A systematic review of intravesical bacillus Calmette-Guérin plus transurethral resection vs transurethral resection alone in Ta and T1 bladder cancer

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Objective To assess, in a systematic review, the effectiveness of intravesical bacillus Calmette-Guérin (BCG) in preventing tumour recurrence in patients with medium/high risk Ta and T1 bladder cancer.

Patients and methods An electronic database search of Medline, Embase, the Cochrane Library, Cancerlit, Healthstar and BIDS was undertaken, plus hand searching of the Proceedings of ASCO, for randomized controlled trials, in any language, comparing transurethral resection (TUR) alone with TUR followed by intravesical BCG in patients with Ta and T1 bladder cancer.

Results The search identified 26 publications comparing TUR with TUR + BCG. Six trials were considered acceptable, representing 585 eligible patients, 281 in the TUR-alone group and 304 in the TUR + BCG group. The major clinical outcome chosen was tumour recurrence. The weighted mean log hazard ratio for the first recurrence, taken across all six trials, was −0.83 (95% confidence interval −0.57 to −1.08, P < 0.001), which is equivalent to a 56% reduction in the hazard, attributable to BCG. The Peto odds ratio for patients recurring at 12 months was 0.3 (95% confidence interval of 0.21–0.43, P < 0.001), significantly favouring BCG therapy. Manageable toxicities associated with intravesical BCG were cystitis (67%), haematuria (23%), fever (25%) and urinary frequency (71%). No BCG-induced deaths were reported.

Conclusion TUR with intravesical BCG provides a significantly better prophylaxis of tumour recurrence in Ta and T1 bladder cancer than TUR alone. Randomized trials are still needed to address the issues of BCG strain, dose and schedule, and to better quantify the effect on progression to invasive disease.

Keywords evidence-based medicine, bacillus Calmette-Guérin, BCG, bladder cancer, recurrence

Introduction

The incidence of bladder cancer is increasing and represents the fifth most common cancer in European men, and the fourth most common in the USA. Most patients present with early-stage disease confined to the urothelium (Ta) or the lamina propria (T1). The standard treatment for Ta and T1 disease is transurethral resection (TUR), but in 40–80% of patients tumours recur within 12 months [1]. Intravesical therapy with anti-neoplastic agents is a common procedure after TUR with the aim of preventing tumour recurrence. The rationale for intravesical treatment is that high concentrations of active agent within the bladder destroy neoplastic cells with a reduced risk of systemic exposure. Recurrent tumours may arise from coexisting microscopic lesions.
Patients and methods

All randomized or quasi-randomized controlled clinical trials in superficial bladder cancer comparing intravesical BCG + TUR with TUR alone were relevant for inclusion in this study. Randomized studies in which other intravesical chemotherapeutic agents were used but had a BCG + TUR arm and a TUR arm were included. The search strategy included an electronic search of Medline to identify all relevant randomized clinical trials comparing intravesical BCG + TUR with TUR alone in superficial bladder cancer from 1966 to September 2000 (Appendix). Additional electronic searches of the following databases were conducted: EMBASE (Excerpta Medica Database), Cancerlit, Database of Abstracts of Reviews of Effectiveness (DARE), Healthstar, the Bath Information and Data System (BIDS) and the Cochrane Library. Hand searching of recent Proceedings of the American Society for Clinical Oncology was also undertaken (1996–2000). The reference list contained within each primary reference was scrutinized for additional randomized trials. Reports of randomized trials in any language were eligible for assessment.

The studies included were those on adults with histologically confirmed Ta and T1 superficial bladder cancer, and eligible patients were those with a medium or high risk of recurrence [10]. Medium-risk patients were those with a solitary tumour at presentation and tumour recurrence at 3 months, or multiple tumours at presentation and no tumour at 3 months. High-risk patients were those with multiple tumours at presentation and recurrence at 3 months. We considered intravesical BCG of any schedule to be appropriate for assessment provided the control group (TUR alone) did not receive BCG.

The main outcome measure for this review was treatment efficacy, as measured by the time to recurrence after treatment, and the number of patients who had recurrence at 12 months. Local and systemic toxicities were also assessed. Data were extracted from each identified paper by two reviewers independently and included information on the trial design, participants, type of intervention and outcome measures.

