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Intravesical Bacillus Calmette-Guérin with interferon-alpha versus intravesical Bacillus Calmette-Guérin for treating non-muscle-invasive bladder cancer (Review)

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[Intervention Review]

Intravesical Bacillus Calmette-Guérin with interferon-alpha versus intravesical Bacillus Calmette-Guérin for treating non-muscle-invasive bladder cancer

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ABSTRACT

Background

Despite local therapies, commonly transurethral resection (TUR) followed by adjuvant treatments, non-muscle-invasive bladder cancer (NMIBC) has a high rate of recurrence and progression. Intravesical Bacillus Calmette-Guérin (BCG) has been shown to reduce recurrence and progression in people with NMIBC following TUR, however many people do not respond to treatment, have recurrence shortly after, or cannot tolerate standard-dose therapy. The potential for synergistic antitumour activity of interferon (IFN)-alpha (α) and BCG provides some rationale for combination therapy for people who do not tolerate or respond to standard-dose BCG therapy.

Objectives

To assess the effects of intravesically administered BCG plus IFN- α compared with BCG alone for treating non-muscle-invasive bladder cancer.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 8, 2016), MEDLINE (OvidSP) (1946 to 2016), Embase (OvidSP) (1974 to 2016), ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) as well as reference lists of retrieved articles and handsearched abstract proceedings of relevant conferences for the past three years. We applied no language restrictions. The date of last search of all databases was 25 August 2016.

Selection criteria

We included randomised controlled trials (RCTs) and pseudo-randomised trials assessing intravesically administered BCG plus IFN- α versus BCG alone in adults of either gender with histologically confirmed Ta and T1 superficial bladder cancer, with or without carcinoma in situ, treated with TUR.

Data collection and analysis

Two review authors independently assessed study eligibility, extracted data, and assessed the risk of bias of included studies. We used Review Manager 5 for data synthesis and employed the random-effects model for meta-analyses. For prespecified outcomes, where we

were unable to derive time-to-event information (e.g. time-to-recurrence), we assessed dichotomous outcomes (e.g. recurrence) instead. We assessed the quality of the evidence for the main comparisons using the GRADE approach.

Main results

We included five RCTs involving a total of 1231 participants with NMIBC in this review. Due to poor reporting, the risk of bias in the included studies was often unclear. We assessed the studies under two main comparisons: intravesical BCG plus IFN- α versus intravesical BCG alone (four RCTs), and intravesical BCG alternating with IFN- α versus intravesical BCG alone (one RCT).

Intravesical BCG plus IFN- α versus intravesical BCG alone (four RCTs): We observed no clear difference between BCG plus IFN- α and BCG alone for recurrence (average risk ratio (RR) 0.76, 95% confidence interval (CI) 0.44 to 1.32; 4 RCTs; 925 participants; very low-quality evidence) or progression (average RR 0.26, 95% CI 0.04 to 1.87; 2 RCTs; 219 participants; low-quality evidence). The included RCTs did not report on the other primary outcome of this review, discontinuation of therapy due to adverse events. Regarding secondary outcomes, we observed no clear difference for disease-specific mortality (RR 0.38, 95% CI 0.05 to 3.05; 1 RCT; 99 participants; very low-quality evidence). Two RCTs reporting contradictory findings for adverse events could not be pooled due to variation in definitions. There were no data from the included RCTs on time-to-death or disease-specific quality of life.

Intravesical BCG alternating with IFN- α versus intravesical BCG alone (one RCT): We observed shorter time-to-recurrence for participants in the BCG alternating with IFN- α group compared with the BCG alone group (hazard ratio (HR) 2.86, 95% CI 1.98 to 4.13; 1 RCT; 205 participants; low-quality evidence), but no clear differences in time-to-progression (HR 2.39, 95% CI 0.92 to 6.21; 1 RCT; 205 participants; low-quality evidence) and discontinuation of therapy due to adverse events (RR 2.97, 95% CI 0.31 to 28.09; 1 RCT; 205 participants; low-quality evidence). Regarding secondary outcomes, there were no clear differences between the BCG alternating with IFN- α and BCG alone groups for disease-specific mortality (HR 2.74, 95% CI 0.73 to 10.28; 1 RCT; 205 participants; low-quality evidence), time-to-death (overall survival) (HR 1.00, 95% CI 0.68 to 1.47; 1 RCT; 205 participants; low-quality evidence), or systemic or local adverse events (RR 1.65, 95% CI 0.41 to 6.73; 1 RCT; 205 participants; low-quality evidence). There were no data on disease-specific quality of life.

Authors' conclusions

We found low- to very low-quality evidence suggesting no clear differences in recurrence or progression with BCG plus IFN- α compared with BCG alone for people with NMIBC; there was no information to determine the effect on discontinuation of therapy due to adverse events. Low-quality evidence suggests BCG alternating with IFN- α compared with BCG alone may increase time-to-recurrence, however low-quality evidence also suggests no clear differences for time-to-progression or discontinuation of therapy due to adverse events.

Additional high-quality, adequately powered trials using standardised instillation regimens and doses of both BCG and IFN- α , reporting outcomes in subgroups stratified by patient and tumour characteristics, and on long-term outcomes related not only to recurrence but also to progression, discontinuation due to adverse events, and mortality may help to clarify the ideal treatment strategy and provide a more definitive result.

PLAIN LANGUAGE SUMMARY

Local treatment of non-muscle-invasive bladder cancer with Bacillus Calmette-Guérin with or without interferon-alpha

Review question

We reviewed the evidence on the effects of local treatment of the bladder with Bacillus Calmette-Guérin (BCG) and interferon (IFN)-alpha (α) for cancer of the superficial layers of the bladder (known as non-muscle-invasive bladder cancer).

Background

Bladder cancer is a common cancer worldwide. Bladder cancer that is non-muscle invasive is often treated with resection (removal by surgery), but it has a high risk of recurring and progressing to more invasive disease with that treatment alone. Bacillus Calmette-Guérin is a treatment that is commonly administered into the bladder after resection to reduce the risk of recurrence and progression. Some non-randomised studies have shown that adding IFN- α to BCG may further reduce these risks. We aimed to compare the effects of BCG with IFN- α versus BCG alone administered into the bladder in the treatment of people with non-muscle-invasive bladder cancer.

Study characteristics

The evidence is current to 25 August 2016. We included five studies with a total of 1231 participants with non-muscle-invasive bladder cancer. Four studies compared BCG given together with IFN- α versus BCG alone. One study compared BCG alternating with IFN- α versus BCG alone. The follow-up period in the studies ranged from two months to nearly 20 years.

Key results

BCG combined with IFN- α (four studies): We found very low-quality evidence showing no clear difference in recurrence (four studies involving 925 participants) or progression (two studies involving 219 participants) between participants who received BCG combined with IFN- α and those who received BCG alone. None of the studies reported on the important outcome of stopping treatment due to adverse events. There

Intravesical Bacillus Calmette-Guérin with interferon-alpha versus intravesical Bacillus Calmette-Guérin for treating non-muscle-invasive bladder cancer (Review)

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was also very low-quality evidence showing no clear difference between groups for cancer-specific mortality (one study, 99 participants). There were mixed findings for adverse events (two studies, 120 and 670 participants, respectively).

BCG alternating with IFN- α (one study): We found low-quality evidence showing a higher probability of recurrence when BCG was alternated with IFN- α compared with BCG alone (study involving 205 participants). We also found low-quality evidence that showed no clear difference in the probability of progression, risk of stopping treatment due to adverse events, and cancer-specific mortality between those participants receiving BCG alternating with IFN- α and those receiving BCG alone (one study involving 205 participants). There was also no clear difference between groups for overall survival or adverse events (one study involving 205 participants).

None of the five studies reported on quality of life of the participants.

Quality of the evidence

As the included studies were often poorly conducted or reported, we rated the quality of the evidence as low overall. Further research is likely to have an important impact on our confidence in the accuracy of results.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Intravesically administered BCG combined with IFN- α compared to intravesically administered BCG alone for treating non-muscle-invasive bladder cancer

Intravesically administered BCG combined with IFN- α compared to intravesically administered BCG alone for treating non-muscle-invasive bladder cancer

Patient or population: patients with non-muscle invasive bladder cancer

Intervention: BCG combined with IFN- α

Comparison: BCG alone

Outcomes	Nº of participants (studies)	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with intravesically administered BCG alone	Risk difference with intravesically administered BCG combined with IFN- α
Recurrence Follow-up: median 38.3 to 60 months	925 (4 RCTs)	⊕⊕⊕⊕ VERY LOW ^{1 2 3}	RR 0.76 (0.44 to 1.32)	Study population 342 per 1000	82 fewer per 1000 (191 fewer to 109 more)
Progression Follow-up: median 38.3 to 60 months	219 (2 RCTs)	⊕⊕⊕⊕ LOW ^{4 5}	RR 0.26 (0.04 to 1.87)	Study population 124 per 1000	92 fewer per 1000 (119 fewer to 108 more)
Discontinuation of therapy due to adverse events - not measured	-	-	-	-	-
Disease-specific mortality Follow-up: median 60 months	99 (1 RCT)	⊕⊕⊕⊕ VERY LOW ^{6 7}	RR 0.38 (0.05 to 3.05)	Study population 87 per 1000	54 fewer per 1000 (83 fewer to 178 more)
Disease-specific quality of life - not measured	-	-	-	-	-

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

BCG: Bacillus Calmette-Guérin; **CI:** confidence interval; **IFN- α :** interferon-alpha; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

¹Downgraded for study limitations (-1): high risk of bias: 'blinding of participants and personnel' (Nepple 2010); 'blinding of outcome assessment' (Nepple 2010); 'selective reporting' (Bercovich 1995; Minich 2009; Nepple 2010); 'other bias' (Bercovich 1995).

²Downgraded for heterogeneity ($I^2 = 74\%$).

³Downgraded for imprecision (-1): wide 95% confidence interval around the pooled estimate which includes no effect.

⁴Downgraded for study limitations (-1): high risk of bias: 'selective reporting' (Minich 2009).

⁵Downgraded for imprecision (-1): wide 95% confidence interval around the pooled estimate which includes no effect.

⁶Downgraded for study limitations (-1): unclear risk of bias overall (Chiong 2011).

⁷Downgraded for imprecision (-2): wide 95% confidence interval around the pooled estimate which includes no effect, small sample size and few events.

Summary of findings 2. Intravesically administered BCG alternating with IFN- α compared to intravesically administered BCG alone for treating non-muscle-invasive bladder cancer

Intravesically administered BCG alternating with IFN- α compared to intravesically administered BCG alone for treating non-muscle-invasive bladder cancer

Patient or population: patients with non-muscle invasive bladder cancer

Intervention: BCG alternating with IFN- α

Comparison: BCG alone

Outcomes	Nº of participants (studies)	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with intravesically administered BCG alone	Risk difference with intravesically administered BCG alternating with IFN- α
Time-to-recurrence Follow-up: median 8.6 to 10.3 years	205 (1 RCT)	⊕⊕⊕⊖ LOW ^{1 2}	HR 2.86 (1.98 to 4.13)	Study population 431 per 1000	370 more per 1000 (242 more to 471 more)
Time-to-progression Follow-up: median 8.6 to 10.3 years	205 (1 RCT)	⊕⊕⊕⊖ LOW ^{1 3}	HR 2.39 (0.92 to 6.21)	Study population 59 per 1000	76 more per 1000 (5 fewer to 255 more)

Discontinuation of therapy due to adverse events	205 (1 RCT)	⊕⊕⊕⊕ LOW ^{1 3}	RR 2.97 (0.31 to 28.09)	Study population	
Follow-up: median 8.6 to 10.3 years				10 per 1000	19 more per 1000 (7 fewer to 266 more)
Disease-specific mortality	205 (1 RCT)	⊕⊕⊕⊕ LOW ^{1 3}	HR 2.74 (0.73 to 10.28)	Study population	
Follow-up: median 8.6 to 10.3 years				29 per 1000	49 more per 1000 (8 fewer to 235 more)
Disease-specific quality of life - not measured	-	-	-	-	-

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

BCG: Bacillus Calmette-Guérin; **CI:** confidence interval; **HR:** hazard ratio; **IFN-α:** interferon-alpha; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

¹Downgraded for study limitations (-1): high risk of bias: 'blinding of participants and personnel', 'blinding of outcome assessment' ([Jarvinen 2015](#)).

²Downgraded for imprecision (-1): wide 95% confidence interval.

³Downgraded for imprecision (-1): wide 95% confidence interval around the pooled estimate which includes no effect.

BACKGROUND

Description of the condition

Urothelial carcinoma of the bladder is the 11th most common cancer worldwide, the seventh most common cancer in men, and the 17th most common cancer in women (Burger 2013; Ferlay 2013). It is the most common cancer of the urinary system, accounting for more than 90% of newly diagnosed bladder cancer cases. In 2012, there were over 429,000 new cases of bladder cancer diagnosed and more than 165,000 deaths due to bladder cancer across the globe (Cancer Research UK 2014; Ferlay 2013); the median age at diagnosis is 65 to 70 years (Kirkali 2005). The incidence and mortality rates of urothelial bladder cancer vary across countries, being more common in high-income regions, such as Northern America and Western Europe; in 2012, global incidence and mortality rates were 5.3 per 100,000 and 1.9 per 100,000, respectively (Ferlay 2013). The worldwide prevalence of bladder cancer is estimated at 2.7 million; due to its high frequency and relapsing nature, bladder cancer places a large burden on healthcare systems, particularly in high-income communities, however, with global changes in exposure to risk factors, and with growing and ageing populations, this burden is also increasing in low- and middle-income regions (Ploeg 2009).

At presentation, most people with bladder cancer (75% to 85%) are found to have non-muscle-invasive bladder cancer (NMIBC), in which disease is confined to the superficial layers of the bladder (the mucosa and lamina propria) (Burger 2013). According to the tumour, node, metastasis (TNM) classification system, defined by the Union for International Cancer Control, disease of the mucosa is classified as stage Ta, while disease invading the lamina propria is classified as stage T1; flat high-grade tumours confined to the mucosa are classified as carcinoma in situ (CIS) (Kirkali 2005; Lopez-Beltran 2004; Sobin 2009).

Approximately 70%, 20%, and 10% of people with NMIBC present with Ta, T1, and CIS lesions, respectively (Kirkali 2005; van Rhijn 2009). Although described as non-invasive, NMIBC lesions have a high rate of recurrence and progression despite local therapies. For 15% to 25% of people presenting with newly diagnosed bladder cancer, muscle invasion is present (involving the muscular layer of the bladder; known as stage T2), and despite radical therapy, such as radiotherapy or surgery, outcomes can be poor (Burger 2013). Progression from NMIBC to muscle-invasive disease is associated with the risk of metastatic spread, and accordingly, a worse prognosis.

