Cochrane Library

Cochrane Database of Systematic Reviews

Intravesical gemcitabine for non-muscle invasive bladder cancer (Review)

Han MA, Maisch P, Jung JH, Hwang JE, Narayan V, Cleves A, Hwang EC, Dahm P

Han MA, Maisch P, Jung JH, Hwang JE, Narayan V, Cleves A, Hwang EC, Dahm P.
Intravesical gemcitabine for non-muscle invasive bladder cancer.
Cochrane Database of Systematic Reviews 2021, Issue 6. Art. No.: CD009294.
DOI: 10.1002/14651858.CD009294.pub3.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Intravesical gemcitabine for non-muscle invasive bladder cancer

Mi Ah Han[1], Philipp Maisch[2], Jae Hung Jung[3,4], Jun Eul Hwang[5], Vikram Narayan[6], Anne Cleves[7], Eu Chang Hwang[8], Philipp Dahm[9]

[1]Department of Preventive Medicine, College of Medicine, Chosun University, Gwangju, Korea, South. [2]Department of Urology, Rechts der Isar Medical Center, Technical University of Munich, Munich, Germany. [3]Department of Urology, Yonsei University Wonju College of Medicine, Wonju, Korea, South. [4]Center of Evidence Based Medicine, Institute of Convergence Science, Yonsei University, Seoul, Korea, South. [5]Department of Hematology-Oncology, Chonnam National University Medical School, Chonnam National University Hwasun Hospital, Hwasun, Korea, South. [6]Department of Urology, University of Minnesota, Minneapolis, Minnesota, USA. [7]Velindre NHS Trust, Cardiff University Library Services, Cardiff, UK. [8]Department of Urology, Chonnam National University Medical School, Chonnam National University Hwasun Hospital, Hwasun, Korea, South. [9]Urology Section, Minneapolis VA Health Care System, Minneapolis, Minnesota, USA

Contact: Eu Chang Hwang, urohwang@gmail.com, urohwang@naver.com.

Editorial group: Cochrane Urology Group.
Publication status and date: New search for studies and content updated (conclusions changed), published in Issue 6, 2021.

Citation: Han MA, Maisch P, Jung JH, Hwang JE, Narayan V, Cleves A, Hwang EC, Dahm P. Intravesical gemcitabine for non-muscle invasive bladder cancer. *Cochrane Database of Systematic Reviews* 2021, Issue 6. Art. No.: CD009294. DOI: 10.1002/14651858.CD009294.pub3.

ABSTRACT

Background

It remains unclear whether people with non-muscle invasive bladder cancer (NMIBC) benefit from intravesical gemcitabine compared to other agents in the primary or recurrent setting following transurethral resection of a bladder tumor. This is an update of a Cochrane Review first published in 2012. Since that time, several randomized controlled trials (RCTs) have been reported, making this update relevant.

Objectives

To assess the comparative effectiveness and toxicity of intravesical gemcitabine instillation for NMIBC.

Search methods

We performed a comprehensive literature search of the Cochrane Library, MEDLINE, Embase, four other databases, trial registries, and conference proceedings to 11 September 2020, with no restrictions on the language or status of publication.

Selection criteria

We included RCTs in which participants received intravesical gemcitabine for primary or recurrent NMIBC.

Data collection and analysis

Two review authors independently assessed the included studies and extracted data for the primary outcomes: time to recurrence, time to progression, grade III to V adverse events determined by the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0), and the secondary outcomes: time to death from bladder cancer, time to death from any cause, grade I or II adverse events determined by the CTCAE v5.0 and disease-specific quality of life. We performed statistical analyses using a random-effects model and rated the certainty of the evidence using GRADE.

Main results

We included seven studies with 1222 participants with NMIBC across five comparisons. This abstract focuses on the primary outcomes of the three most clinically relevant comparisons.

1. Gemcitabine versus saline: based on two years' to four years' follow-up, gemcitabine may reduce the risk of recurrence over time compared to saline (39% versus 47% recurrence rate, hazard ratio [HR] 0.77, 95% confidence interval [CI] 0.54 to 1.09; studies = 2, participants = 734; I^2 = 49%; low-certainty evidence), but the CI included the possibility of no effect. Gemcitabine may result in little to no difference in the risk of progression over time compared to saline (4.6% versus 4.8% progression rate, HR 0.96, 95% CI 0.19 to 4.71; studies = 2, participants = 654; I^2 = 53%; low-certainty evidence). Gemcitabine may result in little to no difference in the CTCAE grade III to V adverse events compared to saline (5.9% versus 4.7% adverse events rate, risk ratio [RR] 1.26, 95% CI 0.58 to 2.75; studies = 2, participants = 668; I^2 = 24%; low-certainty evidence).

2. Gemcitabine versus mitomycin: based on three years' follow-up (studies = 1, participants = 109), gemcitabine may reduce the risk of recurrence over time compared to mitomycin (17% versus 40% recurrence rate, HR 0.36, 95% CI 0.19 to 0.69; low-certainty evidence). Gemcitabine may reduce the risk of progression over time compared to mitomycin (11% versus 18% progression rate, HR 0.57, 95% CI 0.32 to 1.01; low-certainty evidence), but the CI included the possibility of no effect. We are very uncertain about the effect of gemcitabine on the CTCAE grade III to V adverse events compared to mitomycin (RR 0.51, 95% CI 0.13 to 1.93; very low-certainty evidence). The analysis was only based on recurrent NMIBC.

3. Gemcitabine versus Bacillus Calmette-Guérin (BCG) for recurrent (one-course BCG failure) high-risk NMIBC: based on 6 months' to 22 months' follow-up (studies = 1, participants = 80), gemcitabine may reduce the risk of recurrence compared to BCG (41% versus 97% recurrence rate, HR 0.15, 95% CI 0.09 to 0.26; low-certainty evidence) and progression over time (16% versus 33% progression rate, HR 0.45, 95% CI 0.27 to 0.76; low-certainty evidence). We are very uncertain about the effect of gemcitabine on the CTCAE grade III to V adverse events compared to BCG (RR 1.00, 95% CI 0.21 to 4.66; very low-certainty evidence).

In addition, the review provides information on the comparison of gemcitabine versus BCG and gemcitabine versus one-third dose BCG.

Authors' conclusions

Based on findings of this review, gemcitabine may have a more favorable impact on recurrence and progression-free survival than mitomycin but we are very uncertain as to how major adverse events compare. The same is true when comparing gemcitabine to BCG in individuals with high risk disease who have previously failed BCG. The underlying low- to very low-certainty evidence indicates that our confidence in these results is limited; the true effects may be substantially different from these findings; therefore, better quality studies are needed.

PLAIN LANGUAGE SUMMARY

Intravesical gemcitabine for non-muscle invasive bladder cancer

Review question

In people with tumors of the superficial layer of the urinary bladder (namely non-muscle invasive bladder cancer [NMIBC]), how does gemcitabine that is put into the bladder compare to other medicines after the tumor has been removed?

Background

NMIBC can be taken out of the bladder using small instruments and a light source (called transurethral surgery). However, these tumors often come back (recurrence) with an aggressive feature such as spread into the deep layers of the bladder. To prevent this, we can put various medicines into the bladder. In this review, we wanted to know whether gemcitabine (a chemotherapy medication) was better or worse than other medicines.

Study characteristics

The evidence is current to 11 September 2020. We included only studies in which chance determined whether people received gemcitabine or other medicines. We found seven studies with 1222 participants. Two studies compared gemcitabine versus saline. One study compared gemcitabine versus mitomycin (a chemotherapy medication). Three studies compared gemcitabine versus BCG (Bacillus Calmette-Guérin; a medicine used to help keep cancer from growing). One study compared gemcitabine versus one-third dose BCG.

Key results

Gemcitabine may reduce the risk of recurrence over time, but may have a similar effect on progression (cancer getting worse) and severe unwanted effects compared to saline. Gemcitabine may prevent recurrence and progression compared to mitomycin. We are very unsure about the effect of gemcitabine on the severe unwanted effects compared to mitomycin. In people who had a high-risk NMIBC with the cancer coming back after one course of treatment with BCG, gemcitabine may cause less tumor recurrence and progression compared to giving BCG again. We are very unsure about the effect of gemcitabine on the severe unwanted effects compared to BCG retreatment. The review also includes information on how gemcitabine compares to BCG and how it compares to one-third dose BCG.

Reliability of the evidence

The reliability of the evidence was low or very low for most of the treatments we compared, meaning that we were often uncertain about whether the findings were true. Further research will likely change these findings.