Statistics

The effectiveness of BCG + TUR vs TUR alone was estimated using the log hazard ratio ([(TUR + BCG)/TUR]) and by the Peto odds ratio at 12 months. The hazard ratio represents the overall risk of recurrence per unit time for the treatment group compared with the control group. A ratio of 1 is indicative of no effect, whereas a value of < 1 indicates a reduced rate of recurrence in the treatment arm. The hazard ratio was normalized by log transformation.

Results

The search identified 26 published trials comparing TUR plus intravesical BCG with TUR alone, listed in Table 1 [7–9,11–33]. Six trials were included in the full meta-analysis [12–17]. Two trials were not randomized and were excluded [7,8]. In one study all participants received intravesical BCG and were then randomized to maintenance or non-maintenance BCG; this trial was also excluded [11]. Another randomized trial was excluded because there were insufficient data on the risk of recurrence in all participants [9]. The remaining publications were excluded because they represented duplicate reports [18–33].

In two of the included trials [16,17], it was unclear whether a proportion of low-risk patients had been included and a sensitivity analysis was carried out to determine the effect of exclusion of these two studies. The six trials represent 585 eligible patients, 304 in the TUR + BCG arm and 281 in the TUR-alone arm. In the case of data based on time to first recurrence, or when the recurrence frequency was reported at specific times, an attempt was made to calculate the log hazard ratio (ln(hr)) and its variance. One study [12] applied a Cox regression using BCG as a covariate, and in this case the coefficient was used as a direct estimate of the ln(hr). Both low- and high-risk cases were included in the analysis, but as the risk was represented by a covariate in the regression, the coefficient was accepted with no further adjustment. Another trial [13] tabulated raw case data, giving grade, stage, the number of previous recurrences, the number of recurrences after intervention and the time to recurrence. Using these data we applied a Cox regression using the presence or absence of BCG as an additional covariate, and used the coefficient as an estimate of ln(hr). However, as these data were restricted to medium- and high-risk cases (at least two previous recurrences), only 14 cases were available for analysis, so that the conclusion, although valid, must be

<table>
<thead>
<tr>
<th>Included</th>
<th>Excluded</th>
</tr>
</thead>
<tbody>
<tr>
<td>[12]†</td>
<td>[11] [23]b</td>
</tr>
<tr>
<td>[13]†</td>
<td>[18]† [24]† [29]†</td>
</tr>
<tr>
<td>[14]</td>
<td>[19]† [25]† [30]†</td>
</tr>
<tr>
<td>[15]</td>
<td>[7]† [9] [31]†</td>
</tr>
<tr>
<td>[16]</td>
<td>[20]† [26]† [32]†</td>
</tr>
<tr>
<td>[17]</td>
<td>[21]† [27]† [33]†</td>
</tr>
<tr>
<td></td>
<td>[22]† [28]† [8]†</td>
</tr>
</tbody>
</table>

Repeat publications: a[14], b[15], c[13], d[12]. *Recurrent patients only; †not randomized trials.
treated with some caution. One study gave a Kaplan–Meier plot of the time to first recurrence [15], and although a chi-square was quoted its precision was insufficient to permit a direct calculation of the ln(hr). In that case we used the method of Parmar et al. [34] to estimate the ln(hr) from the Kaplan–Meier plot, using exact follow-up times indicated on the plot. Another study also gave a Kaplan–Meier plot of time to first recurrence [17] and here also the quoted chi-square had insufficient precision. As these authors also tabulated the number of patients recurring at five time-points after intervention, we applied a univariate Cox regression assuming uniform censoring between the minimum and maximum follow-up times. The ln(hr) found using this method (−1.52, variance 0.32) agreed reasonably well with that found using the method of Parmar et al. [34] applied to the Kaplan–Meier plot (−1.32, variance 0.32). A similar Cox regression was applied to the tabulated data of a further study [16], although in this case the minimum follow-up time was 24 months so that the number at risk was known exactly. One trial gave only the number of recurrences at 12 and 18 months [14]. As the minimum follow-up was at least 12 months, the mean ln(hr) over the first year can be approximated by the relative risk [34]. The log hazard ratios of all the trials were combined as a weighted mean using the reciprocal of the variance. The heterogeneity statistic was calculated as a chi-square using the weighted sum of squares.