Risk factors for urothelial bladder cancer can be differentiated into environmental and inherited genetic predispositions, with each risk factor influencing incidence and pathophysiology differently (Burger 2013). Cigarette smoking and occupational exposure to chemical carcinogens have been strongly linked with environmental risks of bladder cancer (Brennan 2000; Freedman 2011). Smoking is recognised as the most important risk factor, estimated to account for 50% of tumours (Freedman 2011), while occupational exposure to aromatic amines, polycyclic aromatic hydrocarbons, and chlorinated hydrocarbons (often in industrial areas processing paint, dye, metal, and petroleum products), is estimated to account for a further 20% of cases (Burger 2013; Vineis 1991). Other risk factors are less consistently reported, and some remain controversial, including dietary factors (i.e. consumption of alcohol, coffee, and tea), and some medical conditions (Burger

2013; Chu 2013); gender, race, and socioeconomic status have been implicated in the genesis of bladder cancer (Burger 2013). Evidence increasingly highlights the importance of genetic factors in influencing bladder cancer risk; for example, family history of bladder cancer has been shown to be a potential risk factor for offspring bladder cancer (Pina 2001).

Description of the intervention

While the management of NMIBC varies internationally, transurethral bladder tumour resection (TUR) is used for the initial diagnosis and treatment (Babjuk 2017; Brausi 2011). Following initial diagnosis and TUR management, prognosis depends on a number of pathological and clinical factors; recurrence at three months for people with multifocal tumours is estimated to range from 7% to 46% (Brausi 2002). The European Organisation for Research and Treatment of Cancer (EORTC) has summarised what are believed to be six of the most important prognostic factors, including: the number of tumours; prior recurrence rate; tumour size; tumour stage; tumour grade; and the presence of concomitant CIS. Based on these factors, 'risk scores' can be calculated, and patients classified as at low, intermediate, and high risk of recurrence and progression, with risks of recurrence at five years ranging from 31% to 78%, and risks of progression ranging from 0.8% to 45% (Babjuk 2017; Sylvester 2006).

To overcome the problems of tumour recurrence, progression in NMIBC, or both, intravesical antitumour agents (chemotherapy or immunotherapy) may be given as adjunct treatment after TUR (Whelan 2007). In people with Ta or T1 bladder cancer, an immediate postoperative chemotherapeutic instillation following TUR may be recommended (Babjuk 2017; Brausi 2011), and has been associated with a 12% absolute reduction in tumour recurrence (Sylvester 2004). No agent has been shown to be of superior efficacy; mitomycin C, epirubicin, and doxorubicin have all shown beneficial effects (Sylvester 2004). The benefit from immediate postoperative chemotherapeutic instillation is less clear for intermediate- or high-risk disease (Brausi 2011).

A commonly used intravesical immunotherapeutic agent for NMIBC, first described by Morales et al in 1976, is *Bacillus Calmette-Guérin* (BCG) (Morales 1976). A Cochrane review (that is currently being updated) assessing intravesical BCG for Ta and T1 bladder cancer found that BCG instillation after TUR reduced disease recurrence at 12 months compared with TUR alone (Shelley 2000). The review concluded that in people with medium- to high-risk Ta or T1 bladder cancer, intravesical BCG following TUR has a significant advantage over TUR alone in delaying tumour recurrence (Shelley 2000). Intravesical BCG is now commonly used in the treatment of NMIBC; in people with intermediate-risk disease, BCG induction (e.g. a course of six weekly instillations) and BCG maintenance (of up to three years), or intravesical chemotherapy (particularly mitomycin C), is recommended; BCG induction and maintenance is recommended for people with high-risk disease (Babjuk 2017; Brausi 2011; Shelley 2010).

Intravesical BCG causes a significant reduction in the incidence of tumour recurrence and disease progression in people with NMIBC, but a large proportion of patients do not respond to treatment, have recurrence shortly after, or cannot tolerate standard-dose therapy, as BCG immunotherapy may be associated with both local and systemic toxicities (Shelley 2000). In the Shelley 2000 Cochrane review, toxicities included cystitis (67% of participants),

haematuria (23%), fever (25%), and urinary frequency (71%); no BCG-induced deaths were reported across the six included randomised trials. A recent randomised trial reported that of 1316 participants treated with BCG, 70% experienced local or systemic adverse events, and 8% stopped treatment due to such adverse events (Brausi 2014). Due to these limitations, other agents, including interferon (IFN)-alpha (α) to be used concomitantly with BCG, have been evaluated.

Interferon-alpha is a type I IFN cytokine that includes at least 13 subtypes that share the same receptor system and have similar function (Ferrantini 2007; Rizza 2010). Interferon-alpha was first described for its antiviral activity, and has a long history of use in viral diseases (such as hepatitis C), and in clinical oncology, as a treatment for a variety of malignancies (including chronic myeloid leukaemia, some B- and T-cell lymphomas, renal cell carcinoma, and malignant melanoma) (Ferrantini 2007; Rizza 2010). The antitumour effects of IFN- α are attributed to its ability to induce multiple biological effects, which include: inducing or promoting apoptosis, or both; inhibiting cell growth; and promoting the differentiation and activity of host immune cells (Ferrantini 2007; Rizza 2010).

How the intervention might work

The efficacy of intravesical BCG in NMIBC is due to a non-specific immune response, including the local infiltration of macrophages, T lymphocytes (including T helper (Th) cells), and natural killer cells, and the subsequent production of Th1 cytokines (such as IFN-gamma (γ), interleukin (IL)-2, IL-12, and tumour necrosis factor (TNF)- α) (Schenkman 2004). Helper T1 cells ultimately lead to the destruction, and thus treatment of urothelial carcinoma of the bladder (Schenkman 2004). A small animal study demonstrated that a single instillation of intravesical BCG could disseminate to the para-aortic lymph nodes, causing the priming of IFN- γ , producing T cells in mice (Biot 2012). Repeated instillations of BCG were shown to elicit a more robust T-cell response in bladder cells (Biot 2012).

Helper T2 cytokines counteract the effects of Th1 cytokines. Interferon-alpha has been shown to increase production of IFN- γ , IL-12, and TNF- α in BCG-stimulated cells of people with bladder cancer in vitro, while decreasing BCG-mediated production of Th2 cytokines (Luo 1999). This observation and other similar ones, such as in vitro studies with human bladder cancer cells (Zhang 1999), suggest that IFN- α may act synergistically to enhance local antitumour activity of BCG by changing the balance between Th1 and Th2 cytokine production, in favour of Th1 cytokines.

The potential for synergistic antitumour activity of IFN- α and BCG provides some rationale for combination therapy for patients who do not tolerate or respond to standard-dose BCG monotherapy. Some non-randomised studies have shown promise (Joudi 2006; Lam 2003; O'Donnell 2001; Punnen 2003). In a small retrospective study of reduced doses of BCG plus IFN- α in 12 participants with urothelial carcinoma with BCG failure, six (50%) were disease-free at 12 months (Punnen 2003). In a further uncontrolled multicentre trial of over 1000 people with NMIBC, participants who were BCG naive and who received standard-dose BCG plus IFN- α had a 24-month recurrence-free rate of 59%; those participants with BCG failure who received one-third of the standard BCG dose plus IFN- α had a 24-month recurrence-free rate of 45% (Joudi 2006).

Why it is important to do this review

Non-randomised studies have provided some support for the use of dual therapy of IFN- α with BCG for the treatment of NMIBC (Joudi 2006; Lam 2003; O'Donnell 2001; Punnen 2003). Three previous Cochrane reviews have demonstrated some benefit with BCG instillation following TUR compared with epirubicin (though the review authors judged the overall quality of the evidence to be low), mitomycin C (though the significant difference in this review was found in a subgroup of participants at "high-risk" of tumour recurrence), and TUR alone in preventing recurrence of NMIBC (Shang 2011; Shelley 2000; Shelley 2003). However, the combination of intravesical BCG plus IFN- α in NMIBC has not been systematically evaluated.

It was therefore important to systematically review the best-available randomised controlled trial evidence to determine the effectiveness of intravesical BCG plus IFN- α in NMIBC. We used the GRADE approach to rate the quality of evidence (Guyatt 2008), and focused on patient-important outcomes. We considered this information to be of value to people with NMIBC and their families, clinicians, and policymakers, when making decisions concerning treatment.

OBJECTIVES

To assess the effects of intravesically administered BCG plus IFN- α compared with BCG alone for treating non-muscle-invasive bladder cancer.

We conducted this review according to a predefined published protocol (Shepherd 2016).

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised and quasi-randomised trials. We planned to consider individually randomised trials and cluster-randomised trials, as well as cross-over trials (providing separate data were available from the period prior to cross-over). We excluded non-randomised trials.

We included studies irrespective of language of publication and publication status.

Types of participants

We included studies of adults (over 18 years of age) of either gender with histologically confirmed Ta and T1 superficial bladder cancer, with or without CIS, treated with TUR.

Participants with NMIBC were categorised as low, intermediate, or high risk in accordance with the EORTC and the European Association of Urology (EAU) classification (Babjuk 2017).

We planned to include studies that evaluated only a subset of relevant participants if separate data were available for the relevant subsets.

Types of interventions

We investigated the following comparisons of experimental versus comparator interventions.

Experimental interventions

- Intravesically administered BCG plus IFN- α

We included studies of BCG of any strain, dose, and schedule, and studies of any dose or schedule of IFN- α . All participants had undergone TUR prior to receiving the intervention.

Comparator interventions

- Intravesically administered BCG alone

We included studies of BCG of any strain, dose, and schedule. All participants had undergone TUR prior to receiving the intervention.

Comparisons

- Intravesically administered BCG plus IFN- α versus intravesically administered BCG alone
- Intravesically administered BCG alternating with IFN- α versus intravesically administered BCG alone

Although we did not specify the second comparison in our protocol, we considered it important to include in the review (see [Differences between protocol and review](#)).

Concomitant interventions were the same in the experimental and comparator groups to establish fair comparisons.

If we included a study with more than two intervention arms, we only included experimental and comparator intervention groups that met the eligibility criteria of the review.

Types of outcome measures

We did not use the measurement of the outcomes included in this review as an eligibility criterion for considering studies.

If we were unable to derive time-to-event information, we attempted to assess a dichotomous outcome (e.g. recurrence, mortality) instead. We considered outcomes measured up to and including six months after randomisation as short term, later than six months up to and including 24 months as mid term, and later than 24 months as long term.

Primary outcomes

1. Time-to-recurrence, as measured from the date of randomisation to the date of biopsy or resection, with confirmation of tumour of any grade or stage
2. Time-to-progression, as measured from the date of randomisation to the date of biopsy or resection, with confirmation of muscle-invasive bladder cancer
3. Discontinuation of therapy due to adverse events

Secondary outcomes

1. Disease-specific survival, as measured from the date of randomisation to the date of death from bladder cancer
2. Time-to-death, as measured from the date of randomisation to date of death from any cause
3. Systemic or local adverse events (e.g. local: drug-induced cystitis, haematuria, urinary frequency; systemic: fever, nausea, vomiting, anorexia, systemic BCG infection, skin rash, general malaise)
4. Disease-specific quality of life, using validated instruments

Main outcomes for 'Summary of findings' table

We presented 'Summary of findings' tables reporting the following outcomes, listed according to priority.

1. Time-to-recurrence or recurrence
2. Time-to-progression or progression
3. Discontinuation of therapy due to adverse events
4. Disease-specific mortality
5. Disease-specific quality of life

Where we were unable to derive time-to-event information for the outcomes time-to-recurrence and time-to-progression, and assessed the dichotomous outcomes recurrence and progression instead, we included these outcomes in the 'Summary of findings' table. Additionally, where we were unable to obtain information for the outcome disease-specific survival, and assessed the outcome disease-specific mortality instead, we included that outcome in the 'Summary of findings' tables (see [Differences between protocol and review](#)).

Search methods for identification of studies

We performed comprehensive searches, applying no restrictions on the language of publication or publication status. We re-ran the searches within three months of the anticipated publication of the full review.

Electronic searches

We searched the following sources from their respective inception to the current date on 14 March 2016. The date of last search of all databases was 25 August 2016.

- Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 8, 2016) (for the search strategy, see [Appendix 1](#))
- MEDLINE (OvidSP) (1946 to 2016) ([Appendix 2](#))
- Embase (OvidSP) (1974 to 2016) ([Appendix 3](#))

We also searched the following trials registers on 14 March 2016 and again on 25 August 2016.

- ClinicalTrials.gov (www.clinicaltrials.gov/; [Appendix 4](#))
- World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (apps.who.int/trialsearch/; [Appendix 5](#))

If we detected additional relevant keywords during any of the electronic or other searches, we modified the electronic search strategies to incorporate these terms and documented the changes.

Searching other resources

We attempted to identify other potentially eligible trials or ancillary publications by searching the reference lists of retrieved included studies, reviews, meta-analyses, and health technology assessment reports. We also contacted study authors of included trials in order to identify any further studies that we may have missed. We contacted intervention manufacturers for ongoing or unpublished trials.

We handsearched abstract proceedings of relevant meetings from the last three years, including: the International Bladder Cancer Network, the American Urological Association, the European

Association of Urology, the American Society of Clinical Oncology, and the European Society for Radiotherapy & Oncology.

Data collection and analysis

Selection of studies

We used reference management software to identify and remove potentially duplicate records ([EndNote](#)). Two review authors (ARHS, ES) independently scanned the abstracts, titles, or both, of the remaining records retrieved to determine which studies should be assessed further. Two review authors (ARHS, ES) independently investigated all potentially relevant records as full text, mapped records to studies, and classified studies as included, excluded, awaiting classification, or ongoing, in accordance with the criteria for each provided in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011a](#)). We resolved any discrepancies through consensus or recourse to the third review author (NRB). Where resolution of a disagreement was not possible, we designated the study as 'awaiting classification' and contacted the study authors for clarification. We documented reasons for the exclusion of studies that may have reasonably been expected to be included in the review in the [Characteristics of excluded studies](#) table. We presented a PRISMA flow diagram showing the process of study selection ([Liberati 2009](#)).

Data extraction and management

We developed a dedicated data extraction form that we pilot tested ahead of time.

Two review authors (ARHS, ES) independently abstracted the following information for studies that fulfilled the inclusion criteria.

- Study design
- Study dates (if dates were not available, then that was reported as such)
- Study settings and country
- Participant inclusion and exclusion criteria
- Participant details, baseline demographics
- The number of participants by study and by study arm
- Details of relevant experimental and comparator interventions, such as dose, route, frequency, and duration
- Definitions of relevant outcomes, and method and timing of outcome measurement as well as any relevant subgroups
- Study funding sources
- Declarations of interest by primary investigators
- Study characteristics relevant to 'Risk of bias' assessment

We extracted outcome data relevant to this review as needed for calculation of summary statistics and measures of variance. For dichotomous outcomes, we obtained number of events in each group, total number of participants in each group, summary statistic, and 95% confidence intervals (CI). We attempted to obtain log hazard ratios (HR) with standard errors, and HR with 95% CI for time-to-event outcomes. For continuous outcomes, we planned to obtain means and standard deviations (SD), or data necessary to calculate this information.

We resolved any disagreements by discussion, or, if required, by consulting the third review author (NRB).

We provided information about potentially relevant ongoing studies, including the trial identifier, in the Characteristics of ongoing studies table.