SUMMARY OF FINDINGS

Summary of findings 1. Gemcitabine compared to saline

Patient or population: participants with non-muscle invasive bladder cancer (607 men, 127 women)
Country: Germany, Turkey, and the US
Setting: multicenter, likely inpatients
Intervention: gemcitabine
Comparison: saline

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with saline	Risk difference with gemcitabine
Time to recurrence (absolute effect size estimates based on recurrence rate at 4 years) Follow-up: range 2–4 years MCID: 5% absolute difference	734 (2 RCTs)	⊕⊕⊖⊖ **Low** [a,b,c]	**HR 0.77** (0.54 to 1.09)	**Moderate** 470 per 1000[e]	83 fewer per 1000 (180 fewer to 29 more)
Time to progression (absolute effect size estimates based on progression rate at 4 years) Follow-up: range 2–4 years MCID: 5% absolute difference	654 (2 RCTs)	⊕⊕⊖⊖ **Low** [a,b,c]	**HR 0.96** (0.19 to 4.71)	**Low** 48 per 1000[e]	2 fewer per 1000 (39 fewer to 159 more)
Grade III–V adverse events assessed with: 1 study: measured as serious adverse events; 1 study: CTCAE version 3.0 and version 4.0 Follow-up: range 1–3 months MCID: 5% absolute difference	668 (2 RCTs)	⊕⊕⊖⊖ **Low** [a,c]	**RR 1.26** (0.58 to 2.75)	**Study population** 47 per 1000	12 more per 1000 (20 fewer to 83 more)
Time to death from bladder cancer (absolute effect size estimates based on death rate at 2 years)	328 (1 RCT)	⊕⊖⊖⊖ **Very low** [a,d]	**HR 0.98** (0.02 to 49.40)	**Low** 6 per 1000[f]	0 fewer per 1000

Follow-up: 2 years MCID: 3% absolute difference					(6 fewer to 251 more)
Time to death from any cause (absolute effect size estimates based on death rate at 4 years) Follow-up: range 2–4 years MCID: 3% absolute difference	734 (2 RCTs)	⊕⊖⊖⊖ **Very low** [a,d]	**HR 0.62** (0.39 to 1.00)	**Low**	
				121 per 1000 [e]	44 fewer per 1000 (72 fewer to 0 fewer)
Grade I or II adverse events assessed with: 1 study: measured as serious adverse events; 1 study: CTCAE version 3.0 and version 4.0 Follow-up: range 1–3 months MCID: 5% absolute difference	668 (2 RCTs)	⊕⊕⊖⊖ **Low** [a,c]	**RR 1.13** (0.87 to 1.45)	**Study population**	
				246 per 1000	32 more per 1000 (32 fewer to 111 more)
Disease-specific quality of life	Not reported	—	—	—	—

*__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).

CI: confidence interval; **CTCAE:** Common Terminology Criteria for Adverse Events; **HR:** hazard ratio; **MCID:** minimal clinically important difference; **n:** number of participants; **RCT:** randomized controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: 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 certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded one level for study limitations: high risk of selective reporting and other bias.
[b]Not downgraded further for moderate inconsistency; this contributed to the decision to downgrade twice overall.
[c]Downgraded one level for imprecision: confidence intervals crossed a clinically important threshold and no effect.
[d]Downgraded two levels for imprecision: confidence intervals crossed a clinically important threshold and no effect; wide confidence intervals
[e]Baseline risk for recurrence, progression, and death from any cause came from Messing 2018.
[f]Baseline risk for death from bladder cancer come from Böhle 2009.

Summary of findings 2. Gemcitabine compared to mitomycin

Patient or population: participants with non-muscle invasive bladder cancer[1] (93 men, 16 women)
Country: Italy
Setting: single center, likely inpatients
Intervention: gemcitabine
Comparison: mitomycin

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with mitomycin	Risk difference with gemcitabine
Time to recurrence Follow-up: 3 years MCID: 5% absolute difference	109 (1 RCT)	⊕⊕⊖⊖ **Low** [a],[b]	**HR 0.36** (0.19 to 0.69)	**Study population**	
				400 per 1000	232 fewer per 1000 (308 fewer to 103 fewer)
Time to progression Follow-up: 3 years MCID: 5% absolute difference	109 (1 RCT)	⊕⊕⊖⊖ **Low** [a],[c]	**HR 0.57** (0.32 to 1.01)	**Study population**	
				182 per 1000	74 fewer per 1000 (120 fewer to 2 more)
Grade III–V adverse events (local adverse events which result in delay intravesical treatment were regarded as Grade III–V complications) Follow-up: 3 years MCID: 5% absolute difference	109 (1 RCT)	⊕⊖⊖⊖ **Very low** [a],[d]	**RR 0.51** (0.13 to 1.93)	**Study population**	
				109 per 1000	53 fewer per 1000 (95 fewer to 101 more)
Time to death from bladder cancer	Not reported	—	—	—	
Time to death from any cause	Not reported	—	—	—	
Grade I or II adverse events (local adverse events which did not result in delay intravesical treatment) Follow-up: 3 years MCID: 5% absolute difference	109 (1 RCT)	⊕⊕⊖⊖ **Low** [a],[b]	**RR 0.53** (0.37 to 0.78)	**Study population**	
				727 per 1000	342 fewer per 1000 (458 fewer to 160 fewer)
Disease-specific quality of life	Not reported	—	—	—	—

*__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).

CI: confidence interval; **MCID:** minimal clinically important difference; **HR: h**azard ratio; **RCT:** randomized controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: 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 certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1]The analysis was only based on participants with recurrent non-muscle invasive bladder cancer; the only included trial did not include participants with primary (untreated) disease.
[a]Downgraded one level for study limitations: unclear or high risk of bias on one or more domains.
[b]Downgraded one level for imprecision: outcome based on only a single study of a small number of participants.
[c]Downgraded one level for imprecision: confidence intervals crossed a clinically important threshold and no effect.
[d]Downgraded two levels for imprecision: confidence intervals crossed a clinically important threshold and no effect; wide confidence intervals.

Summary of findings 3. Gemcitabine compared to BCG for recurrent (one-course BCG failure) non-muscle invasive bladder cancer

Patient or population: participants with recurrent (1-course BCG failure) high-risk non-muscle invasive bladder cancer (49 men, 31 women)
Country: Italy
Setting: multicenter, likely inpatients
Intervention: gemcitabine
Comparison: BCG

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with BCG	Risk difference with gemcitabine
Time to recurrence Follow-up: range 6–22 months MCID: 5% absolute difference	80 (1 RCT)	⊕⊕⊖⊖ **Low** [a],[b]	**HR 0.15** (0.09 to 0.26)	**Study population**	
				970 per 1000	561 fewer per 1000 (699 fewer to 372 fewer)
Time to progression Follow-up: range 6–22 months MCID: 5% absolute difference	80 (1 RCT)	⊕⊕⊖⊖ **Low** [a],[b]	**HR 0.45** (0.27 to 0.76)	**Study population**	
				325 per 1000	163 fewer per 1000 (224 fewer to 67 fewer)

Grade III–V adverse events assessed with: CTCAE version 3.0 Follow-up: range 6–22 months MCID: 5% absolute difference	80 (1 RCT)	⊕⊖⊖⊖ **Very low** [a,c]	**RR 1.00** (0.21 to 4.66)	**Study population**	
				75 per 1000	0 fewer per 1000 (59 fewer to 275 more)
Time to death from bladder cancer Follow-up: range 6–22 months MCID: 3% absolute difference	80 (1 RCT)	⊕⊖⊖⊖ **Very low** [a,c]	**HR 0.04** (0.01 to 2.25)	**Study population**	
				17 per 1000	16 fewer per 1000 (17 fewer to 21 more)
Time to death from any cause	Not reported	—	—	—	—
Grade I or II adverse events assessed with: CTCAE version 3.0 Follow-up: range 6–22 months MCID: 5% absolute difference	80 (1 RCT)	⊕⊖⊖⊖ **Very low** [a,c]	**RR 0.92** (0.48 to 1.77)	**Study population**	
				325 per 1000	26 fewer per 1000 (169 fewer to 250 more)
Disease-specific quality of life	Not reported	—	—	—	—

*__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; **CTCAE:** Common Terminology Criteria for Adverse Events; **MCID:** minimal clinically important difference; **HR:** hazard ratio; **RCT:** randomized controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: 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 certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded one level for study limitations: high risk of bias on one or more domains.
[b]Downgraded one level for imprecision: outcome based on only a single study of a small number of participants.
[c]Downgraded two levels for imprecision: confidence intervals crossed a clinically important threshold and no effect; wide confidence intervals.

BACKGROUND

Description of the condition

Under 2018 GLOBOCAN data, urothelial carcinoma of the bladder is the 10th most common malignancy worldwide, with 549,393 new cases and 200,000 cancer-related deaths (Bray 2018). In 2020, an estimated 81,400 new cases of bladder cancer will be diagnosed in the US, with 17,982 estimated deaths occurring during this same period (Siegel 2020). Risk factors for developing bladder cancer include male sex, white race, smoking, personal or family history of bladder cancer, pelvic radiation, environmental/occupational exposures, exposure to certain drugs, chronic infection, irritation of the urinary tract, and certain medical conditions including obesity and diabetes (DeGeorge 2017). Most people with bladder cancer are diagnosed during diagnostic testing resulted from hematuria. In people in whom bladder cancer is suspected, computer tomography urography is used to assess the whole urinary tract, and cystoscopy is used to assess the lower urinary tract (Helenius 2015). At presentation, approximately 75% of patients have a non-muscle invasive disease, and 25% have muscle-invasive or metastatic disease. Non-muscle invasive tumors can be either papillary or non-papillary. Those papillary tumors that are confined to the innermost layer of the bladder (urothelium) are designated Ta tumors, while those that have invaded the basement membrane beneath this layer, the lamina propria, are designated T1 tumors. Most tumors diagnosed are Ta tumors (Burger 2008). People who present with T1 are at higher risk due to the greater propensity of these tumors to recur and progress. Non-papillary tumors include carcinoma in situ (CIS), a flat, high-grade tumor that commonly presents concurrently with papillary tumors and has a high risk of progression (Hansel 2013; Sylvester 2006).

