomycin C alone in patients with superficial bladder cancer. J Urol **160:** 1668–1671, 1998.

25. Witjes JA, van der Meijden AP, Collette L, *et al,* for the European Organisation for Research and Treatment of Cancer Genito-Urinary Tract Cancer Collaborative (EORTC GU) Group and the Dutch South East Cooperative Urological Group: Long-term follow-up of an EORTC randomized prospective trial comparing intravesical bacille Calmette-Guérin-RIVM and mitomycin C in superficial bladder cancer. Urology **52:** 403–410, 1998.

26. Ayed M, Ben Hassine L, Ben Slama R, *et al:* Results of BCG in the treatment of pTa and pT1 bladder tumors: evaluation of a long protocol using 75 mg of Pasteur strain BCG. Prog Urol **8:** 206–210, 1998.

27. Jimenez-Cruz JF, Vera-Donoso CD, Leiva O, *et al:* Intravesical immunoprophylaxis in recurrent superficial bladder cancer (stage T1): multicenter trial comparing bacille Calmette-Guérin and interferon-alpha. Urology **50:** 529–535, 1997.

28. Bohle A, Jcham D, and Bock PR: 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. Int Braz J Urol **28:** 585–586, 2002.

29. Sylvester RJ, van der Meijden AP, Witjes JA, *et al:* Bacillus Calmette-Guérin versus chemotherapy for the intravesical treatment of patients with carcinoma in situ of the bladder: a meta-analysis of the published results of randomized clinical trials. J Urol **174:** 86–92, 2005.