We attempted to contact authors of included studies to obtain key missing data as needed.

Dealing with duplicate and companion publications

In the event of duplicate publications, companion documents, or multiple reports of a primary study, we maximised yield of information by mapping all publications to unique studies and collating all available data, and used the most complete data set aggregated across all known publications. In case of doubt, we gave priority to the publication reporting the longest follow-up associated with our primary or secondary outcomes.

Assessment of risk of bias in included studies

Two review authors (ARHS, ES) independently assessed the risk of bias of each included study. We resolved disagreements by consensus, or, if required, by consulting the third review author (NRB).

We assessed risk of bias using the Cochrane tool for assessing risk of bias ([Higgins 2011b](#)). We assessed the following 'Risk of bias' domains.

- Random sequence generation (selection bias)
- Allocation concealment (selection bias)
- Blinding of participants and personnel (performance bias)
- Blinding of outcome assessment (detection bias)
- Incomplete outcome data (attrition bias)
- Selective reporting (reporting bias)
- Other sources of bias

We judged the domains as 'low risk', 'high risk', or 'unclear risk', and evaluated individual bias items as described in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011b](#)).

We presented a 'Risk of bias' summary figure to illustrate these findings.

For performance bias (blinding of participants and personnel) and detection bias (blinding of outcome assessment), we evaluated the risk of bias separately for each outcome, and grouped outcomes according to whether they were measured subjectively or objectively when reporting our findings in the 'Risk of bias' tables. We defined the following endpoints as subjective outcomes: time-to-recurrence, time-to-progression, discontinuation of therapy due to adverse events, disease-specific survival, adverse events, and disease-specific quality of life. We defined the following endpoint as objective: time-to-death.

We also assessed attrition bias (incomplete outcome data) on an outcome-specific basis, and presented the judgement for each outcome separately when reporting our findings in the 'Risk of bias' tables.

We further summarised the risk of bias across domains for each outcome in each included study, as well as across studies and domains for each outcome.

Measures of treatment effect

For dichotomous data, we calculated risk ratios (RR) with 95% CIs. We calculated HR and corresponding 95% CI to assess the intervention effect for time-to-event outcomes. We planned to express continuous data as mean differences (MD) with 95% CIs, unless different studies used different measures to assess the same outcome, in which case we planned to express data as standardised mean differences (SMD) with 95% CIs. We analysed the data using Review Manager 5 software ([RevMan](#)).

Unit of analysis issues

The unit of analysis was the individual participant. We handled trials with more than two intervention groups for inclusion in the review in accordance with guidance provided in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011c](#)).

Dealing with missing data

We attempted to obtain missing data from study authors to perform intention-to-treat analyses; if data were not available, we performed available-case analyses. If possible, we planned to investigate attrition rates (e.g. dropouts, losses to follow-up, and withdrawals) and critically appraise issues of missing data. We did not impute missing data.

Assessment of heterogeneity

In the event of excessive heterogeneity unexplained by subgroup analyses, we planned not to report outcome results as the pooled effect estimate in a meta-analysis but instead to provide a narrative description of the results of each study.

We identified heterogeneity (inconsistency) through visual inspection of the forest plots to assess the amount of overlap of CIs, and the I^2 statistic, which quantifies inconsistency across studies, to assess the impact of heterogeneity on the meta-analysis ([Higgins 2002](#); [Higgins 2003](#)). We interpreted I^2 as follows.

- 0% to 40%: may not be important
- 30% to 60%: may indicate moderate heterogeneity
- 50% to 90%: may indicate substantial heterogeneity
- 75% to 100%: considerable heterogeneity

The importance of the observed value of I^2 depended on magnitude and direction of effects, as well as strength of evidence for heterogeneity (e.g. P value from a χ^2 test) ([Deeks 2011](#)).

When we found heterogeneity, we attempted to determine the possible reasons for it by examining individual study and subgroup characteristics (see [Subgroup analysis and investigation of heterogeneity](#)).

Assessment of reporting biases

We attempted to obtain study protocols to assess for selective outcome reporting.

In future updates of this review, if we include 10 or more studies investigating a particular outcome, we will use funnel plots to assess small-study effects. There are several possible explanations for the asymmetry of a funnel plot, including true heterogeneity of effect with respect to trial size, poor methodological design (and

hence bias of small trials), and publication bias, therefore we will interpret results carefully.

Data synthesis

We summarised data using a random-effects model. We interpreted random-effects meta-analyses with due consideration of the whole distribution of effects. In addition, we performed statistical analyses according to the statistical guidelines contained in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011a](#)). For dichotomous outcomes, we used the Mantel-Haenszel method; for continuous outcomes, we planned to use the inverse-variance method; and for time-to-event outcomes, we used the inverse-variance method. We used Review Manager 5 software to perform analyses ([RevMan](#)).

Subgroup analysis and investigation of heterogeneity

We expected the following characteristics to introduce clinical heterogeneity, therefore where sufficient data were available, we planned to perform the following predefined subgroup analyses.

- Risk (low risk versus intermediate risk versus high risk) according to the EORTC/EAU risk classification system ([Babjuk 2017](#))
- Dose and schedule of BCG (e.g. standard dose (81 mg weekly for six weeks) versus low dose (27 mg weekly for six weeks) versus very low dose (13.5 mg weekly for six weeks))
- Dose and schedule of IFN- α (e.g. higher dose (100 million units (MU) weekly for six weeks) versus lower dose (50 MU weekly for six weeks))

If EAU risk categories were not available, and if sufficient data were available, we planned to perform subgroup analyses based on:

- number of tumours (one versus more than one)
- tumour size (< 3 cm versus $\geq$ 3 cm)
- tumour stage (Ta versus T1)
- presence of CIS (absent or present)
- tumour grade (Grade 1 versus Grades 2 and 3)
- primary versus recurrent disease

Where there were sufficient studies, we used the test for subgroup differences in Review Manager 5 to compare subgroup analyses ([RevMan](#)).

Sensitivity analysis

We planned to perform sensitivity analyses based on risk of bias by excluding studies judged to be at 'high risk' or 'unclear risk' of bias for the particular outcome.

Summary of findings tables

We presented the overall quality of the evidence for each outcome according to the GRADE approach, which takes into account five criteria, related to internal validity (risk of bias, inconsistency, imprecision, publication bias) and external validity (directness of results) ([Guyatt 2008](#); [Guyatt 2011](#); [Schünemann 2011](#)). For each comparison, two review authors (ARHS, ES) independently rated the quality of evidence for each outcome as 'high', 'moderate', 'low', or 'very low' using [GRADEpro GDT](#); we resolved any discrepancies by consensus, or, if needed, by consulting the third review author (NRB). For each comparison, we presented a summary of the evidence for the main outcomes in a 'Summary of findings'

table (Guyatt 2011; Schünemann 2011). If meta-analysis was not possible, we planned to present results in a narrative 'Summary of findings' table.

RESULTS

Description of studies

Results of the search

Through database searching of the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (OvidSP), and Embase

(OvidSP), we identified 204 records (see Figure 1). We identified a further 22 records through other sources including: one record identified through personal communication; 18 records identified through trial registry searching; and three records identified through handsearching. After removal of duplicates, we screened the titles and abstracts of 149 records, and excluded 130. We screened 19 full-text articles, and excluded two studies that were non-randomised trials. We included a total of five trials (17 records) in the review: two records were published in Italian, one record was published in Russian, and the remaining 14 records were published in English. We did not identify any relevant ongoing trials.

Figure 1. Study flow diagram (searched 14 March 2016, updated 25 August 2016).

Figure 1. (Continued)

quantitative
synthesis
(meta-analysis)

Included studies

Details of the included studies are presented in the [Characteristics of included studies](#) tables. We included five studies (17 records) in the review that randomised a total of 1231 participants. The smallest study randomised 36 participants ([Bercovich 1995](#)); the largest study randomised 670 participants ([Neppele 2010](#)). All of the included studies were randomised controlled trials. Two study authors responded to requests for full-text manuscripts ([Bercovich 1995](#); [Minich 2009](#)). We contacted authors of all included studies for further information on study methodology and results (see [Characteristics of included studies](#)).

Three studies were multi-institutional ([Chiong 2011](#); [Jarvinen 2015](#); [Neppele 2010](#)), and two did not specify ([Bercovich 1995](#); [Minich 2009](#)). One study specified its setting as part of the FinnBladder IV study group ([Jarvinen 2015](#)), located in Finland, while the other four studies did not specify the study location (though the authors were affiliated to institutions in Italy ([Bercovich 1995](#)), Singapore ([Chiong 2011](#)), Belarus ([Minich 2009](#)), and the United States ([Neppele 2010](#))).

The studies included a variety of participant groups. All studies reported more male participants than female. Mean age of participants overall ranged from 61.9 to 68.4 years and was provided in all but one study ([Jarvinen 2015](#)).

All included studies enrolled people with NMIBC (at least stage Ta, T1), with three also specifically including people with CIS ([Bercovich 1995](#); [Chiong 2011](#); [Neppele 2010](#)). One study specified no prior intravesical therapy ([Chiong 2011](#)); one specified no prior BCG for bladder cancer ([Neppele 2010](#)); and one specified that people with previous instillation therapy have at least one of the recurrences at six months after the last instillation ([Jarvinen 2015](#)). Prior intravesical therapy was not specified in the remaining studies.

The follow-up duration varied between the studies. The follow-up range was reported as 0.2 to 19.8 years in [Jarvinen 2015](#); the median ranged from 38.3 months, in [Minich 2009](#), to 60 months, in [Chiong 2011](#) (and up to 207 months in a subsequent abstract for this study, [Esuvaranathan 2014](#), which has not yet been published as a full manuscript). Mean follow-up was reported in [Bercovich 1995](#) as 16.72 (SD 8.7) months in the BCG plus IFN- α group and 24.11 (SD 8.15) months in the BCG alone group. One study did not clearly report duration of follow-up ([Neppele 2010](#)).

In four studies, the experimental group received BCG in combination with IFN- α (co-administration) ([Bercovich 1995](#); [Chiong 2011](#); [Minich 2009](#); [Neppele 2010](#)), and in one study, alternating monthly injections of BCG and IFN- α were administered ([Jarvinen 2015](#)). In one study, two arms were administered BCG alone at different doses (27 mg and 81 mg) ([Chiong 2011](#)); the data for these two arms were pooled in our analyses. [Neppele 2010](#) was a 2x2 factorial study design that considered two comparisons of BCG and IFN- α versus BCG alone. In one comparison, each of the groups was given recommended daily allowance dose of vitamins, and in

the other comparison, each of the groups was given a megadose of oral vitamins. We pooled the data for BCG and IFN- α and BCG alone in our analyses, regardless of vitamin allocation.

The dose range of BCG and IFN- α in the experimental groups varied, as did the duration of treatment. Bacillus Calmette-Guérin dose ranged from 27 mg, in [Chiong 2011](#), to 125 mg, in [Minich 2009](#), given in combination with IFN- α dose of 6 MU ([Minich 2009](#)), 10 MU ([Bercovich 1995](#); [Chiong 2011](#)), or 50 MU ([Jarvinen 2015](#); [Neppele 2010](#)). Induction courses were comparable across four studies: once weekly for six weeks ([Bercovich 1995](#); [Chiong 2011](#); [Minich 2009](#); [Neppele 2010](#)); one study did not administer BCG induction ([Jarvinen 2015](#)). Three studies gave maintenance courses: monthly for 10 months in [Bercovich 1995](#), monthly for one year in [Jarvinen 2015](#), and three consecutive weekly instillations at 4, 7, 13, 19, 25, and 37 months if participants remained bladder cancer-free (with a reduced BCG dose (16.6 mg) in combination with IFN- α) in [Neppele 2010](#). One study gave a "booster" course of three, once-per-week instillations ([Chiong 2011](#)).

The dose of BCG in the comparator groups also varied, ranging from 27 mg, in [Chiong 2011](#), to 125 mg, in [Minich 2009](#). In all studies but one ([Bercovich 1995](#)), the BCG dose was the same in the experimental and comparator groups. [Bercovich 1995](#) lowered the BCG dose in the experimental group (75 mg BCG dose in the experimental group, 150 mg BCG dose in the comparator group).

There was also variation in the strains of BCG used across the studies: BCG Pasteur F in [Bercovich 1995](#); Connaught strain in [Chiong 2011](#); Russian strain in [Minich 2009](#); and TICE strain in [Jarvinen 2015](#) and [Neppele 2010](#).

Three studies gave co-interventions: [Jarvinen 2015](#) used perioperative intravesical mitomycin C; [Neppele 2010](#) administered two co-interventions consisting of a recommended daily allowance dose of oral vitamins and a megadose of oral vitamins; and after intravesical injection in [Bercovich 1995](#), ketoprofen was given at a dose of 200 mg per day for two days associated with norfloxacin or cinoxacin 1 g per day for three days, for the treatment of infections.

Three studies specified funding sources: [Chiong 2011](#): National Medical Research Council Singapore; [Jarvinen 2015](#): Finnish Cancer Foundation and pharmaceutical companies (Teknika, Organon, Pharmacia, Roche, and Schering-Plough); and [Neppele 2010](#): Schering-Plough and Mission Pharmacal. [Chiong 2011](#) and [Jarvinen 2015](#) reported no conflicts of interest, and [Neppele 2010](#) declared conflicts of interest for two study authors (related to financial interests or other relationships with pharmaceutical companies, or both). Two studies reported neither funding sources nor conflicts of interest ([Bercovich 1995](#); [Minich 2009](#)).

Excluded studies

We excluded two studies; the reasons for exclusion are described in [Figure 1](#) and [Characteristics of excluded studies](#). [Joudi 2006](#) and [O'Donnell 2004](#) were not randomised controlled trials.

Risk of bias in included studies

We assessed the risk of bias of the included studies according to the seven domains outlined in the Cochrane 'Risk of bias' tool ([Higgins](#)

[2011b](#)). We extracted the methodological details of the studies from the published data. No study protocols were made available for us to further assess the risk of bias. For details on risk of bias, see [Figure 2](#) and [Figure 3](#) and [Characteristics of included studies](#).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias): Subjective outcomes	Blinding of participants and personnel (performance bias): Objective outcomes	Blinding of outcome assessment (detection bias): Subjective outcomes	Blinding of outcome assessment (detection bias): Objective outcomes	Incomplete outcome data (attrition bias): Time-to-recurrence	Incomplete outcome data (attrition bias): Time-to-progression	Incomplete outcome data (attrition bias): Discontinuation of therapy due to adverse events	Incomplete outcome data (attrition bias): Disease-specific survival	Incomplete outcome data (attrition bias): Time-to-death	Incomplete outcome data (attrition bias): Systemic or local adverse events	Incomplete outcome data (attrition bias): Disease-specific quality of life	Selective reporting (reporting bias)	Other bias
Bercovich 1995	?	?	?	?	?	?	?	?	?	?	?	?	?	-	-
Chiong 2011	?	?	?	?	?	?	-	-	?	-	?	-	?	?	+
Jarvinen 2015	+	+	-	-	-	+	+	+	+	+	+	+	?	+	?
Minich 2009	?	?	?	?	?	?	?	?	?	?	?	?	?	-	+
Nepple 2010	+	+	-	?	-	?	?	?	?	?	?	?	?	-	?

