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Intravesical Bacillus Calmette-Guérin in Ta and T1 bladder cancer (Review)

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[Intervention Review]

Intravesical Bacillus Calmette-Guérin in Ta and T1 bladder cancer

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ABSTRACT

Background

Intravesical therapy with Bacillus Calmette-Guérin (BCG) aims to reduce the incidence of tumour recurrence following transurethral resection (TUR) for patients with superficial bladder cancer.

Objectives

The objective of this review was to compare the incidence of tumour recurrence after the standard therapy of transurethral resection versus transurethral resection plus intravesical Bacillus Calmette-Guérin.

Search methods

We searched the Cochrane Controlled Trials Register (March 2000), Medline (February, 2000), EMBASE (February, 2000), Cancerlit (February, 2000), Healthstar (February, 2000), Database of Abstracts of Reviews of Effectiveness (February, 2000) and the Bath Information Data Service. The Proceedings of the American Society Clinical Oncology was hand searched (1996 to 1999).

Selection criteria

Randomised or quasi-randomised trials of transurethral resection alone versus transurethral resection plus intravesical Bacillus Calmette-Guérin. Patients with Ta and T1 bladder cancer of medium or high risk of tumour recurrence, were eligible for inclusion.

Data collection and analysis

Four reviewers assessed trial quality and two abstracted the data independently. The Peto odds ratios and log hazard ratios were determined to compare the number of patients with disease recurrence at 12 months and the rate of recurrence, respectively.

Main results

Six randomised trials were included involving 585 eligible patients. There were significantly fewer patients with disease recurrence at 12 months in the BCG plus TUR group compared to those that received TUR alone (odds ratio 0.30, CI 0.21 to 0.43). The overall log hazard ratio for recurrence (-0.83, variance 0.02) indicated a significant benefit of BCG treatment in reducing tumour recurrence. Toxicities associated with BCG consisted mainly of cystitis (67%), haematuria (23%), fever (25%) and urinary frequency (71%). No BCG-induced deaths were reported.

Authors' conclusions

In patients with medium/high risk Ta or T1 bladder cancer, immunotherapy with intravesical BCG following TUR appears to provide a significant advantage over TUR alone in delaying tumour recurrence.

PLAIN LANGUAGE SUMMARY

Local treatment with Bacillus Calmette-Guérin following surgery for superficial bladder cancer reduces the risk of the cancer returning.

Worldwide, bladder cancer is common in both men and women. In most cases, the cancer occurs in the superficial layers of the bladder and can be surgically removed. However, in many people the cancer returns. Drugs placed directly into the bladder tissue following surgery are therefore often used to try to prevent the cancer recurring. Bacillus Calmette-Guérin (BCG) is a live attenuated bacterium used for immunization against tuberculosis, and is safe and effective for that purpose; it has also been licensed by the US FDA and other national regulatory agencies for use in superficial bladder-cancer treatment. The review found that BCG treatment was effective in preventing cancer recurrence following surgery. Further studies into making treatment more effective are needed.

BACKGROUND

Cancer of the urinary bladder accounts for approximately 2% of all malignant disease and is the fourth most common cancer in men and the ninth in women. The mortality rate and incidence of new cases of bladder cancer increases with age, and worldwide continues to rise by 5% to 10% every 5 years (Wingo 1995). Approximately 80% of all new bladder cancers present as superficial tumours confined to the epithelium or *lamina propria* (Young 1996). Superficial disease may consist of non-invasive tumours (Ta), tumours invading the lamina propria (T1) and carcinoma in situ (Tis). Each of these tumour types differ in prognosis. Transurethral resection (TUR) is considered to be the standard treatment for single low grade Ta tumours which have a low potential to recur (Coptcoat 1998). TUR involves endoscopic visualization via the urethra, with endoscopic resection and/or cystodiathermy to destroy the tumour. TUR is also the initial treatment for multifocal higher grade Ta tumours, T1 and Tis with the aim of preventing tumour recurrence and disease progression. However, new tumours (recurrence) will develop in 50% to 70% of these patients and, when recurrences are numerous, it becomes difficult to ablate all the tumours by this procedure. In about 10% to 30% of these cases, the tumours recur with invasion into the muscle layer of the bladder (tumour progression) resulting in a poorer prognosis because of the potential to metastasize (Raghavan 1990).