The initial management of non-muscle invasive bladder cancer (NMIBC) is transurethral resection (TUR) to remove all visible tumors, and depth includes the muscularis propria. After the initial transurethral surgery, 50% to 70% of tumors have recurred (Perlis 2013), and 10% to 30% of tumors are progressing (grade and stage progression) within five years (Lamm 2014). Factors associated with recurrence and progression include high stage, high grade, large tumor size, multifocality, high number of the previous recurrence, presence of concomitant CIS, lymphovascular invasion, and histologic variants (Kamat 2016). Therefore, frequent cystoscopic surveillance is required for detecting early recurrence, but this procedure may impact the person's quality of life and has considerable implications for health care in terms of cost.

Description of the intervention

To overcome the problem of tumor recurrence, anti-tumor agents may be instilled into the bladder for a short time to bathe the tumor cells. This is called intravesical therapy and is frequently used as an adjunctive following TUR. The objective is to eradicate residual tumor cells missed in the original resection and to prevent or delay tumors from recurring or progressing to more invasive disease (Babjuk 2019; Peyton 2019). Therefore, intravesical therapy has an essential role in the management of NMIBC. For intravesical drug instillation, usually a two-way catheter is sterilely inserted into the bladder. When the bladder is completely drained, anti-tumor agents such as Bacillus Calmette-Guérin (BCG), or chemotherapeutic drugs (e.g. mitomycin, epirubicin, or gemcitabine) are passed into the bladder through the catheter and the drug solution retained for 1.5 hours to 2 hours. After that, the participant voids to remove the drug solution. Gemcitabine 2 g in 50 mL or 100 mL of saline can be used once a week for six weeks (namely induction therapy) (Addeo 2010; Bendary 2011; Di Lorenzo 2010; Gontero 2013; Porena 2010), or immediate single instillation after transurethral resection of bladder tumor (TURBT) (Böhle 2009; Messing 2018), in NMIBC.

Adverse events of the intervention

Adverse events from intravesical anti-tumor agent instillation can be divided into local and systemic. The common local adverse events are urinary frequency, urinary urgency, dysuria, hematuria, bladder or pelvic pain, and prostatitis. However, most of these are usually self-limiting (Griffin 2013). Systemic adverse events are rare and primarily result in myelosuppression (Griffin 2013). However, studies have reported that gemcitabine induced no higher than grade III Common Terminology Criteria for Adverse Events (CTCAE) for local and systemic adverse events. The most reported adverse events are voiding dysfunction, pain, hematuria, pyrexia, and alopecia (Böhle 2009; Maffezzini 2009; Messing 2018).

How the intervention might work

Gemcitabine is a pyrimidine antimetabolite that inhibits DNA synthesis by inhibition of DNA polymerase and ribonucleotide reductase, cell cycle-specific for the S-phase of the cycle (also blocks cellular progression at G1/S-phase). Gemcitabine is phosphorylated intracellularly by deoxycytidine kinase to gemcitabine monophosphate, which is further phosphorylated to active metabolites gemcitabine diphosphate and gemcitabine triphosphate. Gemcitabine diphosphate inhibits DNA synthesis by inhibiting ribonucleotide reductase; gemcitabine triphosphate is incorporated into DNA and inhibits DNA polymerase. These metabolites are responsible for the cytotoxic action of gemcitabine by blocking DNA synthesis and leading to programmed cell death (apoptosis) (Laufer 2003; Mini 2006). Gemcitabine has several pharmacologic properties that are conducive for its use as an intravesical agent in the management of NMIBC. First, gemcitabine has demonstrated activity in killing cultured bladder cancer cells in vitro (Kilani 2002). Second, the low molecular weight and the high lipid solubility allow sufficient uptake into malignant urothelial cells for cytotoxicity in vivo (Sternberg 2000). Third, gemcitabine has a high plasma clearance so that any drug that does enter the systemic circulation after intravesical administration will be quickly eliminated, reducing the risk of systemic toxicity (Cozzi 1999; Laufer 2003).

Why it is important to do this review

There are two systematic reviews on this topic (Jones 2012; Ye 2018). The systematic review and meta-analysis by Ye and colleagues, which included randomized controlled trials (RCTs) and retrospective observational studies, concluded that intravesical gemcitabine instillation may have similar efficacy and lower incidence of dysuria and hematuria compared with BCG (Ye 2018). However, this review had many inherent limitations. One previous Cochrane Review for gemcitabine for the treatment of NMIBC based on RCTs demonstrated that intravesical gemcitabine therapy had similar effects in intermediate-risk patients, but less effective in high-risk patients and superior in BCG-refractory patients compared to intravesical BCG therapy. Also, the Cochrane Review reported that single-dose intravesical instillation after transurethral surgery is ineffective compared to saline (Jones 2012). After publication of this review, Cochrane introduced more

rigorous methodology, which included assessment of risk of bias and production of 'Summary of findings' tables (the GRADE approach; Schünemann 2017). Furthermore, the results of several randomized trials for gemcitabine have been reported since the Jones 2012 review. Therefore, the previous review must be considered outdated. This is an update of the Cochrane Review first published in 2012 (Jones 2012).

OBJECTIVES

To assess the comparative effectiveness and toxicity of intravesical gemcitabine instillation for NMIBC.

METHODS

Criteria for considering studies for this review

Types of studies

We included RCTs. We excluded quasi-randomized and non-randomized studies, cohort studies, case series, cross-over trials, and cluster-randomized trials. We did not exclude studies on the basis of publication status or language.

Types of participants

We included studies that used participants with NMIBC (Stage 0a, Stage 0is and Stage I) (Babjuk 2019; NCCN guideline 2019), with any tumor grade (Epstein 1998; Humphrey 2016) as determined via cross-sectional imaging, cystoscopic appearance, or biopsy. We included studies irrespective of intravesical therapy dose or schedule. Participants who received prior intravesical therapy and failed to respond, such as BCG-refractory participants, were also eligible. We excluded participants with previous or concurrent upper urinary tract or prostatic urethral urothelial cancer, cancers other than bladder, and previous systemic treatment or radiation therapy for any cancer.

Types of interventions

We investigated the following comparisons of experimental versus comparator interventions.

Experimental interventions

- Intravesically administered gemcitabine

All participants had undergone TUR prior to receiving the intervention.

Comparator interventions

- Observation (no intervention).
- Intravesically administered placebo or non-chemotherapeutic drugs (e.g. saline).
- Intravesically administered chemotherapy other than gemcitabine.
- Intravesically administered full dose BCG (excluded in case of single intravesical therapy immediate after TUR).
- Intravesically administered 1/3 dose BCG (excluded in case of single intravesical therapy immediate after TUR).

All participants had undergone TUR prior to receiving the intervention.

Comparisons

- Intravesically administered gemcitabine versus observation (no intervention).
- Intravesically administered gemcitabine versus intravesically administered placebo or non-chemotherapeutic drugs (e.g. saline).
- Intravesically administered gemcitabine versus intravesically administered chemotherapy other than gemcitabine.
- Intravesically administered gemcitabine versus intravesically administered BCG (excluded in case of single intravesical therapy immediate after TUR).
- Intravesically administered gemcitabine versus intravesically administered 1/3 of BCG

Concomitant interventions were the same in the experimental and comparator groups to establish fair comparisons. We also analyzed those studies separately in which patients with recurrent disease that had failed a given intravesical agent were re-exposed to that same agent in the control group. 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. We listed all treatment arms in the Characteristics of included studies table.

Types of outcome measures

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

Primary outcomes

- Time to recurrence (time-to-event outcome).
- Time to progression (time-to-event outcome).
- Grade III to V adverse events (dichotomous outcome).

Secondary outcomes

- Time to death from bladder cancer (time-to-event outcome).
- Time to death from any cause (time-to-event outcome).
- Grade I or II adverse events (dichotomous outcome).
- Disease-specific quality of life (continuous outcome).

Method and timing of outcome measurement

- Time to recurrence: measured from the time of randomization to the time of the recurrence.
  - Definition of recurrence: any type of recurrence; judged based on imaging modalities (e.g. computed tomography), cystoscopy, or histopathologic proof of recurrence.
- Time to progression: measured from the time of randomization to the time of the progression.
  - Definition of progression: increase in T stage from CIS (Stage 0is) or Ta (Stage 0a) to T1 (Stage I), development of T2 or greater (≥ stage II) or lymph node disease or distant metastasis, or an increase in tumor grade from low to high (Lamm 2014).
- Grade III to V adverse events: determined by the CTCAE v5.0 (CTCAE), occurring at any time during treatment (e.g. hematuria that required hospitalization for catheter irrigation [grade III], life threatening/disabling [grade IV], and death [grade V]).
- Time to death from bladder cancer: measured from the time of randomization to the time of death due to bladder cancer.

- Time to death from any cause: measured from the time of randomization to the time of death due to any cause.
- Grade I or II adverse events: measured by CTCAE v5.0 (CTCAE), occurring at any time during treatment (e.g. asymptomatic hematuria [grade I] and symptomatic hematuria requiring temporary bladder irrigation [grade II]).
- Quality of life: measured by validated instruments such as the European Organisation for Research and Treatment of Cancer (EORTC) core quality-of-life questionnaire version 3.0 (QLQ C-30), 12-item Short Form (SF-12), 36-item Short Form (SF-36), or Functional Assessment of Cancer Therapy (FACT) questionnaire.

If the authors did not use the CTCAE v5.0, we graded the adverse events as described in their respective studies. We defined a clinically meaningful minimal duration of follow-up as three months (12 weeks). If we were unable to retrieve the necessary information to assess time-to-event outcomes, we tried to assess the number of events per total number of included participants in each relevant study for dichotomized outcomes at one year, two years, three years, and five years after administering intravesical therapy.