Allocation

Random sequence generation

Two studies reported adequate methods for sequence generation and were judged as at low risk of bias (Jarvinen 2015; Nepple 2010). In the other three included studies (Bercovich 1995; Chiong 2011; Minich 2009), information on sequence generation was not reported or was insufficient to allow a judgement (unclear risk of bias).

Allocation concealment

Two studies provided adequate methods for concealing allocation (low risk of bias) (Jarvinen 2015; Nepple 2010). The other three studies did not report information on allocation concealment (unclear risk of bias) (Bercovich 1995; Chiong 2011; Minich 2009).

Blinding

Blinding of participants and personnel

Subjective outcomes

In two studies, blinding was not detailed (Bercovich 1995; Minich 2009); another study was described as "double blind", however no further details were provided (unclear risk of bias) (Chiong 2011). Participants and providers were not blinded to IFN- α administration in Nepple 2010. Due to the nature of the interventions (BCG versus BCG alternating with IFN- α) in Jarvinen 2015, it was considered unlikely that participants and personnel were blinded to the intervention for subjective outcomes. We judged the last two studies to be at high risk of performance bias, as the subjective outcomes reported were considered likely to be influenced by lack of blinding.

Objective outcomes

Jarvinen 2015 was the only trial to report on the one review outcome we judged to be objective (time-to-death; reported as "overall survival"). However, due to the absence of blinding, we considered risk of performance bias to be high.

Blinding of outcome assessment

Subjective outcomes

In two studies, blinding was not detailed (Bercovich 1995; Minich 2009); another study was described as "double blind", however no further details were provided (unclear risk of bias) (Chiong 2011). Providers were not blinded to IFN- α administration in Nepple 2010. Due to the nature of the interventions (BCG versus BCG alternating with IFN- α) in Jarvinen 2015, it was considered unlikely that personnel were blinded to the intervention for subjective outcomes. We judged the last two studies to be at high risk of detection bias, as the subjective outcomes reported were considered likely to be influenced by lack of blinding.

Objective outcomes

Jarvinen 2015 was the only trial to report on the one review outcome we judged to be objective (time-to-death; reported as "overall survival"); we considered risk of detection bias to be low.

Incomplete outcome data

We assessed risk of bias for incomplete outcome data on an outcome-specific basis (see [Characteristics of included studies](#) for further details).

In three studies (Bercovich 1995; Minich 2009; Nepple 2010), where outcome data have been provided, information reported in the published manuscripts was insufficient to determine risk of attrition bias (unclear risk of bias). No information was provided regarding whether there were postrandomisation losses to follow-up, withdrawals, or study group changes, and if so, how missing data were managed.

We judged Chiong 2011 to be at high risk of attrition bias for reported outcomes, with limited detail regarding postrandomisation losses to follow-up and withdrawals provided; discrepancies in numbers of "non evaluable" participants across study manuscripts; and a relatively large proportion of participants "not evaluable" in the longer-term follow-up (32/140).

We judged Jarvinen 2015 to be at low risk of attrition bias, as while 31 out of 236 participants were excluded postrandomisation, the exclusions and reasons for exclusions were balanced between groups, and the study reported intention-to-treat analyses.

Selective reporting

We judged three studies to be at high risk of reporting bias (Bercovich 1995; Minich 2009; Nepple 2010). No mortality or progression outcomes were reported in Bercovich 1995, and adverse events were incompletely reported in text. In Nepple 2010, no mortality or progression outcomes were reported; the secondary outcome (severity of treatment toxicity) was prespecified but not reported; and some results relating to recurrence and progression were reported incompletely in text, for example "Overall 231 of 670 patients (34%) had documented recurrence, including muscle invasive disease in 47 (7%) and discovery of metastatic disease in 7 (1%)" (it was not clear to which groups these participants had been allocated). In Minich 2009, discontinuation of adverse events was reported incompletely in text.

We judged one study to be at unclear risk of reporting bias (Chiong 2011), as to date, data from the long-term follow-up have been reported in abstract form only, thus it was not possible to confidently assess selective reporting.

We judged one study to be at low risk of reporting bias (Jarvinen 2015), as all expected outcomes were reported; of note, however, median time-to-recurrence "was not attained" in the BCG alone group.

Other potential sources of bias

We judged two studies to be at low risk of other bias (Chiong 2011; Minich 2009), with comparable groups at baseline, and no other obvious sources of bias identified.

We judged one study to be at high risk of other bias due to limited reporting of baseline characteristics and exclusion of an additional study arm (IFN- α alone) from reporting due to lack of effect on recurrence (Bercovich 1995).

We judged two studies to be at unclear risk of other bias (Jarvinen 2015; Nepple 2010). Both studies reported conflicts of interest, and it was not clear what impact, if any, these had on the conduct of the studies. In Jarvinen 2015, baseline characteristics were largely balanced, however it was unclear whether timing of single immediate chemotherapy instillation differed significantly

between groups. Regarding additional treatments during follow-up, there were more treatments in the BCG alternating with IFN- α group (27 versus 16), which the authors suggest “may have additionally contributed to decreasing the progression rate and the difference between the groups”. In [Nepple 2010](#), baseline characteristics were not reported by treatment group, thus it was not possible to assess comparability of groups.

Effects of interventions

See: [Summary of findings for the main comparison](#) Intravesically administered BCG combined with IFN- α compared to intravesically administered BCG alone for treating non-muscle-invasive bladder cancer; [Summary of findings 2](#) Intravesically administered BCG alternating with IFN- α compared to intravesically administered BCG alone for treating non-muscle-invasive bladder cancer

Intravesically administered BCG plus IFN- α versus intravesically administered BCG alone

We included four studies in this comparison ([Bercovich 1995](#); [Chiong 2011](#); [Minich 2009](#); [Nepple 2010](#)).

See [Summary of findings for the main comparison](#).

Primary outcomes

Time-to-recurrence or recurrence

One study reported on time-to-recurrence (presented as disease-free interval) and found no clear difference overall between the BCG plus IFN- α and BCG alone groups (hazard ratio (HR) 1.11, 95% confidence interval (CI) 0.86 to 1.43; 1 study; 670 participants) ([Analysis 1.1](#)) ([Nepple 2010](#)). The duration of follow-up was not clearly reported in [Nepple 2010](#).

All four studies reported dichotomous data for recurrence ([Bercovich 1995](#); [Chiong 2011](#); [Minich 2009](#); [Nepple 2010](#)), and overall no clear difference was observed (average risk ratio (RR) 0.76, 95% CI 0.44 to 1.32; 4 studies; 925 participants; very low-quality evidence) ([Analysis 1.2](#)). We identified substantial heterogeneity ($I^2 = 74\%$) for this outcome. In [Bercovich 1995](#), recurrence was reported after a mean follow-up of 16.72 (SD 8.7) months for the BCG plus IFN- α group and 24.11 (SD 8.15) months for the BCG alone group; in [Chiong 2011](#), participants were followed for a median of 60 months; in [Minich 2009](#), median duration of follow-up was 38.3 months; and the duration of follow-up was not clearly reported in [Nepple 2010](#).

An abstract, [Esuvaranathan 2014](#), has reported later follow-up data for [Chiong 2011](#), although not in a format that we could include in the meta-analysis. “The evaluable study cohort (n = 108) was followed up to 207 months, with a total of 35 recurrences Five years after randomisation, the probability of being recurrence-free were 56.4% and 78.2% in the full-dose BCG and combination arms respectively (p = 0.037). The mean time to recurrence was 118 months for full-dose BCG compared to 145 months for the combination arm.” We were unable to obtain additional information from the authors.

Progression

Two studies reported dichotomous data for progression ([Chiong 2011](#); [Minich 2009](#)), and overall no clear difference between groups was observed (average RR 0.26, 95% CI 0.04 to 1.87; 2 studies; 219 participants) ([Analysis 1.3](#)). We identified moderate

statistical heterogeneity ($I^2 = 42\%$) for this outcome. In [Chiong 2011](#), participants progressed to muscle-invasive disease at a median of 39 months after therapy, while in [Minich 2009](#), progression was observed between 3.6 and 29.7 months. We judged the quality of the evidence for this outcome to be low.

Discontinuation of therapy due to adverse events

None of the studies reported data on discontinuation of therapy due to adverse events that could be included in a meta-analysis.

[Minich 2009](#) reported that the frequency of discontinuation of therapy due to adverse events between groups was not statistically different (P = 0.743), with 10 participants not completing the full course of treatment due to adverse events. It was not reported to which group these participants had been assigned.

Secondary outcomes

Disease-specific mortality

One study reported dichotomous data for disease-specific mortality (not our prespecified outcome disease-specific survival) and observed no clear difference between groups (RR 0.38, 95% CI 0.05 to 3.05; 1 study; 99 participants; very low-quality evidence) ([Analysis 1.4](#)) ([Chiong 2011](#)). In [Chiong 2011](#), the cancer-specific deaths were at a median of 60 months.

Time-to-death

None of the studies reported on time-to-death.

Systemic or local adverse events

[Minich 2009](#) reported on the occurrence of any adverse events during the course of treatment (including disorientation/delirium and macroscopic haematuria), and observed a 67% relative reduction in the risk of any adverse events in the BCG plus IFN- α group (RR 0.33, 95% CI 0.13 to 0.86; 1 study; 120 participants) ([Analysis 1.5](#)).

[Nepple 2010](#) reported on the occurrence specifically of fever or constitutional symptoms, and observed a 122% relative increase in the occurrence of fever (RR 2.22, 95% CI 1.27 to 3.91; 1 study; 670 participants) and a 61% relative increase in the occurrence of constitutional symptoms (RR 1.61, 95% CI 1.10 to 2.36; 1 study; 670 participants) for participants in the BCG plus IFN- α group compared with the BCG alone group ([Analysis 1.5](#)).

[Bercovich 1995](#) and [Chiong 2011](#) reported data regarding adverse events incompletely:

[Bercovich 1995](#) reported: “The results point out that the combination treatment is superior to BCG full dose therapy in terms of side effects.” It was noted that all participants in the BCG alone group had strangury and fever, and four had macroscopic haematuria. The incidence of adverse events in the BCG plus IFN- α group was not reported.

[Chiong 2011](#) reported on autoimmune clinical manifestations (including arthritis, arthralgia, iritis, and uveitis) for eight (6%) of the 140 participants of whom “two received full dose BCG (81 mg), three received one third BCG (27 mg) and three received one-third BCG (27 mg) with 10 million units of IFN- α 2b”. On average, the manifestations were observed following the sixth intravesical instillation (ranging from the third to the ninth). The

denominators for the groups were not reported, which prevented inclusion of these data in a meta-analysis. Further, [Chiong 2011](#) (in [Esuvaranathan 2014](#)) reported: "Overall the treatment was well tolerated. Both local and systemic symptoms were significantly decreased in the low-dose BCG plus IFN- α 2b arm compared to full-dose BCG during the first 6 instillations but not for the booster instillations." These results have been reported in abstract format only.

Disease-specific quality of life

None of the studies reported on disease-specific quality of life.

Subgroup and sensitivity analysis

We planned to conduct subgroup analyses based on risk according to the EORTC/EAU risk classification system, dose and schedule of BCG, and dose and schedule of IFN- α . Data from the four studies were insufficient to conduct subgroup analyses based on risk classification or BCG dose, with all studies administering a different dose of BCG (induction courses: [Chiong 2011](#): 27 mg BCG; [Neppl 2010](#): 50 mg BCG; [Bercovich 1995](#): 75 mg BCG; [Minich 2009](#): 125 mg BCG; all weekly for six weeks). We were able to conduct a subgroup analysis for recurrence based on dose of IFN- α , comparing the studies that administered higher-dose IFN- α (50 MU) versus lower-dose IFN- α (6 to 10 MU) weekly for six weeks during induction. The subgroup interaction test ($\text{Chi}^2 = 6.49$, $P = 0.01$, $I^2 = 84.6\%$) indicated a possible difference in effect for recurrence based on dose of IFN- α . A reduction in recurrence was observed in the studies administering a lower dose of IFN- α (RR 0.58, 95% CI 0.36 to 0.94; 3 studies; 255 participants), a difference which was not observed in the one study that administered a higher dose (RR 1.14, 95% CI 0.93 to 1.41; 1 study; 670 participants) ([Analysis 1.2](#)). However, the results of this analysis should be interpreted with caution, given the small number of studies and participants included in these subgroups.

We were not able to perform other planned subgroup analyses due to the limited number of studies included in this review and paucity of data for primary outcomes. We did not conduct sensitivity analyses, as we judged none of the four studies included in this comparison to be at low risk of bias overall.

Intravesically administered BCG alternating with IFN- α versus intravesically administered BCG alone

We included one study in this comparison ([Jarvinen 2015](#)).

See [Summary of findings 2](#).

Primary outcomes

Time-to-recurrence

In [Jarvinen 2015](#), the time-to-recurrence was accelerated in the BCG alternating with IFN- α group compared with the BCG alone group (HR 2.86, 95% CI 1.98 to 4.13; 1 study; 205 participants; low-quality evidence) ([Analysis 2.1](#)). The study reported the median time-to-recurrence as 10 months in the BCG alternating with IFN- α group, and "was not attained" in the BCG alone group ([Jarvinen 2015](#)).

Time-to-progression

In [Jarvinen 2015](#), there was no clear difference in time-to-progression between the BCG alternating with IFN- α group and

the BCG alone group (HR 2.39, 95% CI 0.92 to 6.21; 1 study; 205 participants; low-quality evidence) ([Analysis 2.2](#)). The study reported no progressions in the BCG alone group after seven years of follow-up, with two progressions occurring after 10 years in the BCG alternating with IFN- α group ([Jarvinen 2015](#)).

Discontinuation of therapy due to adverse events

In [Jarvinen 2015](#), there was no clear difference in discontinuation of therapy due to adverse events (RR 2.97, 95% CI 0.31 to 28.09; 1 study; 205 participants; low-quality evidence) ([Analysis 2.3](#)). The reasons for discontinuation were: BCG alternating with IFN- α group: intensive local pain after BCG at six months, nausea at six months, fatigue at eight months; BCG alone group: severe skin reaction after BCG at six months ([Jarvinen 2015](#)).

Secondary outcomes

Disease-specific mortality

[Jarvinen 2015](#) reported on disease-specific mortality (not our prespecified outcome disease-specific survival). There was no clear difference in disease-specific mortality between the BCG alternating with IFN- α and BCG alone groups (HR 2.74, 95% CI 0.73 to 10.28; 1 study; 205 participants; low-quality evidence) ([Analysis 2.4](#)). The study reported that all deaths from carcinoma occurred during the first 10 years of follow-up, and most (7/11) during the first five years of follow-up ([Jarvinen 2015](#)).