Direct instillation of selected chemotherapeutic agents into the bladder (intravesical therapy) is often used as an adjunct to TUR to improve the clinical outcome in superficial disease as defined by a reduction in tumour recurrence. Among these agents is the non-specific immune stimulant Bacillus Calmette-Guérin (BCG) first used by Morales in 1976 (Morales 1976) to treat superficial bladder cancer. Whilst the precise mechanism is unknown, intravesical BCG elicits a local host immune response against tumour cells accompanied by the release of interleukin-1, interleukin-2 and tumour necrosis factor (Bohle 1990). Intravesical BCG has been reported to reduce the number of recurrences and tumour progression in Ta and T1 disease, and induce complete remission in Tis (Lamm 1995). Side effects may occur with intravesical BCG, both locally (cystitis) and centrally (fever, malaise, nausea). They can be severe in about 5% of patients and a few fatalities have been reported. A number of different strains of BCG have been used for intravesical therapy and although some comparisons have been made in clinical trials (Fellows 1994), there are no clear guidelines as to what strain to use. A number of different doses and schedules have been used (Hudson 1987), including concomitant percutaneous administration of BCG (Lamm 1991) and questions remain as regards optimization of these parameters.

Intravesical BCG appears to be the preferred agent in the USA and Canada for prophylaxis against recurrence in Ta and T1, and treatment of Tis. The recently published clinical guidelines convened by the American Urological Association (Smith 1999), recommends the use of either intravesical BCG or mitomycin-C for Ta, T1 and Tis bladder cancer. However, studies by the European Organisation for Research and Treatment of Cancer comparing intravesical BCG against mitomycin-C in superficial bladder cancer have been inconclusive (Debruyne 1989).

Our goal was to conduct a systematic review and, where possible, a meta-analysis to evaluate and quantify the efficacy and safety of intravesical BCG following TUR compared with TUR alone. A subsequent review will be concerned with comparing intravesical BCG with other intravesically administered agents in superficial bladder cancer.

OBJECTIVES

The primary aim was to assess the efficacy of intravesically administered BCG following TUR in patients with Ta and T1 superficial bladder cancer compared to TUR alone. Efficacy is defined as tumour recurrence, as measured by the number of patients developing recurrence at 12 months and the hazard ratio. The secondary objective was to evaluate and compare adverse events in the two treatment groups. A tertiary aim was to undertake a subgroup analysis to assess the effects of BCG strain, dose and schedule on the above clinical outcomes.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised or quasi-randomised controlled clinical trials in superficial bladder cancer, comparing intravesical BCG plus TUR with TUR alone. All randomised studies in which other intravesical chemotherapeutic agents have been used but have a BCG plus TUR arm and a TUR arm were included.

Types of participants

Studies on adults with histologically confirmed Ta and T1 superficial bladder cancer. Eligible patients were those that had medium or high risk of recurrence according the criteria of Hall 1994. These criteria were as follows: Medium risk are those patients with solitary tumour at presentation and tumour recurrence at 3 months or multiple tumours at presentation and no tumour at 3 months. High risk patients are those with multiple tumours at presentation and recurrence at 3 months. To assess for the effects of TUR and intravesical BCG on tumour progression, patients should be at risk of progression based on the criteria of Kurth 1995, which were high grade, recurrent tumours greater than 3 centimetres in diameter.

Types of interventions

All randomised or quasi-randomised studies comparing intravesically administered BCG plus TUR with TUR alone. BCG of any strain, dose and schedule would be considered appropriate.

Types of outcome measures

The main outcome measure in this review was treatment efficacy, as measured by the time to recurrence after treatment, and the number of patients that recur at 12 months post-TUR. Local toxicities such as cystitis, haematuria and urinary frequency, and systemic toxicities including fever, malaise and nausea were assessed.

Search methods for identification of studies

An electronic search of Medline was undertaken to identify all relevant randomised clinical trials comparing intravesical BCG plus TUR against TUR alone in superficial bladder cancer before October 1999. The search strategy was as follows:

1. randomised controlled trial.pt

2. controlled clinical trial.pt
3. randomised controlled trials/
4. random allocation/
5. double blind method/
6. single-blind method/
7. or/1-6
8. (animal not human).sh.
9. 7 not 8
10. clinical trial.pt.
11. exp clinical trials/
12. (clin$adj25 trial$).tw.
13. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).tw.
14. placebos/
15. placebo$.tw.
16. random$.tw.
17. research design/
18. or/10-17
19. 18 not 8
20. 19 not 9
21. comparative study/
22. exp evaluation studies/
23. follow up studies/
24. prospective studies/
25. (control$ 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

Additional electronic searches of the following databases were conducted: EMBASE (Excerpta Medica Database), Cancerlit, Database of Abstracts of Reviews of Effectiveness and the Cochrane Library. Hand searching of recent Proceedings of the American Society for Clinical Oncology was also undertaken (1996 to 1999). The reference list contained within each primary reference was scrutinised for additional randomised trials. Reports of randomised trials in any language were eligible for assessment.