We considered a 5% absolute risk difference as clinically important for time to recurrence, time to progression, and grade I to V adverse events. We considered a 3% absolute risk difference as clinically important for time to death from bladder cancer and time to death from any cause. We used published threshold for disease-specific quality of life instruments (e.g. EORTC QLQ-C30: minimal clinically important difference: 10; Osoba 1998).

Search methods for identification of studies

We performed comprehensive searches, applying no restrictions on the language of publication or publication status.

Electronic searches

We assessed the search strategies used for the previous reviews and amended them to incorporate changes in medical subject heading terminology and added additional databases. All searches were from inception to 11 September 2020. See Appendix 1 for the full search strategies.

- The Cochrane Library (Wiley): 2020, Issue 9.
- MEDLINE (via OvidSP): 1946 to 11 September 2020.
- MEDLINE In Process & Epub Ahead of Print (via Ovid): searched 11 September 2020.
- Embase (via OvidSP): 1947 to 11 September 2020.
- Web of Science Core Collection (via Thomson Reuters): 1990 to 11 September 2020.
- LILACS (Latin American and the Caribbean Health Sciences Literature; via Virtual Health Library): 1982 to 11 September 2020.
- Scopus (via Elsevier): 1960 to 11 September 2020.
- OpenGrey (Native Interface): 1980 to 11 September 2020.

We searched the following trials registers.

- ClinicalTrials.gov (clinicaltrials.gov/): 2008 to 11 September 2020.
- World Health Organization International Clinical Trials Registry Platform search portal (apps.who.int/trialsearch/): 2009 to 11 September 2020.

Searching other resources

We tried to identify other potentially eligible trials or ancillary publications by searching the reference lists of included trials, reviews, and meta-analyses. We also contacted the authors of included trials to identify any further studies that we may have missed. We searched the abstract proceedings of any relevant meetings conducted during 2017 to 2020 by the American Urological Association, European Association of Urology (EAU), and American Society of Clinical Oncology to search for unpublished studies.

Data collection and analysis

In this review, we followed the methodologic recommendations given by Cochrane (Higgins 2017a).

Selection of studies

We used reference management software to identify and remove potential duplicate records (EndNote), and then imported these references into Covidence, a web-based program for systematic review development. When more than one report of the same trial was available, we included the most up-to-date publication in the analysis. If a study had more than one publication, we grouped publications so that each study, rather than each publication, was the unit of interest. Two review authors (ECH, PM) independently scanned the abstract or title (or both) of the records retrieved, to determine which studies should be assessed further. Two review authors (ECH, PM) investigated all potentially relevant records as full text; mapped records to studies; and classified studies as included studies, excluded studies, studies awaiting classification, or ongoing studies, in accordance with the criteria for each provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017a). We planned to resolve any discrepancies through consensus or recourse to a third review author (JHJ). If resolution of a disagreement was not possible, we planned to designate the study as 'awaiting classification' and to contact study authors for clarification. We documented reasons for exclusion of studies that may have reasonably been expected to be included in the review in the Characteristics of excluded studies table. We presented an adapted PRISMA flow diagram showing the process of study selection (Liberati 2009).

Data extraction and management

We developed a data extraction form that we piloted ahead of time.

For studies that fulfilled the inclusion criteria, two review authors (ECH, PM) independently extracted the following information, which we report in the Characteristics of included studies table.

- Study design.
- Study dates (if dates were not available then this was reported as such).
- Study settings and country.
- Participant inclusion and exclusion criteria (including participant comorbidities, disease stage, pretreatment).
- Participant details, baseline demographics (including participant age, disease stage).

- Number of participants by study and by study arm.
- Details of relevant experimental and comparator interventions (including dose, frequency, and duration).
- Definitions of relevant outcomes, method and timing of outcome measurement, and any relevant subgroups.
- Study funding sources.
- Declarations of interest by primary investigators.

We extracted outcome data relevant to this Cochrane Review as needed for calculation of summary statistics and measures of variance. For dichotomous outcomes such as adverse events, we attempted to obtain numbers of events and totals for population of a 2 × 2 table, as well as summary statistics with corresponding measures of variance. For continuous outcomes such as quality-of-life scores, we attempted to obtain means and standard deviations or data necessary to calculate this information (Hozo 2005). For time-to-event outcomes, we extracted the hazard ratio (HR) from published data according to published guidance (Parmar 1998; Tierney 2007), with corresponding measures of variance or data necessary to calculate this information.

We planned to resolve any disagreements by discussion, or, if required, by consultation with a third review author (JHJ or VN).

We provided information, including trial identifier, about potentially relevant ongoing studies 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 maximized the yield of information by mapping all publications to unique studies and collating all available data. We 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 (ECH and PM) independently assessed the risks of bias for each included study. We resolved disagreements by consensus, or by consulting with a third review author (PD). We used the Cochrane 'Risk of bias' assessment tool for the following domains (Higgins 2017b).

- 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 potential sources of bias (e.g. baseline imbalance).

We judged 'Risk of bias' domains as 'low risk,' 'high risk,' or 'unclear risk.' We presented the results of this assessment graphically. For selection bias (random sequence generation and allocation concealment) and reporting bias (selective reporting), we evaluated the risks of bias at a trial level.

For performance bias (blinding of participants and personnel), we defined all outcomes as similarly susceptible to performance bias and assessed them in one group.

For detection bias (blinding of outcome assessments), we grouped outcomes as susceptible to detection bias (subjective) or not susceptible to detection bias (objective) outcomes.

We defined the following outcome measures as subjective.

- Time to recurrence.
- Time to progression.
- Time to death from bladder cancer.
- Grade I or II adverse events.
- Disease-specific quality of life.

We defined the following outcomes as objective.

- Grade III to V adverse events.
- Time to death from any cause.

We assessed attrition bias (incomplete outcome data) on an outcome-specific basis, and presented the judgment for each outcome separately when reporting our findings in the 'Risk of bias' tables. If appropriate, we created groups of outcomes with similar reporting characteristics (e.g. grade III to V events and any adverse events) to facilitate both the 'Risk of bias' ratings and presentation. We further summarized the risk of attrition bias across domains for each outcome in each included study, as well as across the studies and domains for each outcome, in accordance with the approach for the summary assessment of the risk of bias presented in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017b).

Measures of treatment effect

We expressed dichotomous data as risk ratios (RRs) with 95% confidence intervals (CIs). For continuous outcomes measured on the same scale, we estimated the intervention effect using the mean difference (MD) with a 95% CI. For continuous outcomes measuring the same underlying concept (e.g. disease-specific quality of life), but using different measurement scales, we planned to report the standardized mean difference (SMD) with 95% CIs. We expressed time-to-event data as HRs with 95% CIs. We analyzed the data using Review Manager 5 (Review Manager 2014).

Unit of analysis issues

The unit of analysis was each individual participant. We planned to consider the level at which randomization occurred, and the multiple observations of the same outcome. If more than one comparison from the same trial was eligible for inclusion in the same meta-analysis, we either combined study groups to create a single pair-wise comparison or appropriately reduced the sample size so that the same participants did not contribute multiple times (if possible, splitting the 'shared' group into two or more groups). While the latter approach offers some solution to adjusting the precision of the comparison, it does not account for correlations arising from the same set of participants being in multiple comparisons (Higgins 2011).

Dealing with missing data

We obtained missing data from corresponding study authors, if feasible, and performed intention-to-treat analyses of data were available. Otherwise, we performed available-case analyses. We investigated attrition rates (e.g. dropouts, losses to follow-ups, and withdrawals), and the critically appraised issues of missing data. We did not impute missing data.

Assessment of heterogeneity

We identified heterogeneity (inconsistency) through visual inspection of the forest plots to assess the amount of overlap of CIs. We also used 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 the I^2 statistic as follows (Deeks 2017):

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

When we found heterogeneity, we attempted to determine possible reasons for it by examining individual study and subgroup characteristics.

Assessment of reporting biases

We attempted to obtain study protocols to assess selective outcome reporting. As we included only one or two studies in each comparison in our review, we could not use funnel plots to assess any small-study effects.

Data synthesis

We performed data synthesis using Review Manager 5 (Review Manager 2014) in accordance with the guidelines contained in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017a). In the meta-analyses, we used a random-effects model. For dichotomous outcomes, we used the Mantel-Haenszel method. For continuous outcomes, we used the inverse variance method. For time-to-event outcomes, we used the generic inverse variance method.

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 EORTC and EAU risk classification system (Babjuk 2019; Sylvester 2006).
- Dose of gemcitabine (e.g. 2000 mg versus 1000 mg).

If EAU risk categories were not available, and if there were sufficient data, we planned to perform subgroup analyses based on (Babjuk 2019; Sylvester 2006):

- number of tumors (one versus more than one);
- tumor size (less than 3 cm versus 3 cm or greater);
- tumor stage (Ta versus T1);
- presence of CIS (absent or present);
- tumor grade (Grade 1 versus Grades 2 and 3 or low grade versus high grade);
- primary versus recurrent disease.

We used the test for subgroup differences in Review Manager 5 to compare subgroup analyses if there was at least one study with the data available for our predefined subgroups (Review Manager 2014). Furthermore, unless the trial(s) were stratified for the subgroups, we downgraded the certainty of evidence.

Sensitivity analysis

We planned to perform sensitivity analyses to explore the influence of the following factors on effect size, if applicable.

- Restricting the analysis by taking the risk of bias into account and excluding studies classified as having a high risk or unclear risk of bias.

Summary of findings and assessment of the certainty of the evidence

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

- Time to recurrence.
- Time to progression.
- Grade III to V adverse events.
- Time to death from bladder cancer.
- Time to death from any cause.
- Grade I or II adverse events.
- Disease-specific quality of life.