Overall survival

[Jarvinen 2015](#) reported on overall survival (deaths from any cause) (not our prespecified outcome time-to-death), and observed no clear difference between the BCG alternating with IFN- α and BCG alone groups (HR 1.00, 95% CI 0.68 to 1.47; 1 study; 205 participants) ([Analysis 2.5](#)). The study reported the median survival time as 12.9 years in the BCG alternating with IFN- α group and 12.2 years in the BCG alone group ([Jarvinen 2015](#)).

Systemic or local adverse events

In [Jarvinen 2015](#), there was no clear difference between groups for adverse events (RR 1.65, 95% CI 0.41 to 6.73; 1 study; 205 participants) ([Analysis 2.6](#)). In the BCG and IFN- α group, one participant had intensive local pain at six months, one complained of nausea at six months, one complained of fatigue at eight months, and there were two cases of epididymitis; in the BCG alone group, one participant had a severe skin reaction at six months, one frequently had high fever, and one participant had a contracted bladder two months after the end of therapy. The study also reported that there were no systemic BCG infections or treatment-related deaths ([Jarvinen 2015](#)).

Disease-specific quality of life

[Jarvinen 2015](#) did not report on disease-specific quality of life.

Subgroup and sensitivity analysis

We performed no subgroup or sensitivity analyses because only one study was included in this comparison and thus no meta-analyses were conducted.

DISCUSSION

Summary of main results

We included five studies in this review, with a total of 1231 participants randomised across the included studies comparing intravesical BCG with IFN- α versus intravesical BCG alone for the treatment of NMIBC, contributing data to two comparisons (intravesical BCG plus IFN- α versus intravesical BCG alone; intravesical BCG alternating with IFN- α versus intravesical BCG alone).

Intravesical BCG plus IFN- α versus intravesical BCG alone

We found very low-quality evidence showing no clear difference in recurrence (across four studies including 925 participants), and low-quality evidence showing no clear difference in progression (across two studies including 219 participants) with BCG plus IFN- α versus BCG alone. None of the studies reported on the other primary outcome, discontinuation of therapy due to adverse events. Regarding secondary outcomes, there was very low-quality evidence (from one study including 99 participants) showing no clear difference in disease-specific mortality between the BCG plus IFN- α and BCG alone groups. We observed mixed results for adverse events. None of the included studies reported on the other secondary outcomes, time-to-death and disease-specific quality of life. A subgroup analysis based on IFN- α dose for the outcome recurrence suggested a possible difference in effect based on dose, in favour of lower-dose IFN- α (6 to 10 MU) compared with a higher dose (50 MU); however, given the small numbers of studies (and participants), and their variable methodological quality, this result should be interpreted with caution.

Intravesical BCG alternating with IFN- α versus intravesical BCG alone

We found low-quality evidence (from one study including 205 participants) showing a higher probability of recurrence with BCG alternating with IFN- α compared with BCG alone. However, we also found low-quality evidence (from one study including 205 participants) showing no clear difference in the probability of progression or the risk of discontinuation of therapy due to adverse events between BCG alternating with IFN- α compared with BCG alone. Regarding secondary outcomes, there was low-quality evidence showing no clear difference in disease-specific mortality between BCG alternating with IFN- α and BCG alone, and, similarly, no clear differences between groups for overall survival and systemic or local adverse events. The included study did not report on disease-specific quality of life.

Overall completeness and applicability of evidence

The studies included in this review examined clinically important populations seen in routine clinical practice. Regarding the primary outcomes, only two studies reported on time-to-recurrence (though three additional trials reported on the dichotomous outcome recurrence); one on time-to-progression (though two additional trials reported on the dichotomous outcome progression); and one on discontinuation of therapy due to adverse events. Reporting of the secondary outcomes for this review also varied. Although none of the included studies reported on the secondary outcome disease-specific survival, two studies reported on disease-specific mortality. Similarly, none of the studies reported on time-to-death, though one study

reported on overall survival. All of the studies reported information regarding adverse events (though some reported this information incompletely). None of the included studies reported on disease-specific quality of life.

The participants and assessed interventions conformed to the review question, though there are several points to be made with regard to the applicability of the evidence. We performed two comparisons, as it was judged that BCG co-administered with IFN- α was a different intervention to BCG alternating with IFN- α . Two included studies evaluated only BCG naive participants (Chiong 2011; Nepple 2010), and three studies had co-interventions (Bercovich 1995; Jarvinen 2015; Nepple 2010); the effects of these factors on the results of this review are not clear. There was notable variation in the doses of BCG and IFN- α in the included studies, and variation in timing and duration of the interventions (three included studies included both induction and maintenance dosing schedules (Bercovich 1995; Chiong 2011; Nepple 2010); one provided only an induction dosing schedule (Minich 2009); and one provided only a maintenance dose schedule (Jarvinen 2015)). The frequency of administration of the intervention in the maintenance dose varied from weekly for three weeks, in Chiong 2011, to monthly for 10 months, in Bercovich 1995. Such variation in doses and schedules may affect the applicability of the results of this review. While we were able to perform a subgroup analysis for recurrence based on IFN- α , we were unable to perform a similar analysis for different doses of BCG, with each study administering a different BCG dose. Each of the studies used a different BCG strain, potentially affecting the applicability of the results of the review based on the availability of a particular BCG strain. Some of the studies provided limited information regarding pathological characteristics (such as stage, grade, primary or recurrent lesions, unifocal or multifocal lesions), consequently we were also unable to conduct subgroup analyses based on risk categories.

Quality of the evidence

We assessed the quality of evidence using the GRADE approach for prespecified outcomes analysed in the two main comparisons. We found that for the first comparison (BCG plus IFN- α versus BCG alone), the evidence was of low (progression) or very low quality (recurrence and disease-specific mortality). These judgements were based on design limitations and imprecision of effect estimates, for all included outcomes. For the second comparison (BCG alternating with IFN- α versus BCG alone), the evidence was of low quality (time-to-recurrence, time-to-progression, discontinuation of therapy due to adverse events, and disease-specific mortality). These judgements were based on design limitations in the included studies and imprecision. The 'Risk of bias' figures (Figure 2; Figure 3) indicate that many aspects of quality were unclear for several of the included studies, often due to a lack of reporting of methodology.

Potential biases in the review process

We followed the recommendations outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* to minimise biases (Higgins 2011a). In order to reduce the potential for publication bias, we performed an extensive literature search without language or publication status restrictions, and additionally searched trial registries for unpublished, planned, or ongoing studies. It is possible that additional studies may have been conducted but not yet published, or that additional studies

have been published but not yet identified. Should any such studies be identified, we will include them in further updates of this review. At least two review authors independently assessed studies for inclusion and performed data extraction and assessment of risk of bias for all of the included studies.

We considered only randomised controlled trials for inclusion in this review. Although some recent evidence has suggested that on average, there may not be large differences in the risk estimates of adverse events from randomised controlled trials and observational studies (Golder 2011), it is widely recognised that for the comprehensive assessment of rare or serious adverse events, or both, and the assessment of adverse events outside of the randomised trial setting (where participants are 'highly selected'), it is often necessary to consider studies of other designs (such as controlled clinical trials, cohort studies, case-control studies, and even case series and case reports) (Loke 2011), which was beyond the scope of this review.

Agreements and disagreements with other studies or reviews

We have not identified any other systematic reviews specifically comparing BCG with IFN- α versus BCG alone for NMIBC. Two recently published reviews of diagnosis and treatment of NMIBC included comparisons of BCG with IFN- α versus BCG alone (Chou 2015; Zhu 2013). The comparison in Zhu 2013 focused only on the outcome of recurrence-free survival and included two studies: one randomised trial that we included in our review, Nepple 2010, and a case series, Bazarbashi 2000. Similar to the findings in our review, Zhu 2013 reported no difference for recurrence between those treated with BCG plus IFN- α and those treated with BCG alone. Another recently published review undertook two comparisons similar to our review (BCG plus IFN- α versus BCG alone and BCG alternating with IFN- α versus BCG alone) and had similar findings (Chou 2015). One study was included in the first comparison of BCG plus IFN- α versus BCG alone (Nepple 2010), and one study for the second comparison (Kaasinen 2000), which reported the earlier follow-up data for the trial included in our review (Jarvinen 2015). The findings of Chou 2015 were similar to those in our review: BCG alternating with IFN- α had a higher risk of recurrence when compared with BCG alone, and no difference was observed in the

risk of recurrence or progression between BCG plus IFN- α and BCG alone.

AUTHORS' CONCLUSIONS

Implications for practice

There was low- to very low-quality evidence indicating no clear difference for recurrence, progression, or disease-specific mortality with BCG plus IFN- α compared with BCG alone. Low-quality evidence showed accelerated time-to-recurrence with BCG alternating with IFN- α compared with BCG alone; however, low-quality evidence also showed no clear differences for time-to-progression, discontinuation of therapy due to adverse events, and disease-specific mortality with BCG alternating with IFN- α compared to BCG alone.

Implications for research

Additional high-quality, adequately powered trials using standardised instillation regimens and doses of both BCG and IFN- α , reporting outcomes in subgroups stratified by participant and tumour characteristics (grade, stage, primary or recurrent lesions, unifocal or multifocal tumours), and on long-term outcomes related not only to recurrence, but also to progression and mortality may help to clarify the ideal treatment strategy and provide a more definitive result for this comparison. The inclusion of patient-reported quality of life data and reporting of adverse events will also aid in the assessment of the safety and tolerability of these treatments.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Bercovich 1995

Methods	<p><u>Start date, end date of recruitment:</u> May 1991, end date not specified</p> <p><u>Follow-up period:</u> Mean follow-up: 24.11 +/- 8.15 months for BCG alone group and 16.72 +/- 8.7 for BCG plus IFN-α. Follow-up was planned every 3 months for the first 24 months and then every 6 months.</p> <p><u>Design:</u> Randomised controlled trial</p> <p><u>Ethics approval obtained:</u> Not reported</p>
Participants	<p><u>Setting:</u> Not reported (author affiliated to institution in Italy)</p> <p><u>Population/inclusion criteria:</u> CIS, Ta, T1, G1-G3 transitional cell tumours, after complete TURBT or diathermocoagulation</p> <p><u>Exclusion criteria:</u> Not reported</p> <p><u>Method of recruitment:</u> Not reported</p> <p><u>Informed consent obtained:</u> Not reported</p> <p><u>Total number randomly assigned:</u> 36 participants were enrolled in the 2 relevant trial arms.</p> <p><u>Baseline imbalances:</u> Not reported</p> <p><u>Withdrawals or exclusions:</u> Introduction of Bercovich 1995 paper states that there were initially 3 treatment groups (BCG plus IFN-α, BCG alone, and IFN-α alone), but the IFN-α alone arm was discontinued because of "evidence of no effect in blocking disease recurrence".</p> <p><u>Characteristics (age, race, gender, severity of illness, comorbidities):</u></p> <p>Age (mean, years):</p> <ul style="list-style-type: none"> • BCG alone: 65.7 • BCG plus IFN-α: 66.3 <p>Stage:</p> <ul style="list-style-type: none"> • BCG alone: Ta 61.1%; T1 38.9% • BCG plus IFN-α: Ta 50%; T1 50% <p>Grade:</p> <ul style="list-style-type: none"> • BCG alone: G1 55.6%; G2 38.9%; G3 5.6% • BCG plus IFN-α: G1 38.9%; G2 44.4%; G3 16.7%
Interventions	<p><u>Intervention</u></p> <p>Total number randomised: 18 enrolled</p>

Bercovich 1995 (Continued)

Description: IFN- α 2b 10 MU and BCG Pasteur F 75 mg diluted in 0.9% NaCl, once a week for 6 weeks and once a month for 10 months. After participant emptied bladder, drugs were injected along with 50 mL saline. Participants were instructed not to urinate for 1 hour after the injection.

Integrity of delivery/compliance: Not reported

Comparison

Total number randomised: 18 enrolled

Description: BCG Pasteur F 150 mg diluted in 0.9% NaCl, once a week for 6 weeks and once a month for 10 months. After participant emptied bladder, drugs were injected along with 50 mL saline. Participants were instructed not to urinate for 1 hour after the injection.

Integrity of delivery/compliance: Not reported

Other co-interventions for both groups: After intravesical injection, ketoprofen 200 mg per day for 2 days associated with norfloxacin or cinoxacin 1 g per day for 3 days was administered for the treatment of eventual infections.

Outcomes

Time-to-recurrence

Time points measured: Follow-up was planned every 3 months for the first 2 years, then every 6 months.

Time points reported: Number of recurrences was reported for both the BCG plus IFN- α and BCG alone groups (mean follow-up was 24.11 +/- 8.15 months for BCG alone group and 16.72 +/- 8.7 months for BCG plus IFN- α group).

Outcome definition: Not reported

Person measuring/reporting: Not reported

Subgroups: Not reported

Time-to-progression

Not reported

Discontinuation of therapy due to adverse events

Not reported

Disease-specific survival

Not reported

Time-to-death

Not reported

Systemic or local adverse events

Time points measured: Not reported

Time points reported: Not clearly reported; the occurrence of specific adverse events was reported for the BCG alone group only.

Outcome definition: Not reported

Person measuring/reporting: Not reported

Subgroups: Not reported

Disease-specific quality of life

Bercovich 1995 (Continued)

Not reported

Funding sources	Not reported
Declarations of interest	Not reported
Notes	Data extraction performed using translated manuscripts of Irianni 1993 and Bercovich 1995 ; manuscripts provided by study authors. Authors last contacted 3 October 2016 for further information; received response 31 October 2016 (no additional outcome data provided).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"A double arm random study" and "were randomized". No further details provided.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) Subjective outcomes	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) Objective outcomes	Unclear risk	Not applicable (time-to-death not reported)
Blinding of outcome assessment (detection bias) Subjective outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) Objective outcomes	Unclear risk	Not applicable (time-to-death not reported)
Incomplete outcome data (attrition bias) Time-to-recurrence	Unclear risk	Manuscript reports that 18 participants enrolled into the relevant groups (unclear whether this was total randomised). An additional study arm (IFN- α only) was discontinued due to evidence of no effect in blocking disease recurrence. No further details provided.
Incomplete outcome data (attrition bias) Time-to-progression	Unclear risk	Not reported
Incomplete outcome data (attrition bias) Discontinuation of therapy due to adverse events	Unclear risk	Not reported
Incomplete outcome data (attrition bias) Disease-specific survival	Unclear risk	Not reported
Incomplete outcome data (attrition bias)	Unclear risk	Not reported

Bercovich 1995 (Continued)

Time-to-death

Incomplete outcome data (attrition bias) Systemic or local adverse events	Unclear risk	Manuscript reports that 18 participants enrolled into the relevant groups (unclear whether this was total randomised). An additional study arm (IFN- α only) was discontinued due to evidence of no effect in blocking disease recurrence. While the reporting of recurrences assumes no attrition or exclusions, the authors do not clearly report on whether there were any postrandomisation losses to follow-up, withdrawals, or trial group changes.
Incomplete outcome data (attrition bias) Disease-specific quality of life	Unclear risk	Not reported
Selective reporting (reporting bias)	High risk	No mortality or progression outcomes reported, unlike most other studies in this area. Adverse events incompletely reported for BCG alone group.
Other bias	High risk	Limited reporting of baseline characteristics to determine comparability of groups. Interim results presented (in Irianni 1993) after 18 participants enrolled. Additional third study arm (IFN- α only) was later disregarded/excluded from reporting due to evidence of no effect in blocking disease recurrence.