The values of the ln(hr) are given in Table 2. When all six studies were included, the overall ln(hr) was −0.83 (95% CI −1.08 to −0.57, P < 0.001). This is equivalent to a mean hazard ratio of 0.44, suggesting a clear effect of BCG in the reduction in the hazard of recurrence over the time intervals studied. There was no evidence of heterogeneity between the studies (chi-square 9.34, P = 0.1). When two studies [16,17] were removed to determine the effect of a possible inclusion of low-risk cases, the overall ln(hr) increased slightly to −0.78 (95% CI −1.07 to −0.50, P < 0.001). In this case the heterogeneity statistic was marginally significant (chi-square 7.76, P = 0.05), largely because of the low hazard ratio in one study [14]. A sub-analysis of two studies [16,17] yielded a ln(hr) of −0.98 (95% CI −1.52 to −0.44, P = 0.0036), and in this case there was no evidence of heterogeneity (chi-square 1.17, P = 0.28).

Odds ratios were calculated using the numbers of patients recurring at specified time intervals. The numbers at risk were either stated explicitly [13,14,16] or were estimated from the maximum and minimum follow-up times assuming uniform censoring [17]. In the case of two trials [12,15] the number of recurrences and cases at risk at 12 months were estimated from the Kaplan–Meier plot using a modification of the method of Parmar et al. [34], also assuming uniform censoring.

The total number of patients presenting with tumour recurrence at 12 months was 79/275 (28.7%) in the BCG+TUR group, compared with 144/257 (56.0%) in the TUR-alone group. The meta-analysis including all six studies is shown in Table 3, the combined Peto odds ratio of 0.30 (P < 0.001) indicating that BCG + TUR was better than TUR alone. In the case of studies including medium to high-risk patients [12–15] the odds ratio was 0.33

Table 2 Log hazard ratios and variances for the included trials. A subgroup meta-analysis was undertaken on group 1 (medium/high-risk patients) and group 2 (possibility of low-risk patients included in the study). The weighted mean ln(hr) was for the combined meta-analysis

<table>
<thead>
<tr>
<th>Trial</th>
<th>Log hazard ratio ((TUR + BCG)/TUR)</th>
<th>Variance</th>
<th>TUR</th>
<th>TUR + BCG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medium/high-risk patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[12]</td>
<td>0.482</td>
<td>0.058</td>
<td>43/116</td>
<td>28/98</td>
</tr>
<tr>
<td>[13]</td>
<td>0.613</td>
<td>0.462</td>
<td>4/6</td>
<td>3/6</td>
</tr>
<tr>
<td>[14]</td>
<td>0.740</td>
<td>0.150</td>
<td>31/39</td>
<td>6/43</td>
</tr>
<tr>
<td>[15]</td>
<td>0.742</td>
<td>0.049</td>
<td>39/43</td>
<td>27/41</td>
</tr>
<tr>
<td>Subgroup meta-analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>−0.783</td>
<td>0.022</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Medium/high risk but unclear if low risk included

| [16] | −0.818 | 0.099 | 14/33 | 11/67 |
| [17] | −1.520 | 0.323 | 13/20 | 4/20 |

Subgroup meta-analysis

| −0.983 | 0.076 |

Overall meta-analysis: weighted mean ln(hr)

| −0.827 | 0.017 |

Table 3 The Peto odds ratio for the number of patients with disease recurrence at 12 months for the six trials. A subgroup meta-analysis was conducted on the medium/high-risk patients and those with a possibility of low-risk patients included in the study. A Peto odds ratio of >1 favours TUR and of <1 favours BCG+TUR

<table>
<thead>
<tr>
<th>Study/group</th>
<th>BCG+ TUR, n/N</th>
<th>TUR, n/N</th>
<th>Weight, %</th>
<th>Peto odds ratio (99% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medium/high-risk patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[12]</td>
<td>28/98</td>
<td>43/116</td>
<td>42.2</td>
<td>0.68 (0.32–1.44)</td>
</tr>
<tr>
<td>[13]</td>
<td>3/6</td>
<td>4/6</td>
<td>2.8</td>
<td>0.53 (0.03–9.58)</td>
</tr>
<tr>
<td>[14]</td>
<td>6/43</td>
<td>31/39</td>
<td>18.3</td>
<td>0.07 (0.02–0.23)</td>
</tr>
<tr>
<td>[15]</td>
<td>27/41</td>
<td>39/43</td>
<td>12.8</td>
<td>0.23 (0.06–0.91)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>64/188</td>
<td>117/204</td>
<td>76.1</td>
<td>0.33 (0.19–0.58)</td>
</tr>
</tbody>
</table>