We presented the findings and the certainty of the available evidence according to GRADE methodology (Schünemann 2017). We assessed the overall certainty of the evidence for each outcome according to the GRADE approach, which takes into account five criteria related, not only to internal validity (risk of bias, inconsistency, imprecision, and publication bias), but also to external validity (directness of results) (Guyatt 2008). Two review authors (MAH, ECH, or JHJ) independently rated the certainty of the evidence for each outcome as 'high,' 'moderate,' 'low,' or 'very low.' We resolved discrepancies by consensus, or, if needed, by the arbitration of a third review author (PD). We presented a summary of the evidence for the main outcomes in summary of findings table, which we generated using the GRADEpro GDT (gradepro.org). This table provides key information about the best estimate of the magnitude of an effect in relative terms and presents absolute differences for each relevant comparison of alternative management strategies; numbers of participants and studies addressing each important outcome; and the rating of our overall confidence in the effect estimates for each outcome (Guyatt 2011; Schünemann 2017).

RESULTS

Description of studies

We identified 1002 records through electronic database searching and four records in existing systematic review.

Results of the search

After removal of duplicates, we screened the titles and abstracts of 650 records, and excluded 615 obviously irrelevant records. We screened 35 full-text records (22 studies), and excluded 10 records (10 studies) that did not meet the inclusion criteria or were not relevant to the review. We included seven studies (19 records) in the review. The flow of literature through the assessment process is shown in the PRISMA flowchart (Figure 1).

Figure 1. Study flow diagram.

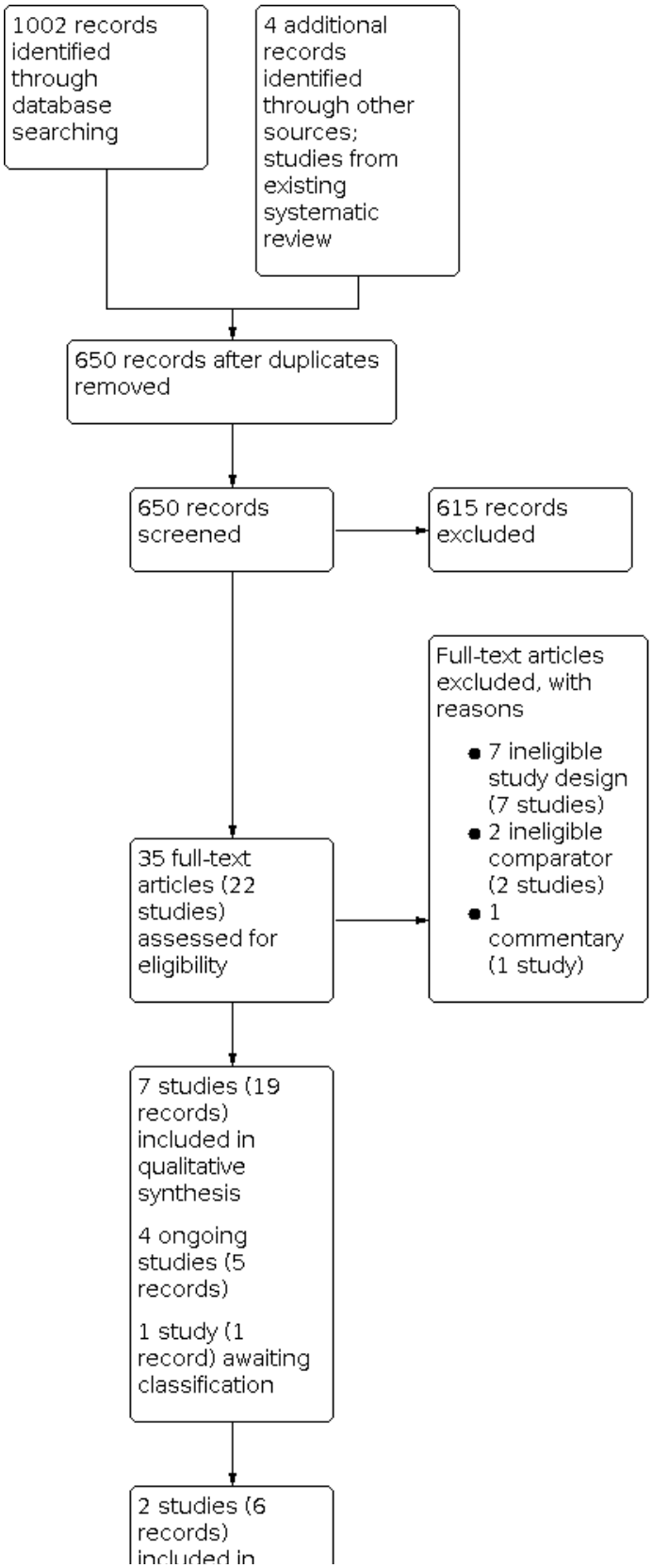
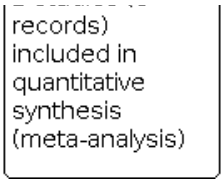


Figure 1. (Continued)



Included studies

Details of included studies are presented in the Characteristics of included studies table; Table 1; and Table 2.

Source of data

We included six published studies and one abstract proceeding (Bendary 2011). All studies were published in English. We attempted to contact all corresponding authors of included trials to obtain additional information on study methodology and results, and received replies from four (Böhle 2009; Cao 2011; Di Lorenzo 2010; Gontero 2013; see Appendix 2).

Study design and settings

All studies were parallel RCTs. Two studies were reported as 'double-blinded' (Böhle 2009; Messing 2018). Three studies were open-label trials (Di Lorenzo 2010; Gontero 2013; Porena 2010). The remaining two trials had no information regarding blinding. All studies were probably conducted in an inpatient setting. Four studies were multicenter (Böhle 2009; Di Lorenzo 2010; Gontero 2013; Messing 2018), while three studies were single center trials (Addeo 2010; Bendary 2011; Porena 2010). The studies were performed from 2003 to 2012.

Participants

We included 1222 randomized participants (gemcitabine 611, mitomycin 55, BCG 171, saline 385), of which 644 completed the trials (gemcitabine 310, mitomycin 55, BCG 119, saline 160) (Table 2). However, one study that compared gemcitabine to BCG did not report the number of participants who completed the trial in each group (Bendary 2011). All studies included men and women.

All studies included participants with NMIBC, but two studies included small numbers of participants with muscle-invasive bladder cancer in the analysis (7.7% in Böhle 2009, 3.7% in Messing 2018). These two studies originally intended to include the primary and recurrent NMIBC (Böhle 2009; Messing 2018). The remaining studies included each different disease type (recurrent NMIBC: Addeo 2010; primary NMIBC without CIS: Bendary 2011; high-risk BCG failure recurrent NMIBC: Di Lorenzo 2010; intermediate-risk primary and recurrent NMIBC: Gontero 2013; and high-risk primary NMIBC: Porena 2010). Most exclusion criteria included active urinary tract infection, previous pelvic radiation therapy for any malignancy, or prior treatment for any malignancy.

Interventions

Two studies used gemcitabine as an intravesical dose of 2000 mg mixed with 100 mL saline (Böhle 2009; Messing 2018), and the remaining studies administered gemcitabine as an intravesical dose of 2000 mg mixed with 50 mL saline. Each study used different treatment schedule (Table 1). Most studies used intervention as induction and maintenance therapy (Addeo 2010; Di Lorenzo 2010; Gontero 2013; Porena 2010), while two studies used single instillation (Böhle 2009; Messing 2018), and one study used induction therapy only (Bendary 2011).

Comparators

Studies used six different comparators, namely saline, mitomycin, Connaught strain BCG, Tice strain BCG, BCG without a mention for a type of strain and one-third dose Connaught strain BCG. All comparators were also administrated intravesically. Two studies administered saline as an intravesical dose of 100 mL (Böhle 2009; Messing 2018). One study used mitomycin 40 mg mixed with 50 mL saline as a comparator (Addeo 2010). Two studies administered Connaught strain BCG at 81 mg (Di Lorenzo 2010) and 27 mg (Gontero 2013), mixed with 50 mL saline. One study administered Tice strain BCG at 5×10^8 colony-forming units (CFU) mixed with 50 mL saline(Porena 2010). One study administered BCG without mentioning the type of strain at 6×10^8 CFU mixed with 50 mL saline (Bendary 2011). Four studies used the same treatment schedule to that of the intervention (Bendary 2011; Böhle 2009; Messing 2018; Porena 2010), while remaining studies used different treatment schedules to the intervention.

Comparisons

We included five comparisons in this review: two studies compared gemcitabine to saline for primary and recurrent NMIBC (Böhle 2009; Messing 2018), one study compared gemcitabine to mitomycin for recurrent NMIBC (Addeo 2010), two studies compared gemcitabine to BCG in two different disease type (i.e. for primary high-risk NMIBC [Porena 2010] and for recurrent [one-course BCG failure] high-risk NMIBC [Di Lorenzo 2010]), and one study compared gemcitabine to one-third dose BCG for primary and recurrent intermediate-risk NMIBC (Gontero 2013).