Data collection and analysis

Data were extracted independently by two reviewers. Discrepancies were resolved by discussion. All randomised controlled clinical trials were included for assessment. Criteria to assess concealment (randomisation) was scored according to the Cochrane guidelines: A: adequate, B: unclear, C: concealment not used. All studies that met the inclusion criteria were evaluated and analysed according to treatment allocation concealment.

Our major outcome measure in this review is tumour recurrence. A common method for expressing published time-to-event data, i.e. time to first tumour recurrence, is to plot the proportion of patients remaining free of tumour recurrence per month for the complete study period (Kaplan-Meier plot). A useful measure for summarizing this type of curve is to determine the hazard rate which gives the overall rate of tumour recurrence. In this review we are concerned with two groups of patients, namely those that have TUR plus BCG and those receiving TUR alone, and therefore need to compare the differences between the respective survival curves. One way to do this is to calculate the hazard ratio (hr) defined as the ratio of the two hazard rates. A ratio of 1 indicates that both groups have the same incidence of tumour recurrence per unit time, whereas a ratio of less than 1 indicates that the rate of recurrence is less in the treatment group (TUR plus BCG). The hazard ratio can vary from zero to infinity and the value of 1 is not the central value. Therefore to normalise the scale, the hazard ratio is log transformed (ln(hr)).

In the case of published data based on the 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 using Cox regression. Where a Kaplan-Meier plot of time to first recurrence was given, the method of Parmar (Parmar 1998) was used to estimate ln(hr). The relative risk (Parmar 1998) was used to approximate the ln(hr) when only the number of recurrences at 12 and 18 months was presented. The ln(hr) for all the included trials were combined as a weighted mean using the reciprocal of the variance (Parmar 1998).

The odds ratio for patients who have recurrent tumours at 12 months was also calculated for both the TUR plus BCG group and the TUR alone group.

RESULTS

Description of studies

The search identified 26 published trials comparing TUR plus intravesical BCG versus TUR alone. Six trials were included for analysis and were as follows: Krege 1996, Lamm 1985, Pagano 1990, Pinsky 1985, Melekos 1990 and Yamamoto 1990. Two trials (Chopin 1990 and Somogyi 1993) were non-randomised and excluded on this basis. The trial by Badalament 1987 was excluded because randomisation took place after all participants had received intravesical BCG. The randomised trial by Ibrahiem 1988 was also excluded because there was insufficient data to determine the patient's risk category. The remaining reports were excluded as they were duplicate publications of the included trials.

Risk of bias in included studies

Four trials specified the randomisation procedure used and were accepted to be truly randomised. The two other included studies stated that the trials were randomised but the methods were not reported. Based on the participant inclusion criteria, four studies were considered as including medium/high risk patients (Krege 1996; Lamm 1985; Pagano 1990; Pinsky 1985 = group 01). However, in the former two only the patients with recurrent bladder cancer were included for analysis. The remaining two trials (Melekos 1990; Yamamoto 1990) were included (group 02), although it was unclear if there was a proportion of low risk patients as part of the study

populations. A sensitivity analysis was performed to ascertain the influence of the latter two trials on the overall outcome.

Effects of interventions

The six trials included for analysis represented 585 eligible patients, 304 in the BCG plus TUR arm and 281 in the TUR alone arm. The mean age was 65 and 64 in the TUR alone group and TUR plus BCG group, respectively, with the corresponding male to female ratios of 3.9 and 3.5. The mean percentage of patients with Ta and T1 tumours were 49% and 51% (TUR) and 41% and 59% (TUR plus BCG). The maximum follow up duration for the 6 studies ranged from 14 to 36 months.