Chiong 2011

Methods	<p><u>Start date, end date of recruitment:</u> 1995 to 2003</p> <p><u>Follow-up period:</u> Median follow-up 60 months in Chiong 2011. In Esuvaranathan 2014, follow-up was up to 207 months.</p> <p><u>Design:</u> Randomised controlled trial</p> <p><u>Ethics approval obtained:</u> Yes</p>
Participants	<p><u>Setting:</u> Multi-institutional study; setting not reported (authors affiliated to institution in Singapore)</p> <p><u>Population/inclusion criteria:</u> People who underwent TUR for NMIBC (urothelial carcinoma) and were at risk for recurrence or progression (CIS, T1, G2, G3 or multiple or recurrent Ta/G1 tumours) and had no prior intravesical therapy</p> <p><u>Exclusion criteria:</u> Not reported</p> <p><u>Method of recruitment:</u> Not reported</p> <p><u>Informed consent obtained:</u> Yes</p> <p><u>Total number randomly assigned:</u> "All patients (n = 103) had ..." in Chiong 2011; 140, as reported by Vasdev 2009 and Esuvaranathan 2014</p> <p><u>Baseline imbalances:</u> None reported for 99 "evaluable patients" in Chiong 2011</p> <p><u>Withdrawals or exclusions:</u> Esuvaranathan 2007 reported that of 93 participants enrolled, 80 were "evaluable" (7 participants defaulted follow-up, 3 died, and 3 underwent cystectomy for muscle-invasive disease within 3 months of recruitment). Chiong 2011 reported the total number of participants as 103, with 99 "evaluable patients", therefore 4 were lost to follow-up/excluded. Esuvaranathan 2014 reported that of the 140 participants, "The evaluable study cohort (n = 108) was followed up to 207 months", therefore 32 were lost to follow-up/excluded.</p> <p><u>Characteristics (age, race, gender, severity of illness, comorbidities):</u> Reported for 99 participants in Chiong 2011 for BCG plus IFN-α (n = 30); BCG 81 mg (n = 50); BCG 27 mg (n = 19)</p> <p>Age (mean, range) in years:</p>

Chiong 2011 (Continued)

- BCG plus IFN- α : 63.9 (34 to 79)
- BCG 81 mg: 64.6 (28 to 82)
- BCG 27 mg: 61.9 (49 to 80)

Gender

- BCG plus IFN- α : 70% male
- BCG 81 mg: 84% male
- BCG 27 mg: 84.2% male

Race/Ethnicity

- 83.8% Chinese; 8.1% Malay; 6.1% Indian; 2% Caucasian (understood to be white)

Stage

- BCG plus IFN- α : CIS: 26.7%; Ta: 30%; T1: 43.3%
- BCG 81 mg: CIS: 32%; Ta: 16%; T1: 52%
- BCG 27 mg: CIS: 31.6%; Ta: 21%; T1: 47.4%

Grade

- BCG plus IFN- α : G1: 23.3%; G2: 40%; G3: 36.7%
- BCG 81 mg: G1: 22%; G2: 42%; G3: 36%
- BCG 27 mg: G1: 10.5%; G2: 68.4%; G3: 21.1%

Interventions

Intervention

Total number randomised: 30

Description: BCG (Connaught strain) 1/3 dose (27 mg) plus 10 MU of IFN- α 2b. The regimen comprised an induction course of 6 weekly instillations, a 6-week break, and a final booster course of 3 once-per-week instillations.

Integrity of delivery/compliance: Not reported

Comparison 1 (BCG 81 mg)

Total number randomised: 50

Description: BCG (Connaught strain) standard dose (81 mg). The regimen comprised an induction course of 6 weekly instillations, a 6-week break, and a final booster course of 3 once-per-week instillations.

Integrity of delivery/compliance: Not reported

Comparison 2 (BCG 27 mg)

Total number randomised: 19

Description: BCG (Connaught strain) 1/3 dose (27 mg). The regimen comprised an induction course of 6 weekly instillations, a 6-week break, and a final booster course of 3 once-per-week instillations.

Integrity of delivery/compliance: Not reported

Other co-interventions for both groups: Not reported

Outcomes

Time-to-recurrence

Time points measured: The participants were followed up by cystoscopy and urinary cytology every 3 months for 3 years and every 6 months thereafter. Bladder biopsy and urinary cytological examinations were performed when indicated.

Chiong 2011 (Continued)

Time points reported: In [Esuvaranathan 2007](#), participants were followed for a mean of 4.5 years (range 6 to 114 months). In [Chiong 2011](#), median follow-up time was 60 months. [Esuvaranathan 2010](#) reported on recurrence probabilities at 36 and 60 months. [Esuvaranathan 2014](#) reported 207 months' follow-up and probabilities at 5 years' postrandomisation.

Outcome definition: Number of recurrences reported in [Chiong 2011](#). Vesical recurrence was defined as the occurrence of any new focus of NMIBC.

Person measuring/reporting: Not reported

Subgroups: Not reported

Time-to-progression

Time points measured: Participants were followed up by cystoscopy and urinary cytology every 3 months for 3 years and every 6 months thereafter. Bladder biopsy and urinary cytological examinations were performed when indicated.

Time points reported: In [Esuvaranathan 2007](#), participants were followed for a mean of 4.5 years (range 6 to 114 months). In [Chiong 2011](#), median time to progression was 39 months. [Esuvaranathan 2014](#) reported 207 months' follow-up.

Outcome definition: Number of progressions reported in [Chiong 2011](#). Tumour stage progression was defined as muscle invasion (stage T2 or higher).

Person measuring/reporting: Not reported

Subgroups: Not reported

Discontinuation of therapy due to adverse events

Not reported

Disease-specific survival

Time points measured: Not reported

Time points reported: In [Esuvaranathan 2007](#), mean of 24 months (range 12 to 42 months). In [Chiong 2011](#), median time of 60 months

Outcome definition: Cancer-specific mortality was reported in [Chiong 2011](#); no further definition provided.

Person measuring/reporting: Not reported

Subgroups: Not reported

Time-to-death

Not reported

Systemic or local adverse events

Time points measured: Not reported

Time points reported: From the 3rd to 9th instillation in [Vasdev 2009](#). During the first 6 instillations, and for the booster instillations in [Esuvaranathan 2014](#).

Outcome definition: Autoimmune clinical manifestations were reported in [Vasdev 2009](#); "local and systemic symptoms" were reported in [Esuvaranathan 2014](#).

Person measuring/reporting: Not reported

Subgroups: Not reported

Disease-specific quality of life

Chiong 2011 (Continued)

Not reported

Funding sources	Study was funded by the National Medical Research Council Singapore (NMRC/0085/1995 and NMRC/0457/2000), and the NLAM, National University of Singapore provided research grants. Gan 1999 notes that IFN- α was "a generous gift from Schering-Plough, Kenilworth, NJ".
Declarations of interest	None
Notes	Two similar abstracts published in 2014 outline long-term follow-up; full manuscripts are yet to be published. Study authors contacted on 25 April 2016 and 3 October 2016 for further information; awaiting response.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomized to receive"; no further details provided.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) Subjective outcomes	Unclear risk	"Double-blinded"; no further details provided.
Blinding of participants and personnel (performance bias) Objective outcomes	Unclear risk	Not applicable (time-to-death not reported).
Blinding of outcome assessment (detection bias) Subjective outcomes	Unclear risk	As above
Blinding of outcome assessment (detection bias) Objective outcomes	Unclear risk	Not applicable (time-to-death not reported).
Incomplete outcome data (attrition bias) Time-to-recurrence	High risk	In Esuvaranathan 2007 , of 93 participants, "seven patients defaulted follow-up, 3 patients died, and 3 patients underwent cystectomy for muscle-invasive disease, within 3 months of recruitment, and none of these patients were evaluable for outcome analysis" (80 were "evaluable"). In Chiong 2011 , of 103 participants, 99 were "evaluable". Esuvaranathan 2014 , which has been reported in abstract form only, stated that 108 of the 140 participants formed an "evaluable study cohort". No details were available from abstract regarding reasons for losses/exclusions and whether these were balanced across groups.
Incomplete outcome data (attrition bias) Time-to-progression	High risk	As above
Incomplete outcome data (attrition bias) Discontinuation of therapy due to adverse events	Unclear risk	Not reported

Chiong 2011 (Continued)

Incomplete outcome data (attrition bias) Disease-specific survival	High risk	In Esuvaranathan 2007 , of 93 participants, “seven patients defaulted follow-up, 3 patients died, and 3 patients underwent cystectomy for muscle-invasive disease, within 3 months of recruitment, and none of these patients were evaluable for outcome analysis” (80 were “evaluable”). In Chiong 2011 , of 103 participants, 99 were “evaluable”. Esuvaranathan 2014 , which has been reported in abstract form only, stated that 108 of the 140 participants formed an “evaluable study cohort”. No details were available from abstract regarding reasons for losses/exclusions and whether these were balanced across groups.
Incomplete outcome data (attrition bias) Time-to-death	Unclear risk	Not reported
Incomplete outcome data (attrition bias) Systemic or local adverse events	High risk	In Esuvaranathan 2007 , of 93 participants, “seven patients defaulted follow-up, 3 patients died, and 3 patients underwent cystectomy for muscle-invasive disease, within 3 months of recruitment, and none of these patients were evaluable for outcome analysis” (80 were “evaluable”). In Chiong 2011 , of 103 participants, 99 were “evaluable”. Esuvaranathan 2014 , which has been reported in abstract form only, stated that 108 of the 140 participants formed an “evaluable study cohort”. No details were available from abstract regarding reasons for losses/exclusions and whether these were balanced across groups.
Incomplete outcome data (attrition bias) Disease-specific quality of life	Unclear risk	Not reported
Selective reporting (reporting bias)	Unclear risk	Not possible to confidently assess selective reporting from abstracts of the long-term follow-up. To date, results have been reported incompletely. There was no access to trial protocol/registration.
Other bias	Low risk	Baseline characteristics, as reported in Chiong 2011 , were comparable between groups; no other sources of bias identified.

Jarvinen 2015

Methods	<u>Start date, end date of recruitment:</u> 1992 to 1996 <u>Follow-up period:</u> Median (range) for BCG alone group was 10.3 years (0.2 to 19.8) and for the BCG alternating with IFN- α group was 8.6 years (0.8 to 19.8). <u>Design:</u> Randomised controlled trial <u>Ethics approval obtained:</u> Not reported
Participants	<u>Setting:</u> 17 urological units participating in the FinnBladder IV study group <u>Population/inclusion criteria:</u> Participants had at least 2 histologically verified Ta or T1, G1–3 tumours during the previous 18 months. People with previous instillation therapy had at least 1 of the recurrences at 6 months after the last instillation. <u>Exclusion criteria:</u> Radiologic and pathologic assessments were used to exclude upper urinary tract tumours when indicated. Carcinoma in situ during the previous 1.5 years <u>Method of recruitment:</u> Not reported <u>Informed consent obtained:</u> Yes <u>Total number randomly assigned:</u> 236

Jarvinen 2015 (Continued)

Baseline imbalances: None. Authors acknowledged differences in the timing of the delivery of the co-intervention (intravesical mitomycin C).

Withdrawals or exclusions: 31 participants (16 in the BCG alone group and 15 in the BCG alternating with IFN- α group) were excluded for reasons including: inadequate histologic evidence of carcinoma, too-low preceding recurrence rate, CIS, incomplete TURBT, no instillation started (for reasons not related to participant's compliance or general condition), early carcinoma of the renal pelvis without previous urography at randomisation, pT2 tumour, and no data available.

Characteristics (age, race, gender, severity of illness, comorbidities):

BCG alternating with IFN- α (n = 103); BCG alone (n = 102)

- Age (mean (range)): BCG alternating with IFN- α : 67 years (42.8 to 87.3); BCG alone: 68 years (48.7 to 85.6)
- Sex (male): BCG alternating with IFN- α : 66%; BCG alone: 72%
- T category: pTa: BCG alternating with IFN- α : 94%; BCG alone: 97%; pT1: BCG alternating with IFN- α : 5%; BCG alone: 3%; equivocal: BCG alternating with IFN- α : 1%; BCG alone: 0%
- Grade 1: BCG alternating with IFN- α : 63%; BCG alone: 64%
- Grade 2: BCG alternating with IFN- α : 37%; BCG alone: 34%
- Grade 3: BCG alternating with IFN- α : 0%; BCG alone: 2%

Interventions
Intervention

Total number randomised: 118

Description: Alternating intravesical instillations of BCG (5×10^8 CFU in 100 mL saline; OncoTICE 5×10^8 CFU) (equivalent to 50 mg wet weight) or IFN- α 2b (50 MU/100 mL saline; Intron A 50 MU) for 2 hours, given monthly over the course of a year

Integrity of delivery/compliance: Not reported

Comparison

Total number randomised: 118

Description: BCG intravesical instillations (5×10^8 CFU in 100 mL saline; OncoTICE 5×10^8 CFU) (equivalent to 50 mg wet weight) for 2 hours, given monthly over the course of a year

Integrity of delivery/compliance: Not reported

Other co-interventions for both groups: All participants received perioperative MMC 40 mg/100 mL for 2 hours after eradication of visible tumours (TURBT or biopsy and fulguration), followed by 4 weekly MMC 40 mg/100 mL instillations.

Outcomes
Time-to-recurrence

Time points measured: Participants were followed with cytology and cystoscopy every 3 months during the first year and according to a clinician's decision thereafter.

Time points reported: Probability of recurrence was reported at 5-, 10-, and 15-year time points. The overall median follow-up was 10.3 years in the BCG alone group and 8.6 years in the BCG alternating with IFN- α group; median time-to-recurrence was reported for the BCG alternating with IFN- α group (10 months), but was "not attained" in the BCG alone group.

Outcome definition: A biopsy-confirmed Ta or T1 tumour, CIS, or positive cytology

Person measuring/reporting: Not reported

Subgroups: Not reported

Time-to-progression

Jarvinen 2015 (Continued)

Time points measured: Participants were followed with cytology and cystoscopy every 3 months during the first year and according to a clinician's decision thereafter.

Time points reported: Probability of progression was reported at 5-, 10-, and 15-year time points; the overall median follow-up was 10.3 years in the BCG alone group and 8.6 years in the BCG alternating with IFN- α group.

Outcome definition: pT2 or higher disease

Person measuring/reporting: Not reported

Subgroups: Not reported

Discontinuation of therapy due to adverse events

Time points measured: Not reported

Time points reported: Not reported

Outcome definition: "We recorded only major side effects, which in most cases resulted in discontinuation of the instilled agent and/or resulted in additional treatment"

Person measuring/reporting: Not reported

Subgroups: Not reported

Disease-specific survival

Time points measured: The follow-up was calculated from the date of surgery to the date of death or the date of the latest entry of data.