Medium/high, possibly some low-risk patients

| [16] | 11/67 | 14/33 | 14.9 | 0.25 (0.07–0.89) |
| [17] | 4/20 | 13/20 | 8.9 | 0.17 (0.03–0.85) |
| Subtotal | 15/87 | 27/53 | 23.9 | 0.22 (0.08–0.59) |
| Total | 79/275 | 144/257 | 100.0 | 0.30 (0.18–0.49) |
(95% CI 0.22–0.5, \( P < 0.001 \)). The two studies that may have included some low-risk patients [16,17] yielded a combined odds ratio of 0.22 (95% CI 0.10–0.46, \( P < 0.001 \)). In all analyses and sub-analyses, both the log hazard ratio and the Peto odds ratio were significantly in favour of the inclusion of BCG.

The strains of BCG, doses and schedules used in the six included trials are shown in Table 4. Of the six trials, the Pasteur (Paris) BCG strain was used in three [13,14,16], the Connaught (Pasteur Toronto) in one [12], the Armand Frappier (Pasteur Quebec) in one [15] and the Tokyo in one [17]. Five trials used an initial 6-week treatment of intravesical BCG [12–15,17], whereas one [16] used an 8-week treatment. The initial BCG therapy was followed either by further monthly BCG instillations for 4 months [12] or continued every 2 weeks for 6 weeks then monthly for 20 months. One study [14] followed the initial BCG treatment with monthly BCG for 12 months then 3-monthly for 3 months if no tumour was evident, or a repeat of the initial 6 weeks of BCG if tumour was found. Doses of BCG per instillation were 75 mg [14], 80 mg [17], 120 mg [12,13,15] and 150 mg [14]. However, the more important value for the colony-forming units, which represents the biological activity of the intravesically administered BCG rather than the dry weight in milligrams, was reported in only two studies [14,16]. The duration of instillation was either 1 h [12] or 2 h [13–17] and three trials gave concomitant intradermal BCG using doses of 0.5 mg [12], 5 mg [13] and \( 5 \times 10^7 \) c.f.u. [15].

Side-effects induced with intravesical BCG were reported in the included trials (Table 4) but there were no complete data on the side-effects of TUR alone. The main toxicities associated with BCG were cystitis (67%), haematuria (23%), fever (25%) and urinary frequency (71%). No BCG sepsis or deaths were reported in any of the six trials.

Discussion

Superficial TCC of the bladder has the propensity to recur after TUR, but remains superficial in most cases. The recurrent nature of this disease necessitates that patients require constant vigilance with cystoscopic follow-up even after a recurrence-free period of \( \geq 5 \) years [35]. Frequent surveillance for recurrence is tolerable for the patient but reduces the quality of life because of psychological stress and physical trauma, as well as the time and cost of hospital visits.

Several observational studies have indicated the benefit of intravesical BCG in preventing tumour recurrence and progression. However, most clinical researchers agree

Table 4 The BCG strain, dose and schedule of administration for the six trials, and the reported toxicities induced by intravesical BCG