The calculated log hazard ratios and variance (BCG + TUR/TUR) for tumour recurrence are tabulated in 'Table 1'. The trials were initially divided into two groups. Group 01 trials were considered to include only medium or high risk patients for recurrence, and in group 02 trials, it was unclear if a proportion of low risk patients were included. The log hazard ratio and variance for group 01 was -0.78 with a variance of 0.02. This converts into a hazard ratio of 0.46 and indicates that intravesical BCG following TUR reduces the hazard of recurrence by 54% compared to TUR alone. The log hazard ratio and variance for group 02 was -0.98 and 0.08 which translates into a 62% reduction in the hazard with BCG. Both subgroup meta-analyses are in the same direction i.e. favouring the BCG plus TUR arm. A combined meta-analysis of all the trials produced an overall log hazard ratio of -0.83 (variance 0.02) which corresponds to a hazard ratio of 0.44. This indicates that a 56% reduction in the probability of tumour recurrence per unit time was associated with the BCG plus TUR group compared to TUR alone.

The total number of patients presenting with tumour recurrence at 12 months was 79 (26%) in the BCG plus TUR group and 144 (51%) in the TUR alone group. Odds ratio for tumour recurrence at 12 months was calculated using the numbers at risk either stated explicitly (Pagano 1990; Melekos 1990; Lamm 1985) or estimated from the maximum and minimum follow-up times assuming uniform censoring [Yamamoto 1990]. In the case of Pinsky (Pinsky 1985) and Krege (Krege 1996) the number of recurrences and cases at risk at 12 months were estimated from the Kaplan-Meier plot (Parmar 1998).

The Peto odds ratios determined for the number of patients recurring at 12 months, are illustrated graphically using a Forest plot (figure 1). The odds ratio for each trial is shown by a solid square and the horizontal line through it represents the 95% confidence intervals. The vertical central line represents an odds ratio of 1 and results falling on this line indicate no difference between the patients treated with TUR plus BCG and those treated with TUR alone. The six trials were divided into two groups as described above for the meta-analysis of the log hazard ratios.

The odds ratio and confidence intervals for group 01 (definitely medium/high risk patients) was 0.33 (95% CI 0.22,0.50) and that for 02 group (unclear if low risk patients were included) was 0.22 (95% CI 0.10 to 0.46). Both these values indicate a beneficial effect of intravesical BCG after TUR in reducing the number of tumour recurrences at 12 months. The overall Peto odds ratio for all the trials combined was 0.33 (95% CI 0.23 to 0.47) indicating that there was a 67% reduction in the incidence of tumour recurrence at 12 months in the BCG plus TUR group compared to the TUR alone group. There was no evidence of heterogeneity on combining all the trials (heterogeneity statistic, Q = 9.34, df = 5, P = 0.096), which suggests that the trials were statistically similar and that combining them for a meta-analysis was justified.

The strains of BCG, doses and schedules are illustrated in 'Table 2'. Four trials used Pasteur BCG, one Connaught and one Tokyo. Five trials used an initial 6 week treatment, whereas one (Melekos 1990) used an eight-week treatment. Krege 1996 followed the initial BCG therapy with monthly treatment for 4 months, and Yamamoto continued every 2 weeks for 6 weeks then monthly for 20 months. Pagano followed their 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 varied from 75 mg (n = 1), 80 mg (n = 1), 120 mg (n = 3) and 150 mg (n = 1). However, the more important value for the colony forming unit (CFU), which represents the biological activity of the intravesically administered BCG rather than the dry weight in milligrams, was only reported in two studies (Melekos 1990; Pagano 1990). The duration of instillation was either for one hour (Krege 1996) or two hours and three trials gave concomitant intradermal BCG with doses of 0.5 mg (Krege 1996), 5 mg (Lamm 1985) and 5 x 10(7) CFU (Pinsky 1985). The wide range of doses, schedules and the different strains of BCG used in such a small number of studies, precludes any informative analysis as to the association of these variables with outcome.

Only the side effects induced with intravesical BCG were reported in the included trials ('Table 3') although Pagano 1990 states a 2% incidence of orchidoepididymitis with 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.

DISCUSSION

Superficial transitional cell carcinoma of the bladder has the propensity to recur in 50% to 70% of patients. This means that frequent follow-up with cystoscopy is required to monitor patients and remove any recurrent tumour if present. This not only decreases the quality of life for patients with this disease, but also has considerable cost implications for health care. Interventions that can reduce tumour recurrence would be of enormous benefit. The results of this present meta-analysis of available published randomised trials, indicates that immunotherapy with intravesical BCG, as an adjunct to TUR, is significantly more effective in reducing the number of patients with tumour recurrence at 12 months and delaying the time to recurrence, compared to TUR alone.

