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.


O f 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. 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.

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.
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. The Comprehensive Meta-Analysis and Excel 2003 software programs were also used for this analysis.

**Results**

**Trial and Patient Characteristics**

A total of 253–27 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...
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, \( P < 0.0001 \), 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-
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 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.
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 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
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