Time points reported: Probability of disease-specific mortality was reported at 5-, 10-, and 15-year time points; the overall median follow-up was 10.3 years in the BCG alone group and 8.6 years in the BCG alternating with IFN- α group.

Outcome definition: "Disease-specific mortality"; no further details provided

Person measuring/reporting: Not reported

Subgroups: Not reported

Time-to-death

Time points measured: The follow-up was calculated from the date of surgery to the date of death or the date of the latest entry of data.

Time points reported: Probability of overall survival was reported at 5-, 10-, and 15-year time points; the median follow-up time without death was 15.3 years in the BCG alone group and 15.9 years in the BCG alternating with IFN- α group.

Outcome definition: "Overall survival"; no further details provided

Person measuring/reporting: Not reported

Subgroups: Not reported

Systemic or local adverse events

Time points measured: Not reported

Time points reported: Not reported

Outcome definition: "We recorded only major side effects"

Person measuring/reporting: Not reported

Subgroups: Not reported

Jarvinen 2015 (Continued)

Disease-specific quality of life

Not reported

Funding sources	Finnish Cancer Foundation, Teknika, Organon, Pharmacia, Roche, and Schering Plough
Declarations of interest	None
Notes	Authors last contacted 3 October 2016 for further information; received response 25 November 2016 (no additional outcome data provided).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Allocation without blocking was based on a computer-based list in the secretary's possession and was confirmed by fax."
Allocation concealment (selection bias)	Low risk	"Central randomisation was carried out by the FinnBladder secretary."
Blinding of participants and personnel (performance bias) Subjective outcomes	High risk	Due to the nature of the interventions (BCG alone versus BCG alternating with IFN- α), it was considered unlikely that participants and personnel were blinded to the intervention.
Blinding of participants and personnel (performance bias) Objective outcomes	High risk	As above
Blinding of outcome assessment (detection bias) Subjective outcomes	High risk	As above
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Overall survival reported, which was considered an objective outcome unlikely to be influenced by absence of blinding.
Incomplete outcome data (attrition bias) Time-to-recurrence	Low risk	31 participants were excluded following randomisation (BCG alternating with IFN- α : 15/118; BCG alone: 16/118), in similar numbers with similar reasons for exclusion across the 2 treatment groups. Kaasinen 2000 also reported: "Seven patients without recurrence were followed less than 6 months due to death, protocol violation and other intervening disease (2) in 4, while in the remaining 3 further follow up data were not available after 3 months". Intention-to-treat analyses were conducted.
Incomplete outcome data (attrition bias) Time-to-progression	Low risk	As above
Incomplete outcome data (attrition bias) Discontinuation of therapy due to adverse events	Low risk	As above
Incomplete outcome data (attrition bias)	Low risk	As above

Jarvinen 2015 (Continued)

Disease-specific survival

Incomplete outcome data (attrition bias) Time-to-death	Low risk	As above
Incomplete outcome data (attrition bias) Systemic or local adverse events	Low risk	As above
Incomplete outcome data (attrition bias) Disease-specific quality of life	Unclear risk	Not reported
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported. Of note, median time to recurrence "was not attained" in the BCG alone group.
Other bias	Unclear risk	Baseline characteristics were largely balanced. It was unclear whether timing of single immediate chemotherapy instillation differed at baseline between groups, however using the multivariable analysis of potential prognostic variables for primary endpoints with adjustment for significant prognostic variables (including timing of first chemotherapy instillation) did not change the conclusions. Regarding additional treatments during follow-up, there were more treatments in the BCG alternating with IFN- α group (27 versus 16), which the authors suggest "may have additionally contributed to decreasing the progression rate and the difference between the groups".

Minich 2009

Methods	<u>Start date, end date of recruitment:</u> February 2003 to August 2007 <u>Follow-up period:</u> Median follow-up 38.3 months. Response was assessed by cystoscopy every 3 months in the first 2 years, then 6 monthly; 3-year recurrence-free survival reported. <u>Design:</u> Randomised controlled trial <u>Ethics approval obtained:</u> Not reported
Participants	<u>Setting:</u> Not reported (authors affiliated to institution in Belarus) <u>Population/inclusion criteria:</u> Non-muscle invasive transitional cell carcinoma with intermediate- and high-risk of recurrence and progression; randomised after transurethral resection of all tumours <u>Exclusion criteria:</u> Not reported <u>Method of recruitment:</u> Not reported <u>Informed consent obtained:</u> Not reported <u>Total number randomly assigned:</u> 149 (120 to the relevant trial arms) <u>Baseline imbalances:</u> None <u>Withdrawals or exclusions:</u> Small number of participants in the IFN- α monotherapy group was due to cessation of recruitment part way through from interim analysis indicating a higher risk of recurrence. <u>Characteristics (age, race, gender, severity of illness, comorbidities):</u> BCG plus IFN- α (n = 60); BCG alone (n = 60)

Minich 2009 (Continued)

Median age overall: 65 years, range 29 to 83 years

Median age (years):

- BCG alone: 64
- BCG plus IFN- α : 65

Gender

- BCG alone: 78% male
- BCG plus IFN- α : 70% male

Stage

- BCG alone: CIS 2%; Ta 5%; T1 93%
- BCG plus IFN- α : CIS 2%; Ta 5%; T1 93%

Grade

- BCG alone: G1 58%; G2 32%; G3 10%
- BCG plus IFN- α : G1 75%; G2 17%; G3 8%

Interventions
Intervention

Total number randomised: 60

Description: 6 weekly instillations of 125 mg BCG (full dose, Russian strain) plus 6 MU of IFN- α

Integrity of delivery/compliance: Not reported, however it was noted that 108 participants completed the full course of treatment (it was not clear to which groups these participants had been assigned).

Comparison

Total number randomised: 60

Description: 6 weekly instillations of 125 mg BCG (full dose, Russian strain)

Integrity of delivery/compliance: Not reported (see above)

Other co-interventions for both groups: Not reported

Outcomes
Time-to-recurrence

Time points measured: Response was assessed by cystoscopy every 3 months after treatment in the first 2 years and then 6 monthly.

Time points reported: Number of recurrences were reported; follow-up: median 38.3 months.

Outcome definition: Not reported

Person measuring/reporting: Not reported

Subgroups: Not reported

Time-to-progression

Time points measured: Response was assessed by cystoscopy every 3 months after treatment in the first 2 years and then 6 monthly.

Time points reported: Number of progressions were reported, between 3.6 and 29.7 months.

Outcome definition: Not reported

Person measuring/reporting: Not reported

Minich 2009 (Continued)

Subgroups: Not reported

Discontinuation of therapy due to adverse events

Time points measured: Not reported

Time points reported: Reported during the course of treatment

Outcome definition: Not reported

Person measuring/reporting: Not reported

Subgroups: Not reported

Disease-specific survival

Time points measured: Not reported

Time points reported: 1-, 2-, and 3-year survival rates reported only

Outcome definition: Not reported

Person measuring/reporting: Not reported

Subgroups: Not reported

Time-to-death

Not reported

Systemic or local adverse events

Time points measured: Not reported

Time points reported: Reported during the course of treatment (including disorientation/delirium; macroscopic haematuria)

Outcome definition: Not reported

Person measuring/reporting: Not reported

Subgroups: Not reported

Disease-specific quality of life

Not reported

Funding sources	Not reported
Declarations of interest	Not reported
Notes	Data extraction performed using translated manuscript of Minich 2009 ; manuscript provided by author. There was a third arm in this trial: IFN- α alone, which we have not included in the review. Authors last contacted 3 October 2016 for further information; awaiting response.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"After histological confirmation patients were randomised into three groups". After an interim analysis indicated a higher risk of recurrence in the third arm (interferon only), recruitment to that arm ceased; impact on randomisation not reported.

Minich 2009 (Continued)

Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) Subjective outcomes	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) Objective outcomes	Unclear risk	Not applicable (time-to-death not reported).
Blinding of outcome assessment (detection bias) Subjective outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) Objective outcomes	Unclear risk	Not applicable (time-to-death not reported).
Incomplete outcome data (attrition bias) Time-to-recurrence	Unclear risk	While the reporting of recurrences assumes no attrition or exclusions, the authors do not clearly report on whether there were any postrandomisation losses to follow-up, withdrawals, or trial group changes.
Incomplete outcome data (attrition bias) Time-to-progression	Unclear risk	While the reporting of progression assumes no attrition or exclusions, the authors do not clearly report on whether there were any postrandomisation losses to follow-up, withdrawals, or trial group changes.
Incomplete outcome data (attrition bias) Discontinuation of therapy due to adverse events	Unclear risk	Discontinuation of therapy due to adverse events was incompletely reported (a P value provided only); the authors do not clearly report on whether there were any postrandomisation losses to follow-up, withdrawals, or trial group changes.
Incomplete outcome data (attrition bias) Disease-specific survival	Unclear risk	Not reported
Incomplete outcome data (attrition bias) Time-to-death	Unclear risk	Not reported
Incomplete outcome data (attrition bias) Systemic or local adverse events	Unclear risk	While the reporting of adverse events assumes no attrition or exclusions, the authors do not clearly report on whether there were any postrandomisation losses to follow-up, withdrawals, or trial group changes.
Incomplete outcome data (attrition bias) Disease-specific quality of life	Unclear risk	Not reported
Selective reporting (reporting bias)	High risk	Data reported on all outcomes specified in methods section except all-cause mortality; discontinuation of therapy due to adverse events was reported incompletely. There was no access to trial protocol/registration to further assess selective reporting.
Other bias	Low risk	No differences in baseline characteristics; no sources of other bias identified.

Nepple 2010

Methods	<p><u>Start date, end date of recruitment:</u> 1999 to 2003</p> <p><u>Follow-up period:</u> Participants were followed with quarterly cystoscopy for 2 years, then 6 monthly through year 4, then annually.</p> <p><u>Design:</u> Randomised controlled trial; 2x2 factorial study</p> <p><u>Ethics approval obtained:</u> Yes</p>
Participants	<p><u>Setting:</u> Multicentre study at 75 centres; locations not specified (authors affiliated to institution in United States).</p> <p><u>Population/inclusion criteria:</u> Histologically confirmed (tumour resection, biopsy, or abnormal cytology) CIS, Ta, or T1 urothelial cancer diagnosed within 8 weeks; no prior BCG treatment for bladder cancer</p> <p><u>Exclusion criteria:</u> Any muscle-invasive, upper tract of metastatic urothelial carcinoma, any other active malignancy that might impact 5-year survival, pregnancy, immunosuppression or Eastern Cooperative Oncology Group performance status greater than 2</p> <p><u>Method of recruitment:</u> Not reported</p> <p><u>Informed consent obtained:</u> Yes</p> <p><u>Total number randomly assigned:</u> 670</p> <p><u>Baseline imbalances:</u> Not reported</p> <p><u>Withdrawals or exclusions:</u> Not reported</p> <p><u>Characteristics (age, race, gender, severity of illness, comorbidities):</u> Mean age: 68.4 years; 76% of participants were male.</p>
Interventions	<p><u>Intervention 1 (BCG plus IFN-α and RDA vitamins)</u></p> <p>Total number randomised: 176</p> <p>Description: BCG (50 mg TICE strain BCG in 50 mL saline) plus 50 MU of IFN-α2b (Intron A); induction course of 6 weekly intravesical instillations, participants who were rendered bladder cancer-free were given maintenance courses consisting of 3 consecutive weekly instillations of BCG reduced to 1/3 dose (16.6 mg/50 mL) and IFN-α2b 50 MU at 4 months after the start of the induction course, and again at 7, 13, 19, 25, and 37 months as long as they remained bladder cancer-free; if intolerance occurred during the induction or maintenance period, instillation of study agents was discontinued for 2 weeks followed by re-initiation of treatment at a BCG dose of 1/3 of that of the prior dose, with further sequential reductions by 1/3 of the prior dose permitted if intolerance continued, with no change in IFN-α2b dosing.</p> <p>Integrity of delivery/compliance: Not reported</p> <p><u>Comparison 1 (BCG alone and RDA vitamins)</u></p> <p>Total number randomised: 160</p> <p>Description: BCG (50 mg TICE strain BCG in 50 mL saline); induction course of 6 weekly intravesical instillations, participants who were rendered bladder cancer-free were given maintenance courses consisting of 3 consecutive weekly instillations of BCG reduced to 1/3 dose (16.6 mg/50 mL) at 4 months after the start of the induction course, and again at 7, 13, 19, 25, and 37 months as long as they remained bladder cancer-free; if intolerance occurred during the induction or maintenance period, instillation of study agents was discontinued for 2 weeks followed by re-initiation of treatment at a BCG dose of 1/3 of that of the prior dose, with further sequential reductions by 1/3 of the prior dose permitted if intolerance continued.</p> <p>Integrity of delivery/compliance: Not reported</p>

Nepple 2010 (Continued)

Other co-interventions for both groups (Intervention 1 and Comparison 1): Matched blinded vitamins were given in a dose of 2 tablets twice daily throughout the study, starting at the time of group assignment and continuing for the duration of the study. Each RDA tablet contained 25% of the recommended total daily dose.

Intervention 2 (BCG plus IFN- α and megadose vitamins)

Total number randomised: 170

Description: As per Intervention 1

Integrity of delivery/compliance: Not reported

Comparison 2 (IFN- α and megadose vitamins)

Total number randomised: 164

Description: As per Comparison 1

Integrity of delivery/compliance: Not reported

Other co-interventions for both groups (Intervention 2 and Comparison 2): Matched blinded vitamins were given in a dose of 2 tablets twice daily throughout the study, starting at the time of group assignment and continuing for the duration of the study. Each Oncovite (megadose vitamin preparation) tablet contained vitamins A (9000 IU), B₆ (25 mg), C (500 mg), D₃ (400 IU), folate (0.4 mg), and E (100 IU) as well as zinc (7.6 mg).

Outcomes

Time-to-recurrence

Time points measured: Clinical response was assessed by cystoscopy and cytology every 3 months for the first 24 months of the study, every 6 months during years 3 and 4, and annually thereafter.

Time points reported: Not reported

Outcome definition: Time-to-recurrence was the interval from the date of randomisation (or first date free of disease for participants with CIS) to first recurrence confirmed by biopsy or cytology. Any relapse during follow-up was counted as a failure of therapy.

Person measuring/reporting: Not reported

Subgroups: Not reported

Time-to-progression

Not reported

Discontinuation of therapy due to adverse events

Time points measured: Not reported

Time points reported: Not reported

Outcome definition: Treatment intolerance was defined as dysuria that persisted for 3 or more days, fever higher than 101°F (38.3°C) or other severe systemic reaction. If treatment intolerance occurred during the induction or maintenance period, instillation of study agents was discontinued for 2 weeks followed by re-initiation of treatment at a BCG dose of 1/3 that of the prior dose. If intolerance continued, further sequential reductions by 1/3 of the prior dose were permitted (i.e. 1/10th to 1/30th to 1/100th dose). The dosing of IFN- α was not reduced.