It was originally intended to evaluate the effect of intravesical BCG on disease progression and survival in patients with superficial bladder cancer. However, in order to assess disease progression, it is appropriate that patients included in the selected trials should be at high risk of progression. The inclusion criterion for the six trials in this review was based on medium/high risk for tumour recurrence (Hall 1994) which does not necessarily indicate these patients were at high risk of progression. Kurth 1995 evaluated prognostic factors affecting progression in 576 patients with superficial bladder cancer and found that high tumour grade, tumour size (> 3 cm) and previous recurrence were powerful predictors. Only two trials in the present report stated tumour size. Yamamoto 1990 reported 14% and 74% of patients with < 1 cm and < 5 cm tumours, respectively, and Krege 1996 reported only 6% of patients with tumours > 3 cm. Four of the six studies reported tumour grade. In

the studies by Krege 1996, Melekos 1990 and Yamamoto 1990, 36%, 35% and 23% of patients presented with G1, respectively. Although all trials, except for that of Lamm 1985, reported data for disease progression, it was considered that this review should concentrate on tumour recurrence due to the poor or inconclusive data for progression risk.

There are two reports on the effect of intravesical BCG plus TUR on survival compared with TUR alone and both are extensions of the Pinsky 1985 trial. Herr 1995 details the results on a ten-year follow up and Cookson 1997 reports after 15 years. In the former paper, it is stated that control patients (TUR alone) with recurring tumours were eligible to receive BCG, which makes interpretation of progression and survival data difficult. This was re-iterated in the later paper by Cookson 1997.

The American Urological Association recently reported guidelines for the treatment of Ta and T1 bladder cancer (Smith 1999). The data for this report were derived from English articles identified in a MEDLINE search from 1966 to 1998. The use of intravesical BCG or mitomycin C were recommended for prevention of tumour recurrence, although no conclusive statement could be made regarding the delay of tumour progression. Guidance on how to decide whether to use BCG or mitomycin C was not given. It was also stated that most of the studies they reviewed, combined subjects with low grade stage Ta tumours, that are of low risk for recurrence, with T1 lesions and higher grade cancers, confounding data extraction. In the present review, no language restrictions were made, and seven medical and scientific databases were searched, including MEDLINE from 1966 to 2000, and hand searching of the recent proceedings of the American Society of Clinical Oncology was undertaken. Our review represents the total available evidence from properly conducted randomised controlled trials comparing TUR alone versus TUR plus intravesical BCG in Ta and T1 bladder cancer. Our conclusion, that intravesical BCG following TUR is more effective in preventing tumour recurrence compared to TUR alone, is in accordance with that of Smith 1999. We will address the relative clinical efficacy and morbidity of intravesical BCG compared to mitomycin C in a subsequent review.

AUTHORS' CONCLUSIONS

Implications for practice

The evidence from the RCTs clearly indicates that intravesical BCG following TUR is effective for the prophylaxis of tumour recurrence in Ta and T1 bladder cancers. This intervention is associated with local and systemic side effects, but the majority are manageable. We would therefore advocate that intravesical BCG should be routinely considered following TUR for the prophylaxis of tumour recurrence in patients with medium to high risk Ta and T1 bladder cancer.

Implications for research

We suggest that RCTs of sufficient power are undertaken to establish the optimal strain, dose and schedule for intravesical BCG administration. This may allow an efficacious dose to be given with fewer side-effects. Uniformity should be given to the CFU dose, which reflects the 'active ' component, rather than the weight (mg) of BCG since there appears to be a poor correlation between the two variables (van der Meijden APM 1999). The relative efficacy of intravesical BCG compared with other intravesical agents in the treatment of superficial bladder cancer needs to be determined. Our group will focus on this aspect in another review.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Krege 1996

Methods	randomized by permuted block
Participants	224 Ta, T1, G1 -3 (no pTa G1 tumours)
Interventions	TUR vs TUR + BCG 122: 102 Connaught intraves. 120mg 1 hr weekly X 6 then monthly x 4 plus 0.5mg subcut.
Outcomes	recurrence Progression rate/number BCG toxicity
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Lamm 1985

Methods	randomized by closed envelope
Participants	57 mean stage 1.4 and 1.8, mean No. previous recurrences 1.3
Interventions	TUR vs TUR + BCG 27: 30 Pasteur intraves. 120mg weekly X 6 plus 5mg percut.
Outcomes	recurrence rate/number /time BCG toxicity

Lamm 1985 *(Continued)*

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Melekos 1990

Methods	randomized method not stated
Participants	100 primary or recurrent with either single or multiple Ta, T1 GI -III
Interventions	TUR vs TUR + BCG 33: 67 Pasteur intraves. 150mg 2 hr weekly X 8
Outcomes	tumour response recurrence- rate/number/time progression - number BCG toxicity
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Pagano 1990