<table>
<thead>
<tr>
<th>Trial</th>
<th>[12]</th>
<th>[13]</th>
<th>[14]</th>
<th>[15]</th>
<th>[16]</th>
<th>[17]</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCG strain</td>
<td>(C)</td>
<td>P</td>
<td>P</td>
<td>P(AF)</td>
<td>P</td>
<td>Tokyo</td>
</tr>
<tr>
<td>Weekly dose, mg</td>
<td>120</td>
<td>120</td>
<td>75</td>
<td>120</td>
<td>150</td>
<td>80</td>
</tr>
<tr>
<td>c.f.u. ( \times 10^9 )</td>
<td>NR</td>
<td>NR</td>
<td>4–5</td>
<td>NR</td>
<td>6</td>
<td>NR</td>
</tr>
<tr>
<td>Duration of instillation (h)</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Schedule, ( \times ) weekly</td>
<td>( \times ) 6</td>
<td>( \times ) 6</td>
<td>( \times ) 6</td>
<td>( \times ) 6</td>
<td>( \times ) 8</td>
<td>( \times ) 8</td>
</tr>
<tr>
<td>plus monthly</td>
<td>( \times ) 4</td>
<td>( \times ) 4</td>
<td>( \times ) 2</td>
<td>( \times ) 2</td>
<td>( \times ) 2</td>
<td>( \times ) 2</td>
</tr>
<tr>
<td>Subcutaneous/percutaneous, mg</td>
<td>0.5</td>
<td>5</td>
<td>no c.f.u.</td>
<td>( 5 \times 10^7 )</td>
<td>no</td>
<td>no</td>
</tr>
</tbody>
</table>

Toxicity (mean %)

| | | | | | | |
| Cystitis | 34 | 93 | 27 | 88 | 84 | 76 (67) |
| Haematuria | 6 | 34 | 3 | 58 | 21 | 14 (23) |
| Fever | 18 | 28 | 16 | 44 | 27 | 14 (25) |
| Frequency | – | 90 | – | 51 | – | – (71) |
| Flu-like | – | 7 | – | 28 | 10 | – (15) |
| Nausea | – | 11 | – | 5 | 7 | – (8) |
| Malaise | – | 10 | – | 26 | 7 | – (14) |
| Prostatitis | 5 | 1 | 2 | 2 | 1 | – (3) |
| Epididymitis | 10 | 1 | 2 | – | – | – (6) |
| Allergic | 3 | – | – | 19 | – | – (10) |
| BCG-induced cystectomy | 1 | – | – | – | – | – (<1) |
| ‘BCG-itis’ | – | 0 | 0 | 0 | 0 | – |
| Deaths | 0 | 0 | 0 | 0 | 0 | 0 |
| Contracted bladder | – | 0 | 1 | 0 | – | 10 |

*If no tumour was found after the weekly dose, then BCG was given monthly \( \times \) 12 followed by 3-monthly \( \times \) 3, if tumour was present an additional 6 weeks of BCG was given. P, Pasteur; (C), Connaught; AF, Armand Frappier; NR, not reported.

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that the ‘gold standard’ for evaluating the efficacy of an intervention is by conducting randomized controlled trials. The present systematic review assessed world publications of randomized controlled trials comparing BCG + TUR vs TUR alone in medium/high-risk patients with Ta and T1 bladder cancer. This gives a greater statistical power of the analysis than a single trial and gives more credence to the overall findings. The results clearly indicate that adjuvant intravesical BCG provides a significant advantage over TUR alone in reducing the number of patients with tumour recurrence at 12 months after TUR and in delaying the time to recurrence.

Published reports clearly show that several different strains of BCG are applied clinically and in the present study three derivations of the BCG Pasteur strain and one Tokyo strain were used (Table 4). Different weekly doses of intravesical BCG were also used (75–150 mg), although the number of colony-forming units was only reported in two trials [14,16]. The duration of BCG instillation was 1–2 h and the schedule of BCG administration ranged considerably, from a simple once-a-week dose for 6 weeks [13,15] to the more complicated schedule involving repeated instillations for up to 20 months [17]. In addition, three trials used concomitant subcutaneous/percutaneous BCG with doses varying at least 10-fold. The few relevant studies included in this review, and the variation in BCG strain, dose and schedule, preclude any meaningful statistical analysis of these variables and clinical outcome. Clearly, further randomized trials are needed to clarify the optimum conditions for intravesical BCG administration. Some studies are addressing the effect of low-dose BCG, which may allow effective doses with fewer side-effects [36,37].

The toxicities reported with intravesical BCG were mainly cystitis, haematuria, fever and urinary frequency, and were similar to those reported previously [38]. Many patients with a contracted bladder after BCG therapy were reported in one study [17] which may reflect the prolonged treatment schedule used in that trial.