Person measuring/reporting: Not reported

Subgroups: Not reported

Disease-specific survival

Not reported

Nepple 2010 (Continued)

Time-to-death

Not reported

Systemic or local adverse events

Time points measured: Not reported

Time points reported: Not reported

Outcome definition: Treatment intolerance was defined as dysuria that persisted for 3 or more days, fever higher than 101°F (38.3°C) or other severe systemic reaction; fever and "constitutional symptoms" were reported.

Person measuring/reporting: Not reported

Subgroups: Not reported

Disease-specific quality of life

Not reported

Funding sources	Supported by Schering-Plough Corp, Mission Pharmacal
Declarations of interest	Financial interest and/or other relationships with Abbott Laboratories, Alnylam Pharmaceuticals, Viventia, Anadys Pharmaceuticals, Spectrum, Loras, Endo Pharmaceuticals, Medical Enterprises, and Sanofi-Pasteur
Notes	Immediate postoperative intravesical chemotherapy was used in 53 (8%) of the 670 participants: mitomycin: 36; thiotepa: 9; doxorubicin: 3; valrubicin: 2; other: 3. Authors last contacted 3 October 2016 for further information; awaiting response.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were randomised by central computer to receive to BCG or BCG plus interferon." "Patients were randomised using a 1:1:1:1 allocation ratio to 4 treatment arms"
Allocation concealment (selection bias)	Low risk	"Randomised by central computer"
Blinding of participants and personnel (performance bias) Subjective outcomes	High risk	"Patients and providers were not blinded to the IFN, which could have affected reporting"
Blinding of participants and personnel (performance bias) Objective outcomes	Unclear risk	Not applicable (time-to-death not reported).
Blinding of outcome assessment (detection bias) Subjective outcomes	High risk	"Patients and providers were not blinded to the IFN, which could have affected reporting"
Blinding of outcome assessment (detection bias) Objective outcomes	Unclear risk	Not applicable (time-to-death not reported).

Nepple 2010 (Continued)

Incomplete outcome data (attrition bias) Time-to-recurrence	Unclear risk	While the reporting of recurrence assumes no attrition or exclusions, the authors do not clearly report on whether there were any postrandomisation losses to follow-up, withdrawals, or trial group changes.
Incomplete outcome data (attrition bias) Time-to-progression	Unclear risk	Not reported
Incomplete outcome data (attrition bias) Discontinuation of therapy due to adverse events	Unclear risk	Not reported
Incomplete outcome data (attrition bias) Disease-specific survival	Unclear risk	Not reported
Incomplete outcome data (attrition bias) Time-to-death	Unclear risk	Not reported
Incomplete outcome data (attrition bias) Systemic or local adverse events	Unclear risk	While the reporting of adverse events assumes no attrition or exclusions, the authors do not clearly report on whether there were any postrandomisation losses to follow-up, withdrawals, or trial group changes.
Incomplete outcome data (attrition bias) Disease-specific quality of life	Unclear risk	Not reported
Selective reporting (reporting bias)	High risk	No mortality outcomes reported, unlike most other studies in this area. Some results relating to recurrence and progression reported incompletely in text. "Overall 231 of 670 patients (34%) had documented recurrence, including muscle invasive disease in 47 (7%) and discovery of metastatic disease in 7 (1%)." It was not clear to which groups these participants had been allocated. Secondary outcome was reported to be "severity of treatment toxicity", however the reported results were likelihood of fever and likelihood of constitutional symptoms only.
Other bias	Unclear risk	Baseline characteristics not reported by treatment group. Immediate postoperative intravesical chemotherapy was used in 53 (8%) of participants; it was not reported to which groups these participants had been assigned. Unclear whether conflicts of interest had any impact on the conduct of the trial.

BCG: Bacillus Calmette-Guérin

CFU: colony forming units

CIS: carcinoma in situ

G1: grade 1

G2: grade 2

G3: grade 3

IFN- α : interferon-alpha

IU: international units

MMC: mitomycin C

MU: million units

NaCl: sodium chloride

NMIBC: non-muscle-invasive bladder cancer

pTa: pathological tumour stage a

pT1: pathological tumour stage 1
pT2: pathological tumour stage 2
RDA: recommended daily allowance
Ta: tumour stage a
T1: tumour stage 1
T2: tumour stage 2
TUR: transurethral resection
TURBT: transurethral resection of bladder tumour

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

Study	Reason for exclusion
Joudi 2006	This was not a randomised controlled trial.
O'Donnell 2004	This was not a randomised controlled trial.

DATA AND ANALYSES

Comparison 1. Intravesically administered BCG combined with IFN- α versus intravesically administered BCG alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Time-to-recurrence	1	670	Hazard Ratio (Random, 95% CI)	1.11 [0.86, 1.43]
2 Recurrence	4	925	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.44, 1.32]
2.1 IFN- α higher dose (50 MU) weekly for 6 weeks	1	670	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.93, 1.41]
2.2 IFN- α lower dose (6 to 10 MU) weekly for 6 weeks	3	255	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.36, 0.94]
3 Progression	2	219	Risk Ratio (M-H, Random, 95% CI)	0.26 [0.04, 1.87]
4 Disease-specific mortality	1	99	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.05, 3.05]
5 Systemic or local adverse events	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Any (including disorientation/delirium and macro haematuria)	1	120	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.13, 0.86]
5.2 Fever	1	670	Risk Ratio (M-H, Random, 95% CI)	2.22 [1.27, 3.91]
5.3 Constitutional symptoms	1	670	Risk Ratio (M-H, Random, 95% CI)	1.61 [1.10, 2.36]

Analysis 1.1. Comparison 1 Intravesically administered BCG combined with IFN- α versus intravesically administered BCG alone, Outcome 1 Time-to-recurrence. **Analysis 1.2. Comparison 1 Intravesically administered BCG combined with IFN- α versus intravesically administered BCG alone, Outcome 2 Recurrence.** **Analysis 1.3. Comparison 1 Intravesically administered BCG combined with IFN- α versus intravesically administered BCG alone, Outcome 3 Progression.**

Analysis 1.4. Comparison 1 Intravesically administered BCG combined with IFN- α versus intravesically administered BCG alone, Outcome 4 Disease-specific mortality.

Analysis 1.5. Comparison 1 Intravesically administered BCG combined with IFN- α versus intravesically administered BCG alone, Outcome 5 Systemic or local adverse events.

Comparison 2. Intravesically administered BCG alternating with IFN- α versus intravesically administered BCG alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Time-to-recurrence	1	205	Hazard Ratio (Random, 95% CI)	2.86 [1.98, 4.13]
2 Time-to-progression	1	205	Hazard Ratio (Random, 95% CI)	2.39 [0.92, 6.21]
3 Discontinuation of therapy due to adverse events	1	205	Risk Ratio (M-H, Random, 95% CI)	2.97 [0.31, 28.09]
4 Disease-specific mortality	1	205	Hazard Ratio (Random, 95% CI)	2.74 [0.73, 10.28]
5 Overall survival	1	205	Hazard Ratio (Random, 95% CI)	1.0 [0.68, 1.47]
6 Systemic or local adverse events	1	205	Risk Ratio (M-H, Random, 95% CI)	1.65 [0.41, 6.73]

Analysis 2.1. Comparison 2 Intravesically administered BCG alternating with IFN- α versus intravesically administered BCG alone, Outcome 1 Time-to-recurrence.

Analysis 2.2. Comparison 2 Intravesically administered BCG alternating with IFN- α versus intravesically administered BCG alone, Outcome 2 Time-to-progression.

Analysis 2.3. Comparison 2 Intravesically administered BCG alternating with IFN- α versus intravesically administered BCG alone, Outcome 3 Discontinuation of therapy due to adverse events.

Analysis 2.4. Comparison 2 Intravesically administered BCG alternating with IFN- α versus intravesically administered BCG alone, Outcome 4 Disease-specific mortality.

Analysis 2.5. Comparison 2 Intravesically administered BCG alternating with IFN- α versus intravesically administered BCG alone, Outcome 5 Overall survival.

Analysis 2.6. Comparison 2 Intravesically administered BCG alternating with IFN- α versus intravesically administered BCG alone, Outcome 6 Systemic or local adverse events.

APPENDICES

Appendix 1. CENTRAL search strategy

1. MeSH descriptor Urinary Bladder Neoplasms explode all trees
2. (bladder* NEAR/3 (cancer* or carcinoma* or neoplas* or tumor?r* or tum?r*)):ti,ab,kw
3. MeSH descriptor Carcinoma, Transitional Cell explode all trees
4. (tcc or transitional cell):ti,ab,kw
5. MeSH descriptor Ureteral Neoplasms explode all trees
6. MeSH descriptor Urethral Neoplasms explode all trees
7. ((bladder* or urethra* or ureter* or urin* or urotheli* or renal pelvis or calice*) NEAR/3 (cancer* or carcinoma* or adenoma* or adenocarcinoma* or squamous* or neoplas* or tumor?r* or tum?r* or malignan*)):ti,ab,kw
8. (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7)
9. MeSH descriptor BCG vaccine explode all trees
10. bacillus calmette guerin:ti,ab,kw
11. bcg:ti,ab,kw
12. (#9 OR #10 OR #11)
13. MeSH descriptor Interferons explode all trees
14. ((interferon*) or (ifn alpha) or (ifn alfa)):ti,ab,kw
15. (#13 OR #14)
16. (#8 AND #12 AND #15)

Appendix 2. MEDLINE (OvidSP) search strategy

1. exp urinary bladder neoplasms/
2. (bladder\$ adj3 (cancer\$ or carcinoma\$ or neoplas\$ or tumor?r\$ or tum?r\$)).mp.
3. exp carcinoma, transitional cell/
4. (tcc or transitional cell).mp.
5. exp ureteral neoplasms/
6. urethral neoplasms/
7. ((bladder\$ or urethra\$ or ureter\$ or urin\$ or urotheli\$ or renal pelvis or calice\$) adj3 (cancer\$ or carcinoma\$ or adenoma\$ or adenocarcinoma\$ or squamous\$ or neoplas\$ or tumor?r\$ or tum?r\$ or malignan\$)).tw.
8. or/1-7
9. exp BCG vaccine/
10. bacillus calmette guerin.tw
11. bcg.tw
12. or/9-11
13. exp Interferons/
14. interferon\$.mp.
15. (interferon alpha or interferon alfa).mp.
16. or/13-15
17. randomized controlled trial.pt.
18. controlled clinical trial.pt.
19. randomized.ab.
20. placebo.ab.

- 21.clinical trials as topic.sh.
- 22.randomly.ab.
- 23.trial.ti.
- 24.or/17-23
- 25.exp animals/ not humans.sh.
- 26.24 not 25
- 27.8 and 12 and 16 and 26

Appendix 3. Embase (OvidSP) search strategy

1. exp bladder tumor/
2. (bladder\$ adj3 (cancer\$ or carcinoma\$ or neoplas\$ or tumo?r\$ or tum?r\$)).mp.
3. exp transitional cell carcinoma/
4. (tcc or transitional cell).mp.
5. exp ureter tumor/
6. exp urethra tumor/
7. ((bladder\$ or urethra\$ or ureter\$ or urin\$ or urotheli\$ or renal pelvis or calice\$) adj3 (cancer\$ or carcinoma\$ or adenoma\$ or adenocarcinoma\$ or squamous\$ or neoplas\$ or tumo?r\$ or tum?r\$ or malignan\$)).tw.
8. or/1-7
9. exp BCG vaccine/
- 10.bacillus calmette guerin.ti,ab
- 11.bcg.ti,ab
- 12.or/9-11
- 13.exp INTERFERON
- 14.interferon\$.mp.
- 15.(interferon alpha or interferon alfa).mp.
- 16.or/13-15
- 17.crossover procedure/
- 18.double-blind procedure/
- 19.randomized controlled trial/
- 20.single-blind procedure/
- 21.(random\$ or factorial\$ or crossover\$ or cross over\$ or placebo\$ or assign\$ or allocat\$ or volunteer\$).mp.
- 22.((doubl\$ or singl\$) adj blind\$).mp.
- 23.or/17-22
- 24.8 and 12 and 16 and 23

Appendix 4. ClinicalTrials.gov search strategy

Basic search:

(bladder OR urethra OR ureter OR urinary OR urothelial OR urologic OR renal pelvis) AND (bacillus calmette guerin OR bcg) AND (interferon OR ifn)

Appendix 5. WHO ICTRP search strategy

Simple search with each of these lines searched and assessed separately:

Bladder AND bcg AND ifn

Bladder AND bcg AND interferon

Bladder AND bacillus calmette guerin AND ifn

Bladder AND bacillus calmette guerin AND interferon

CONTRIBUTIONS OF AUTHORS

All review authors (Andrew RH Shepherd (ARHS), Emily Shepherd (ES), and Nicholas R Brook (NRB)) contributed to the design, development, and drafting of the protocol, and search strategy development.

ARHS and ES acquired trial reports and conducted trial selection and data extraction

NRB was consulted to resolve discrepancies or disagreements

ARHS led the data analysis, and ES and NRB assisted with data interpretation

All review authors contributed to review drafting, with ARHS in the leading role

All review authors will contribute to future review updates

DECLARATIONS OF INTEREST

ARHS: none known

ES: none known

NRB: none known

SOURCES OF SUPPORT

Internal sources

- None, Other.

External sources

- None, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

This review was based on a published protocol ([Shepherd 2016](#)), with differences as described here.

We included a second comparison, 'intravesically administered BCG alternating with IFN- α versus intravesically administered BCG alone', which we believed was important and relevant to our review objective. We did not consider it appropriate for studies assessing alternating BCG and IFN- α to be pooled with those assessing co-administration of BCG and IFN- α .

As for our first comparison, 'intravesically administered BCG combined with IFN- α versus intravesically administered BCG alone', we were unable to obtain time-to-event information for the outcomes time-to-recurrence and time-to-progression, assessing the dichotomous outcomes recurrence and progression instead; we thus included these outcomes in the 'Summary of findings' table. For both comparisons, we were unable to obtain information for the outcome disease-specific survival, assessing the outcome disease-specific mortality instead; we thus included this outcome in the 'Summary of findings' tables.

NOTES

Parts of the Methods section of this review were based on a standard template developed by the Cochrane Metabolic and Endocrine Disorders Group that has been modified and adapted for use by the Cochrane Urology Group.

INDEX TERMS

Medical Subject Headings (MeSH)

Adjuvants, Immunologic [*administration & dosage] [adverse effects]; Administration, Intravesical; Antineoplastic Agents [*administration & dosage] [adverse effects]; BCG Vaccine; Carcinoma in Situ [mortality] [pathology] [*therapy]; Combined Modality Therapy [adverse effects] [methods]; Disease Progression; Drug Administration Schedule; Interferon-alpha [*administration & dosage] [adverse effects]; Neoplasm Recurrence, Local; Randomized Controlled Trials as Topic; Time Factors; Urinary Bladder Neoplasms [mortality] [pathology] [*therapy]; Withholding Treatment [statistics & numerical data]

MeSH check words

Humans