Methods	randomized method not stated
Participants	133 multiple (> 3) papillary TA, T1
Interventions	TUR vs TUR + BCG 33: 67 Pasteur intraves. 75mg 2 hr weekly X 6
Outcomes	tumour response recurrence- rate/number progression- number/rate BCG toxicity
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Pinsky 1985

Methods	randomized by permuted block
Participants	86 - multiple tumours papilloma, T1, some with Tis
Interventions	TUR vs TUR + BCG 43: 43 Armand Frappier intraves. 120mg 2 hr weekly X 6 plus pecut.
Outcomes	recurrence No./mnth and time progression- time BCG toxicity
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Yamamoto 1990

Methods	randomized by closed envelope method
Participants	44 -- 22 pTA, 22 pT1, G 1 - 3, single tumour 30, multiple 14
Interventions	TUR vs TUR + BCG 21: 23 Tokyo intraves. 80mg weekly X 6, 2 weekly x 12, mnthly x 20
Outcomes	recurrence- rate progression number BCG toxicity
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Badalament 1987	Both treatment and control groups received BCG before randomisation
Bassi 1990	Repeat report of trial (Pagano 1990)
Camacho 1990	Repeat report of trial (Pinsky 1985)

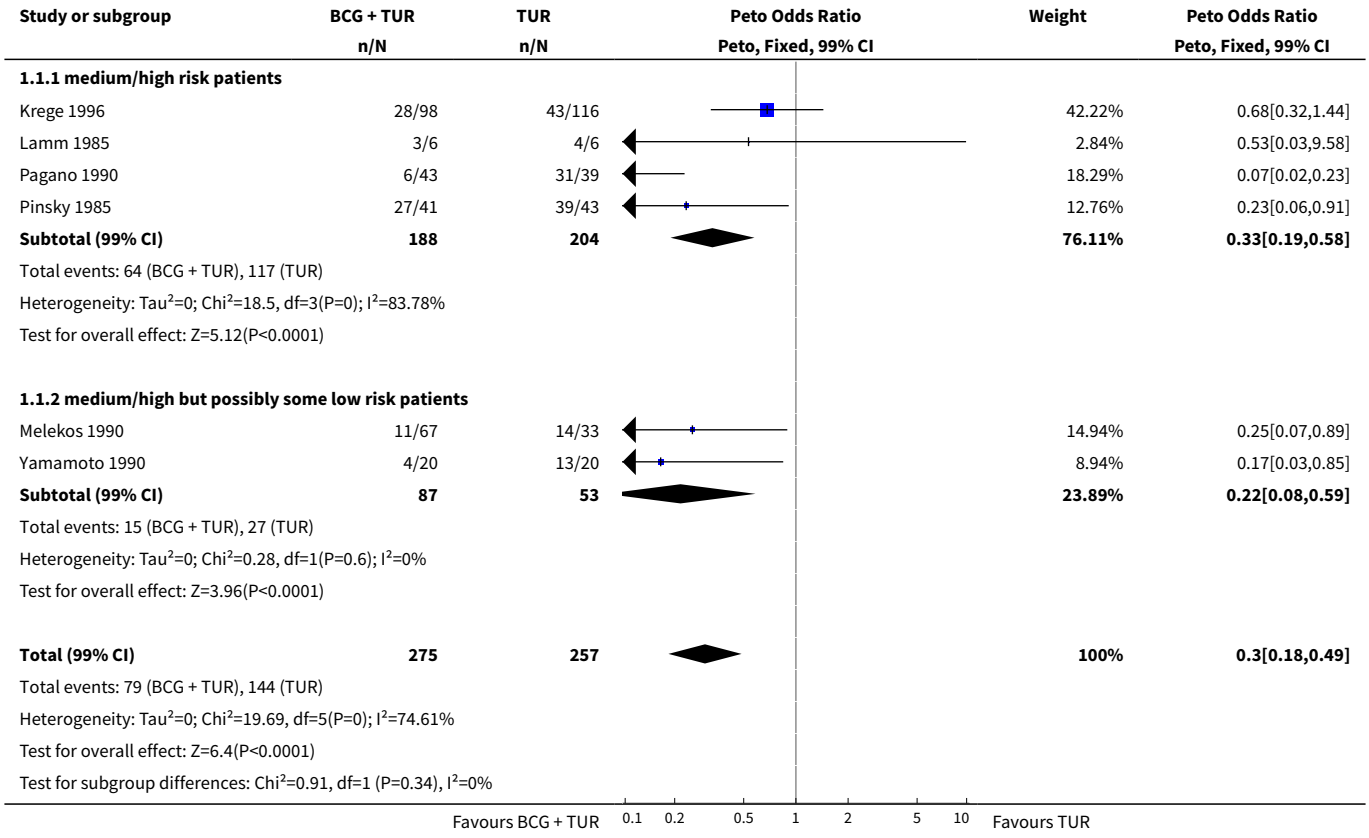
Study	Reason for exclusion
Chopin 1990	Non-randomised
Cookson 1997	Repeat report of trial (Pinsky 1985)
Herr 1983	Repeat report of trial (Pinsky 1985)
Herr 1985	Repeat report of trial (Pinsky 1985)
Herr 1986	Repeat report of trial (Pinsky 1985)
Herr 1988	Repeat report of trial (Pinsky 1985)
Herr 1995	Repeat report of trial (Pinsky 1985)
Ibrahiem 1988	Insufficient data to classify risk for recurrence
Lamm 1980	Repeat report of trial (Lamm 1985)
Lamm 1981	Repeat report of trial (Lamm 1985)
Lamm 1982a	Repeat report of trial (Lamm 1985)
Lamm 1982b	Repeat report of trial (Lamm 1985)
Pagano 1989	Repeat report of Pagano 1990
Pagano 1991	Repeat report of Pagano 1990
Pinsky 1982	Repeat report of trial (Pinsky 1985)
Rubben 1990	Repeat report of Krege 1996
Somogyi 1993	Non-randomised trial.