Outcomes

We identified all primary outcomes in each of the included studies for four comparisons. We extracted approximate HRs for time to recurrence using the Tierney 2007 method from three studies (Addeo 2010; Gontero 2013; Porena 2010), and for time to progression using Parmar 1998 method from three studies (Böhle 2009; Di Lorenzo 2010; Gontero 2013). For Addeo 2010, we regarded local adverse events that resulted in delay intravesical treatment as grade III to V complications and the regarded others as grade I or II complications. For Böhle 2009, we regarded severe adverse events as grade III to V complications and the others as grade I or II complications. Porena 2010 reported adverse events of gemcitabine and BCG, but we could not grade the adverse events in accordance with CTCAE. We were unable to obtain additional data from the authors, therefore we did not include this study in the analysis of this outcome. The remaining studies rated the complications by CTCAE v3.0, which is quite similar that of CTCAE v5.0 (Di Lorenzo 2010; Gontero 2013; Messing 2018).

In terms of secondary outcomes, two studies reported time to death from bladder cancer (Böhle 2009; Di Lorenzo 2010), and we extracted approximate HR using the Tierney 2007 method. Two studies reported time to death from any cause (Böhle 2009; Messing 2018), but we extracted approximate HR from one study (Böhle 2009). Gontero 2013 also reported one event of death from any cause, but we could not extract the HR since the study did not report which intervention (i.e. gemcitabine or one-third BCG) the participant received. Five studies reported Grade I or II adverse events (Addeo 2010; Böhle 2009; Di Lorenzo 2010; Gontero 2013; Messing 2018). One study reported disease-specific quality of life (Gontero 2013).

Two trials provided relevant data for predefined subgroup analysis (Böhle 2009; Messing 2018).

Funding sources and conflicts of interest

One study reported no funding source (Bendary 2011), and three reported the funding source (one supported by the national cancer prevention program [Addeo 2010], one supported by a pharmaceutical company which involved in the whole study process [Böhle 2009], and one supported by the national program and partially pharmaceutical company, but not participated in study analysis [Messing 2018]). The remaining trials did not mention a funding source. Two studies reported no conflicts of interest (Addeo 2010; Di Lorenzo 2010), and two reported their conflicts of interest (Böhle 2009; Messing 2018). The remaining studies did not mention conflicts of interest.

Excluded studies

We excluded 10 studies. Two were single arm studies which evaluated the effect of gemcitabine on solitary low-risk NMIBC (Brausi 2011) and BCG refractory NMIBC (Dalbagni 2006). One study was a conference proceeding with non-randomized study design (Gantz 2018). Two studies had an ineligible comparator; Cao 2011 combined different drugs as a comparator and Gardmark 2005 (which was included in the previous version of this review as an included study [Jones 2012]), used different dose and schedules of gemcitabine as a comparator. Böhle 2010 was commentary for Böhle 2009. Four studies from China were non-randomized (Dong 2017; Lin 2016; Sun 2016; Xia 2019).

We presented details of excluded studies in the Characteristics of excluded studies table.

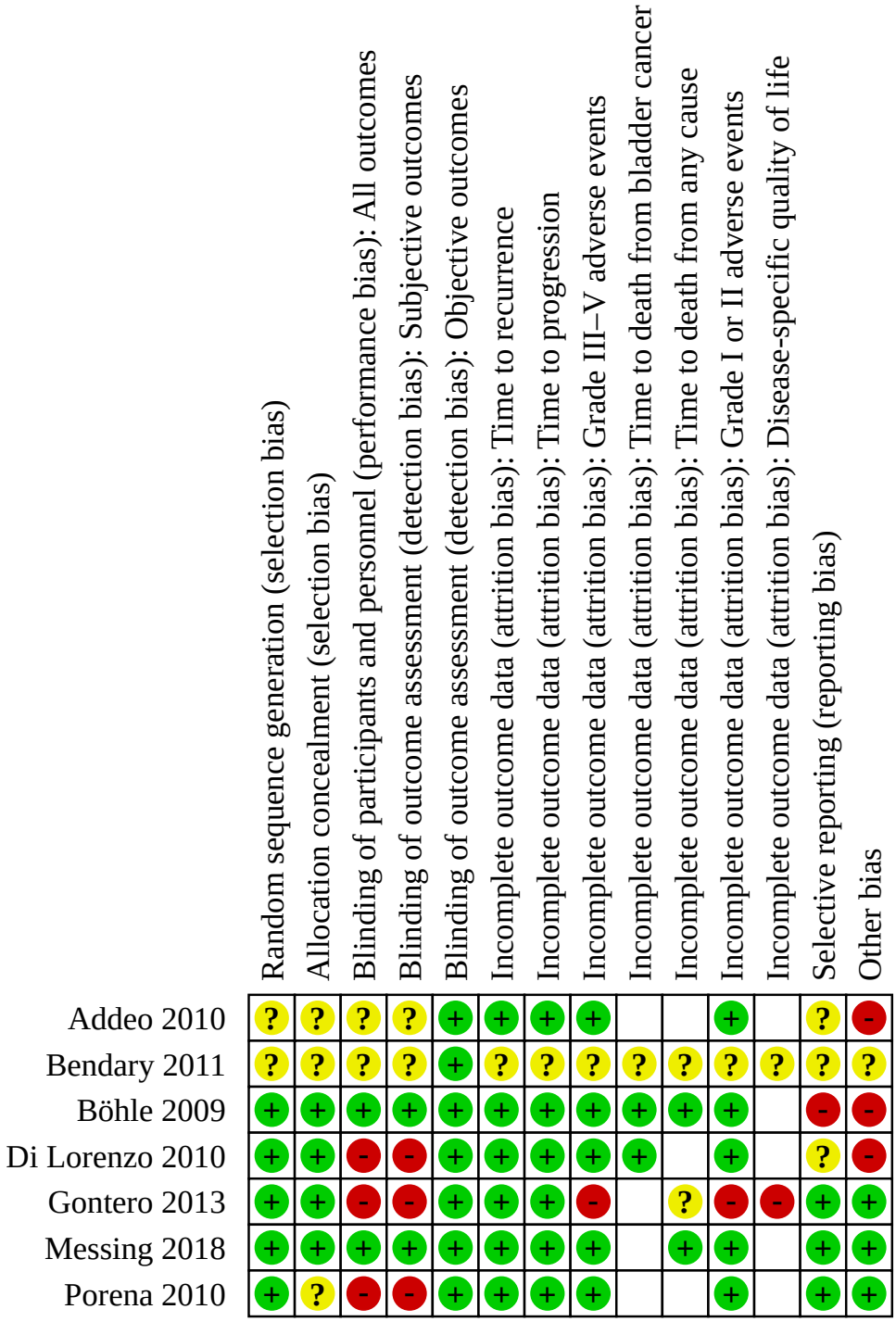
Studies awaiting classification and ongoing trials

We found one study awaiting classification (Xiaohong 2015; Characteristics of studies awaiting classification table), and four ongoing studies, which did not provide usable outcome data at the time that this review was written (ChiCTR1900026643; NCT00192049; NCT02695771; NCT04172675; Characteristics of ongoing studies table).

Risk of bias in included studies

Detailed results of the 'Risk of Bias' assessment are shown in Figure 2, and the judgments for individual domains are provided in the Characteristics of included studies table.

Figure 2. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.



Since Bendary 2011 provided insufficient data (abstract only) to judge risk of bias, we rated this study at unclear risk of bias for all domains except blinding of outcome assessment for objective outcomes.

Allocation

Random sequence generation

We judged five studies at low risk of bias because these trials used appropriate methods of random sequence generation (Böhle 2009; Di Lorenzo 2010; Gontero 2013; Messing 2018; Porena 2010). We rated the remaining studies at unclear risk of bias (Addeo 2010; Bendary 2011).

Allocation concealment

We rated four studies at low risk of bias since allocation was performed centrally (Böhle 2009; Di Lorenzo 2010; Gontero 2013; Messing 2018). We judged the remaining studies at unclear risk of bias (Addeo 2010; Bendary 2011; Porena 2010).

Blinding

Blinding of participants and personnel (performance bias)

We rated Böhle 2009 and Messing 2018 at low risk of bias because participants and personnel were blinded. We rated Di Lorenzo 2010; Gontero 2013; and Porena 2010 at high risk of bias since these were open-label trials. The remaining studies were at unclear risk of bias.

Blinding of outcome assessment (detection bias)

Susceptible (subjective) outcomes (time to recurrence, time to progression, time to death from bladder cancer, grade I or II adverse events, disease-specific quality of life)

We rated Böhle 2009 and Messing 2018 at low risk of bias because outcome assessors were blinded. We rated Di Lorenzo 2010; Gontero 2013; and Porena 2010 at high risk of bias since these were open-label trials. The remaining studies were at unclear risk of bias.

Not susceptible (objective) outcomes (time to death from any cause, grade III to V adverse events)

We rated all trials at low risk of bias because blinding was unlikely to influence the outcome in any of the studies.

Incomplete outcome data

Time to recurrence and time to progression

We judged six studies at low risk of bias, because almost all randomized participants included in the analysis (Addeo 2010; Böhle 2009; Di Lorenzo 2010; Gontero 2013; Messing 2018; Porena 2010). The remaining study was at unclear risk of bias.

Grade III to V adverse events

We rated five studies at low risk of bias (Addeo 2010; Böhle 2009; Di Lorenzo 2010; Messing 2018; Porena 2010). One study was at high risk of bias because substantial proportions of participants were excluded from the final analysis (Gontero 2013). Bendary 2011 was at unclear risk of bias.

Time to death from bladder cancer

Only two studies investigated this outcome and were at low risk of bias (Böhle 2009; Di Lorenzo 2010). We did not rate this domain for the remaining studies, because these studies did not address this outcome (Addeo 2010; Gontero 2013; Messing 2018; Porena 2010). We report the risk of bias as unclear in the table because this is the default value. Bendary 2011 was at unclear risk of bias (abstract).