The effect of intravesical BCG on tumour progression and survival were not evaluated in the present study. Patients with a medium/high risk for tumour recurrence are not necessarily at high risk for disease progression. Indeed, a poor correlation between the number and frequency of tumour recurrence with progression to muscle invasion has been reported [39]. However, the prognostic factors associated with disease progression [40] are tumour size (>3 cm), grade and previous recurrence rate. In the present analysis, only two trials stated tumour size; one [17] reported 14% and 74% of patients with <1 cm and <5 cm tumours, respectively, and the other [12] reported 6% of patients with >3 cm tumours. In three studies [12,16,17], 36%, 35% and 23% of patients presented with low-grade tumours, respectively. Therefore, in the light of poor or unreported prognostic factors for disease progression in the included studies, it was considered inappropriate to evaluate the effect of intravesical BCG on disease progression.

The lack of reporting of patient details was a source of frustration and concern in assessing the quality of included studies. Most urologists would not consider patients with unifocal pTaG1 candidates for intravesical prophylaxis, but it was impossible to determine the proportion of pTaG1 tumours in each comparison arm in all of the included studies. Although one trial [12] indicated that all pTaG1 patients were excluded, other trials were ambiguous or provided no information. Pathological data about the extent of muscle in tumour resections and the degree of differentiation were also not described.

The evaluation of intravesical BCG on disease-specific survival requires long-term follow-up studies. Two reports on the effects of intravesical BCG after TUR vs TUR alone on survival in superficial bladder cancer have been published [20,25], both of which are follow-up studies of the randomized trial included for the present analysis [15]. One study [25] reported the 10-year follow-up and stated that BCG delays tumour progression and disease-related death. The other study [20] analysed the same patients, as a pooled group after a 15-year follow-up study, and reported that 34% of patients died from bladder cancer after this period. However, almost half of the control patients originally randomized to receive TUR alone were given intravesical BCG at various times. This complicates any interpretation of the effect of intravesical BCG + TUR against TUR alone from the published data on survival.

The AUA recently reported guidelines for the treatment of Ta and T1 bladder cancer [41]. The data for that report were derived from English-language articles identified in a Medline search from 1966 to 1998. The use of intravesical BCG or mitomycin C were recommended for preventing tumour recurrence, although no conclusive statement was possible about the delay of tumour progression. Guidance on how to decide whether to use BCG or mitomycin C was not given. The guidelines also stated that most of the studies reviewed combined subjects with low-grade stage Ta tumours, at low risk of recurrence, with T1 lesions and higher grade cancers, thus confounding data extraction. In the present review, there were no language restrictions, and seven medical and scientific databases were searched, including Medline from 1966 to 2000, with a manual search of the recent Proceedings of the American Society of Clinical Oncology. The present review represents the total available evidence from properly conducted randomized controlled trials comparing TUR alone with TUR and...
intravesical BCG in Ta and T1 bladder cancer, and clearly establishes the efficacy of intravesical BCG and consolidates the worldwide use of immunotherapy in this clinical setting. The conclusion that intravesical BCG after TUR is more effective in preventing tumour recurrence than TUR alone is in accord with that of the AUA guidelines [41]. The precise treatment schedule and the role of maintenance treatment for optimum control have yet to be defined. In addition, the relative efficacy and morbidity of BCG compared with other intravesical agents, particularly mitomycin C, needs to be determined. We are addressing this issue in a further ongoing systematic review. It is clear that more randomized controlled trials are needed in this area to provide evidence for an informed choice of agents.

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Appendix

The Medline Search Strategy.

1. randomized controlled trial.pt
2. controlled clinical trial.pt
3. randomized controlled trials/
4. random allocation/
5. double blind method/
6. single-blind method/
7. or/1–6
9. 7 not 8
10. clinical trial.pt.
11. exp clinical trials/
13. ((singl$ or doub$ or treb$ or tripl$) adj25 (blind$ or mask$)).tw.
14. placebos/
15. placebo$.tw.
16. random$.tw.
17. research design/
18. or/10–17

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19. 18 not 8
20. 19 not 9
21. comparative study/
22. exp evaluation studies/
23. follow up studies/
24. prospective studies/
25. (control$ or prospectiv$ or volunteer$).tw
26. or/2–25
27. 26 not 8
28. 26 not (9 or 20)
29. 9 or 20 or 28
30. exp bladder neoplasm/
31. exp BCG vaccine/
32. intravesic$.tw.
33. install$.tw.
34. region$.tw
35. or/31–34
36. 29 and 30 and 35