DATA AND ANALYSES

Comparison 1. BCG + TUR versus TUR

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 number of patients recurring at 12 months	6	532	Peto Odds Ratio (Peto, Fixed, 99% CI)	0.30 [0.18, 0.49]
1.1 medium/high risk patients	4	392	Peto Odds Ratio (Peto, Fixed, 99% CI)	0.33 [0.19, 0.58]
1.2 medium/high but possibly some low risk patients	2	140	Peto Odds Ratio (Peto, Fixed, 99% CI)	0.22 [0.08, 0.59]

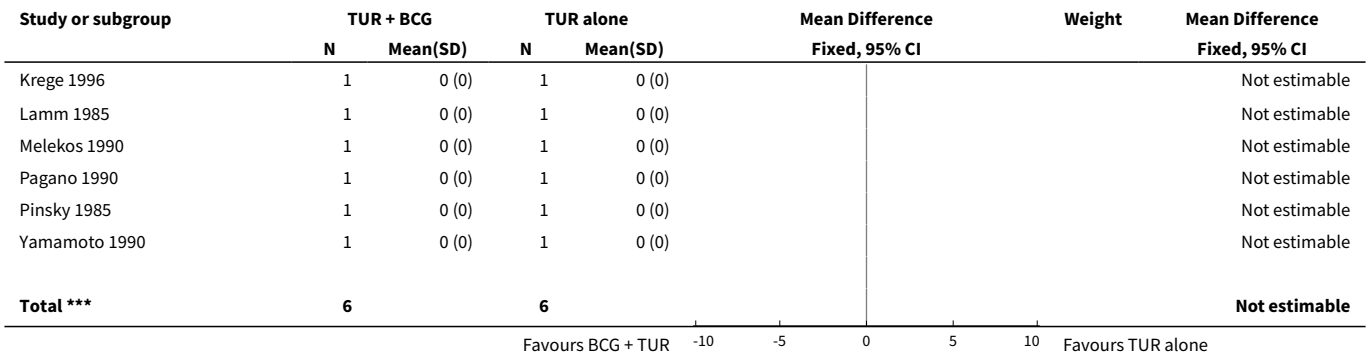
Analysis 1.1. Comparison 1 BCG + TUR versus TUR, Outcome 1 number of patients recurring at 12 months.

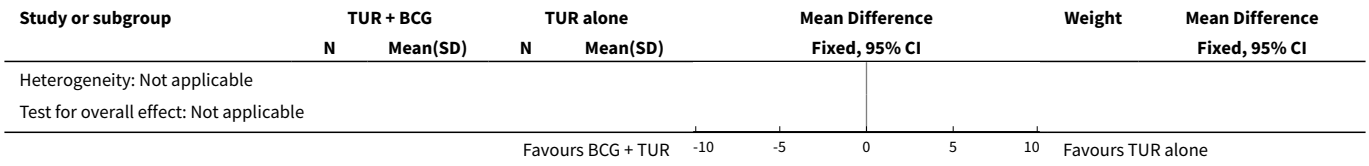


Comparison 2. recurrence-free survival

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ln(HR)	6	12	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 2.1. Comparison 2 recurrence-free survival, Outcome 1 ln(HR).