Time to death from any cause

We rated two studies at low risk of bias (Böhle 2009; Messing 2018). The remaining studies did not investigate this outcome and rated as unclear risk of bias which is a default value (Addeo 2010; Di Lorenzo 2010; Gontero 2013; Porena 2010). Bendary 2011 was at unclear risk of bias (abstract).

Grade I or II adverse events

We rated five studies at low risk of bias (Addeo 2010; Böhle 2009; Di Lorenzo 2010; Messing 2018; Porena 2010). One study was at high risk of bias because substantial proportions of participants were excluded from the final analysis (Gontero 2013). Bendary 2011 was at unclear risk of bias (abstract).

Disease-specific quality of life

Only one study addressed this outcome and we judged it at high risk of bias (Gontero 2013).

Selective reporting

Three studies were at low risk of bias as they reported all outcomes according to their protocol (Gontero 2013; Messing 2018; Porena 2010). Two studies were at unclear risk of bias because the protocol for each study was not available (Addeo 2010; Di Lorenzo 2010). We rated one study as high risk of bias because the results of primary and secondary outcomes were different between protocol (unpublished data) and report, and one outcome was analyzed by post hoc due to lower event rates (Böhle 2009). Bendary 2011 was at unclear risk of bias (abstract).

Other potential sources of bias

We rated three studies at high risk of bias because treatment schedules differed between intervention and comparator in the two studies (Addeo 2010; Di Lorenzo 2010), and there was possibility of a difference in concomitant treatment instillations (BCG) in one study (Böhle 2009). The remaining studies were at low risk of bias.

Effects of interventions

See: **Summary of findings 1** Gemcitabine compared to saline; **Summary of findings 2** Gemcitabine compared to mitomycin; **Summary of findings 3** Gemcitabine compared to BCG for recurrent (one-course BCG failure) non-muscle invasive bladder cancer

Two studies were included in the meta-analysis (Böhle 2009; Messing 2018). While the remaining trials used different comparators and different clinical scenarios for NMIBC, we considered it inappropriate to pool and meta-analyze the data because of considerable clinical heterogeneity (see Table 1).

1. Gemcitabine versus saline

Two studies compared gemcitabine versus saline for primary and recurrent NMIBC (Böhle 2009; Messing 2018; Summary of findings 1).

Primary outcomes

Time to recurrence

Gemcitabine may reduce the risk of recurrence over time compared to saline (HR 0.77, 95% CI 0.54 to 1.09; studies = 2, participants = 734; I^2 = 49%; low-certainty evidence; Analysis 1.1), but the CI included the possibility of no effect. Based on the control event risk of 470 per 1000 participants as drawn from Messing 2018 at four years of follow-up, this would result in 83 fewer recurrences (95% CI 180 fewer to 29 more) per 1000 participants. We downgraded the certainty of the evidence due to study limitations because one study had a high risk of selective reporting and other bias, and imprecision, given that the CI was also consistent with a small or no increase in the risk of recurrence. The observed inconsistency contributed to the decision to downgrade by two levels overall.

Time to progression

Gemcitabine may result in little to no difference in the risk of progression over time compared to saline (HR 0.96, 95% CI 0.19 to 4.71; studies = 2, participants = 654; I^2 = 53%; low-certainty evidence; Analysis 1.2). Based on the control event risk of 48 per 1000 participants as drawn from Messing 2018 at four years of follow-up, this corresponds to two fewer progressions (95% CI 39 fewer to 159 more) per 1000 participants. We downgraded the certainty of the evidence due to study limitations because one study had a high risk of selective reporting and other bias, and imprecision, given that the CI was also consistent with an appreciable increase in the risk of progression. We did not downgrade for inconsistency because heterogeneity may have come from different gemcitabine and saline irrigation times between two studies (Böhle 2009; Messing 2018).

Grade III to V adverse events

Gemcitabine may result in little to no difference in the CTCAE grade III to V adverse events compared to saline (RR 1.26, 95% CI 0.58 to 2.75; studies = 2, participants = 668; I^2 = 24%; low-certainty evidence; Analysis 1.3). Based on the control event risk of 47 per 1000 participants in the trials and one month' to three months' follow-up, this corresponds to 12 more adverse events (95% CI 20 fewer to 83 more) per 1000 participants. We downgraded the certainty of the evidence due to study limitations and imprecision, given that the CI was also consistent with an appreciable increase in CTCAE grade III to V adverse events.

Secondary outcomes

Time to death from bladder cancer

We are very uncertain about the effects of gemcitabine on the risk of death from bladder cancer over time compared to saline (HR 0.98, 95% CI 0.02 to 49.40; studies = 1, participants = 328; very low-certainty evidence; Analysis 1.4). Based on the control event risk of 6 per 1000 participants as drawn from Böhle 2009 at two years of follow-up, this would result in 0 fewer death from bladder cancer (95% CI 6 fewer to 251 more) per 1000 participants. We downgraded the certainty of the evidence due to study limitations (downgraded one level), and very serious imprecision (downgraded two levels).

Time to death from any cause

We are very uncertain about the effects of gemcitabine on the risk of death from any cause over time compared to saline (HR 0.62, 95% CI 0.39 to 1.00; studies = 2, participants = 734; I^2 = 0%; very low-certainty evidence; Analysis 1.5). Based on the control event risk of 121 per 1000 participants as drawn from Messing 2018 at four years of follow-up, this corresponds to 44 fewer deaths from any cause (95% CI 72 fewer to 0 fewer) per 1000 participants. We downgraded the certainty of the evidence due to study limitations (downgraded one level), and very serious imprecision (downgraded two levels).

Grade I or II adverse events

Gemcitabine may result in little to no difference in CTCAE grade I or II adverse events compared to saline (RR 1.13, 95% CI 0.87 to 1.45; studies = 2, participants = 668; I^2 = 0%; low-certainty evidence; Analysis 1.6). Based on the control event risk of 246 per 1000 participants in the trials and one month' to three months' follow-up, this corresponds to 32 more adverse events (95% CI 32 fewer to 111 more) per 1000 participants. We downgraded the certainty of the evidence due to study limitations, and imprecision, given that the CI was also consistent with an appreciable increase in CTCAE grade I or II adverse events.

Disease-specific quality of life

We found no studies that reported disease-specific quality of life.

Subgroup analysis

We performed preplanned subgroup analyses (stratified tumor grade) with regard to primary outcomes.

Tumor grade: low versus high

See Analysis 1.7.

Time to recurrence

Of the 543 participants, 430 had low-grade tumor (gemcitabine n = 208; saline n = 222) and 113 had high-grade tumor (gemcitabine n = 57; saline n = 56). The HR of time to recurrence with gemcitabine was 0.75 (95% CI 0.38 to 1.46), for participants who had low-grade tumor, and 0.74 (95% CI 0.43 to 1.28) for those who had high-grade tumor. The test for interaction was not significant (P = 0.98; I^2 = 0%).

Sensitivity analysis

We performed a sensitivity analysis using Messing 2018, which was at low risk of bias, overall.

See Table 3

Time to recurrence

Gemcitabine probably reduces the risk of recurrence over time compared to saline (HR 0.66, 95% CI 0.48 to 0.90; participants = 406; moderate-certainty evidence). Based on the control event risk of 470 per 1000 participants, this corresponds to 128 fewer recurrences (95% CI 207 fewer to 35 fewer) per 1000 participants. We downgraded the certainty of the evidence due to imprecision, given that the CI was also consistent with a small or no reduction in the risk of recurrence over time.

Time to progression

Gemcitabine results in little to no difference in the risk of progression over time compared to saline (HR 0.51, 95% CI 0.17 to 1.50; participants = 406; high-certainty evidence). Based on the control event risk of 48 per 1000 participants, this would result in 23 fewer progressions (95% CI 40 fewer to 23 more) per 1000 participants.

Grade III to V adverse events

Gemcitabine probably results in little to no difference in CTCAE grade III to V adverse events compared to saline (RR 0.71, 95% CI 0.20 to 2.46; participants = 340; moderate-certainty evidence). Based on the control event risk of 34 per 1000 participants, this corresponds to 10 fewer adverse events (95% CI 27 fewer to 50 more) per 1000 participants. We downgraded the certainty of the evidence due to imprecision, given that the CI was also consistent with an increase in CTCAE grade III to V adverse events.

Time to death from bladder cancer

The study did not address the time to death from bladder cancer.

Time to death from any cause

Gemcitabine may reduce the risk of death from any cause over time compared to saline (HR 0.68, 95% CI 0.36 to 1.27; participants = 406; low-certainty evidence), but the CI included the possibility of no effect. Based on the control event risk of 121 per 1000 participants, this corresponds to 37 fewer deaths from any cause (95% CI 76 fewer to 30 more) per 1000 participants. We downgraded the certainty of the evidence due to imprecision, given that the CI was consistent both with a reduction in the risk of death from any cause over time as well as an increase in the risk of death from any cause (i.e. wide CIs).

Grade I or II adverse events

Gemcitabine probably increases CTCAE grade I or II adverse events slightly compared to saline (RR 1.20, 95% CI 0.86 to 1.66; participants = 340; moderate-certainty evidence), but the CI included the possibility of no effect. Based on the control event risk of 269 per 1000 participants, this corresponds to 54 more adverse events (95% CI 38 fewer to 177 more) per 1000 participants. We downgraded the certainty of the evidence due to imprecision, given that the CI was also consistent with a small or no reduction in CTCAE grade I or II adverse events.

2. Gemcitabine versus mitomycin

One study compared gemcitabine versus mitomycin for recurrent NMIBC (Addeo 2010; Summary of findings 2). There was no data available for gemcitabine versus mitomycin for primary NMIBC.