ADDITIONAL TABLES

Table 1. The log hazard ratios with variances

Trial	ratio BCG/Control	variance
(Medium/High risk Patients)		
Krege 1996	- 0.482	0.058
Lamm 1985	- 0.613	0.462
Pagano 1990	- 1.740	0.150
Pinsky 1985	- 0.742	0.049
Subgroup Meta-analysis	- 0.7827	0.0215
Medium/high risk but unclear if some low risk patients included		
Melekos 1990	- 0.818	0.099
Yamamoto 1990	- 1.520	0.323
Subgroup Meta-analysis	- 0.9827	0.0758
Overall Meta -analysis: Weighted Sum of ln(HR)	- 0.8269	0.0168

Table 2. Strain, Dose and Schedule of BCG administration

	Krege 1996	Lamm 1985	Melekos 1990	Pagano 1990	Pinsky 1985	Yamamoto 1990
Strain	Connaught	Pasteur	Pasteur	Pasteur	Pasteur (Armand Frappier	Tokyo
weekly dose (mg)	120	120	150	75	120	80
CFU	not given	not given	6 x 10 (8)	4-5 x 10 (8)	not given	not given

Table 2. Strain, Dose and Schedule of BCG administration *(Continued)*

Duration of instillation (h)	1	2	2	2	2	2
Schedule	weekly x 6, mnthly x 4	weekly x 6	weekly x 8	weekly x 6, (if no tumour = mthly x 12 then 3 mthly x 3, if tumour present = additional weekly x 6)	weekly x 6	weekly x 6, every 2 weeks x 6, mthly x 20
Concomitant intradermal or percutaneous BCG	0.5mg	5mg	no	no	5 X 10 (7)	no

Table 3. BCG-Induced Toxicities (%)

	Krege 1990	Lamm 1985	Melekos 1990	Pagano 1990	Pinsky 1985	Yamamoto 1990	Mean (%)
cystitis	34	93	84	27	88	76	67
Haematuria	6	34	21	3	58	14	23
Fever	18	28	27	16	44	14	25
Frequency	-	90	-	-	51	-	71
Flu-like	-	7	10	-	28	-	15
Nausea	-	11	7	-	5	-	8
Malaise	-	10	7	-	26	-	14
Prostatitis	5	1	1	2	2	-	3
Epididymitis	10	1	-	2	-	-	6
allergic	3	-	-	-	19	-	10
Contracted bladder	-	0	-	1	0	10	2
BCG-Sepsis	-	0	-	0	0	-	0
Deaths	0	0	0	0	0	0	0

WHAT'S NEW

Date	Event	Description
4 February 2010	Amended	We changed a factual error in the 'plain language summary' that BCG caused tuberculosis. The corrected sentence reads "Bacillus Calmette-Guérin (BCG) is a live attenuated bacterium used for immunization against tuberculosis, and is safe and effective for that purpose; it has also been licensed by the US FDA and other national regulatory agencies for use in superficial bladder-cancer treatment."

HISTORY

Protocol first published: Issue 2, 2000
Review first published: Issue 4, 2000

Date	Event	Description
30 May 2008	Amended	Converted to new review format.
4 July 2000	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Mike Shelley: primary contact, concept, protocol, literature search, data extraction and translations, quality assessment, exploratory analysis, draft manuscript

Jon Court: data extraction, manuscript review, statistical analysis

Howard Kynaston: protocol review, quality assessment, manuscript review, analysis review

Timothy Wilt: protocol review, translations, review analysis, manuscript review

Reg Fish: concept, literature search

Malcolm Mason: alternative contact, protocol review, translations, quality assessment, review analysis, review manuscript

DECLARATIONS OF INTEREST

None.

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External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Adjuvants, Immunologic [*therapeutic use]; Administration, Intravesical; BCG Vaccine [*therapeutic use]; Neoplasm Recurrence, Local [*prevention & control]; Neoplasm Staging; Randomized Controlled Trials as Topic; Transurethral Resection of Prostate; Urinary Bladder Neoplasms [pathology] [*prevention & control]

MeSH check words

Female; Humans; Male