Primary outcomes

Time to recurrence

Gemcitabine may reduce the risk of recurrence over time compared to mitomycin (HR 0.36, 95% CI 0.19 to 0.69; studies = 1, participants = 109; low-certainty evidence; Analysis 2.1). Based on the control event risk of 400 per 1000 participants in the trial included in this analysis and at three years of follow-up, this would result in 232 fewer recurrences (95% CI 308 fewer to 103 fewer) per 1000 participants. We downgraded the certainty of the evidence due to study limitations and imprecision (outcome based on only a single study of a small number of participants).

Time to progression

Gemcitabine may reduce the risk of progression over time compared to mitomycin (HR 0.57, 95% CI 0.32 to 1.01; studies = 1, participants = 109; low-certainty evidence; Analysis 2.2), but the CI included the possibility of no effect. Based on the control event risk of 182 per 1000 participants in the trial included in this analysis and at three years of follow-up, this corresponds to 74 fewer progressions (95% CI 120 fewer to 2 more) per 1000 participants. We downgraded the certainty of the evidence, due to study limitations and imprecision, the CI was also compatible with a small or no increase in the risk of progression.

Grade III to V adverse events

We are very uncertain about the effect of gemcitabine on the CTCAE grade III to V adverse events compared to mitomycin (RR 0.51, 95% CI 0.13 to 1.93; studies = 1, participants = 109; very low-certainty evidence; Analysis 2.3). We downgraded the certainty of the evidence due to study limitations (downgraded one level) and very serious imprecision (downgraded two levels).

Secondary outcomes

Time to death from bladder cancer

We found no studies that reported the time to death from bladder cancer.

Time to death from any cause

We found no studies that reported time to death from any cause.

Grade I or II adverse events

Gemcitabine may reduce the CTCAE grade I or II adverse events compared to mitomycin (RR 0.53, 95% CI 0.37 to 0.78; studies = 1, participants = 109; low-certainty evidence; Analysis 2.4). Based on the control event risk of 727 per 1000 participants in the trial included in this analysis and at three years of follow-up, this corresponds to 342 fewer adverse events (95% CI 458 fewer to 160 fewer) per 1000 participants. We downgraded the certainty of the evidence due to study limitations and imprecision (outcome based on only a single study of a small number of participants).

Disease-specific quality of life

We found no studies that reported disease-specific quality of life.

Subgroup analysis

We were unable to perform any of the predefined subgroup analyses.

Sensitivity analysis

We were unable to perform a sensitivity analysis because there was only one study.

3. Gemcitabine versus BCG

One study compared gemcitabine versus BCG for primary high-risk NMIBC (Porena 2010; summary of findings table provided as Table 4); we did not identify studies in participants with recurrent disease.

Primary outcomes

Time to recurrence

Gemcitabine may increase the risk of recurrence over time compared to BCG (HR 10.07, 95% CI 4.48 to 22.63; studies = 1, participants = 64; low-certainty evidence; Analysis 3.1). Based on the control event risk of 478 per 1000 participants in the trial included in this analysis and at mean 44 months' follow-up, this corresponds to 521 more recurrences (95% CI 468 more to 522 more) per 1000 participants. We downgraded the certainty of the

evidence due to study limitations and imprecision (outcome based on only a single study of a small number of participants).

Time to progression

We are very uncertain about the effect of gemcitabine on the risk of progression over time compared to BCG (HR: not estimable, no events in either arm; studies = 1, participants = 64; very low-certainty evidence; Analysis 3.2). We downgraded the certainty of the evidence due to study limitations (downgraded one level) and very serious imprecision (downgraded two levels); there were no events in either arm.

Grade III to V adverse events

Porena 2010 reported adverse events of gemcitabine and BCG, but we could not grade them in accordance with CTCAE. Therefore, we were unable to estimate this outcome.

Secondary outcomes

Time to death from bladder cancer

We found no studies that reported the time to death from bladder cancer.

Time to death from any cause

We found no studies that reported time to death from any cause.

Grade I or II adverse events

Porena 2010 reported adverse events of gemcitabine and BCG, but we could not grade them in accordance with CTCAE. Therefore, we were unable to estimate this outcome.

Disease-specific quality of life

We found no studies that reported disease-specific quality of life.

Subgroup analysis

We were unable to perform any of the predefined subgroup analyses.

Sensitivity analysis

We were unable to perform a sensitivity analysis because there was only one study.

4. Gemcitabine versus BCG for recurrent (one-course BCG failure) high-risk NMIBC

One study compared gemcitabine versus BCG for recurrent high-risk NMIBC (Di Lorenzo 2010; Summary of findings 3) in participants who had previously undergone one course of BCG treatment and recurred.

Primary outcomes

Time to recurrence

Gemcitabine may reduce the risk of recurrence over time compared to BCG (HR 0.15, 95% CI 0.09 to 0.26; studies = 1, participants = 80; low-certainty evidence; Analysis 4.1). Based on the control event risk of 970 per 1000 participants in the trial included in this analysis and at six months' to 22 months' follow-up, this corresponds to 561 fewer recurrences (95% CI 699 fewer to 372 fewer) per 1000 participants. We downgraded the certainty of the evidence due to study limitations and imprecision (outcome based on only a single study of a small number of participants).

Time to progression

Gemcitabine may reduce the risk of progression over time compared to BCG (HR 0.45, 95% CI 0.27 to 0.76; studies = 1, participants = 80; low-certainty evidence; Analysis 4.2). Based on the control event risk of 325 per 1000 participants in the trial included in this analysis and at six months' to 22 months' follow-up, this corresponds to 163 fewer progressions (95% CI 224 fewer to 67 fewer) per 1000 participants. We downgraded the certainty of the evidence due to study limitations and imprecision (outcome based on only a single study of a small number of participants).

Grade III to V adverse events

We are very uncertain about the effect of gemcitabine on the CTCAE grade III to V adverse events compared to BCG (RR 1.00, 95% CI 0.21 to 4.66; studies = 1, participants = 80; very low-certainty evidence; Analysis 4.3). We downgraded the certainty of the evidence due to study limitations (downgraded one level) and very serious imprecision (downgraded two levels), the CI was consistent both with an appreciable reduction as well as an appreciable increase in CTCAE grade III to V adverse events (i.e. wide CIs).

Secondary outcomes

Time to death from bladder cancer

We are very uncertain about the effect of gemcitabine on the risk of death from bladder cancer over time compared to BCG (HR 0.04, 95% CI 0.01 to 2.25; studies = 1, participants = 80; very low-certainty evidence; Analysis 4.4). Based on the control event risk of 17 per 1000 participants in the trial included in this analysis and at six months' to 22 months' follow-up, this corresponds to 16 fewer deaths from bladder cancer (95% CI 17 fewer to 21 more) per 1000 participants. We downgraded the certainty of the evidence due to study limitations (downgraded one level) and very serious imprecision (downgraded two levels), the CI was consistent both with an appreciable reduction as well as an appreciable increase in the risk of time to death from bladder cancer (i.e. wide CIs).

Time to death from any cause

We found no studies that reported time to death from any cause.

Grade I or II adverse events

We are very uncertain about the effect of gemcitabine on the CTCAE grade I or II adverse events compared to BCG (RR 0.92, 95% CI 0.48 to 1.77; studies = 1 participants = 80; very low-certainty evidence; Analysis 4.5). We downgraded the certainty of the evidence due to study limitations (downgraded one level) and imprecision (downgraded two levels), the CI was consistent both with an appreciable reduction as well as an appreciable increase in CTCAE grade I or II adverse events (i.e. wide CIs).

Disease-specific quality of life

We found no studies that reported disease-specific quality of life.

Subgroup analysis

We were unable to perform any of the predefined subgroup analyses.

Sensitivity analysis

We were unable to perform a sensitivity analysis because there was only one study.

5. Gemcitabine versus one-third dose BCG

One study compared gemcitabine versus one-third dose BCG in participants with either primary and recurrent intermediate-risk NMIBC (Gontero 2013; summary of findings table provided in Table 5).

Primary outcomes

Time to recurrence

We are very uncertain about the effect of gemcitabine on recurrence over time compared to one-third dose BCG (HR 1.17, 95% CI 0.57 to 2.42; studies = 1, participants = 118; very low-certainty evidence; Analysis 5.1). We downgraded the certainty of the evidence due to study limitations (downgraded one level) and imprecision (downgraded two levels), the CI was consistent both with an appreciable reduction in the risk of recurrence over time as well as an appreciable increase in the risk of recurrence (i.e. wide CIs).

Time to progression

Gemcitabine may result in little to no difference in the risk of progression over time compared to one-third dose BCG (HR 1.63, 95% CI 0.39 to 6.83; studies = 1, participants = 118; low-certainty evidence; Analysis 5.2). Based on the control event risk of 51 per 1000 participants in the trial included in this analysis and at one year' follow-up, this corresponds to 31 more progressions (95% CI 31 fewer to 250 more) per 1000 participants. We downgraded the certainty of the evidence due to study limitations and imprecision, the CI was consistent with an appreciable increase in the risk of progression.

Grade III to V adverse events

We are very uncertain about the effect of gemcitabine on the CTCAE grade III to V adverse events compared to one-third dose BCG (RR: not estimable, no events in either arm; studies = 1, participants = 88; very low-certainty evidence; Analysis 5.3). We downgraded the certainty of the evidence due to study limitations (downgraded one level) and imprecision (downgraded two levels). There were no events in either arm.

Secondary outcomes

Time to death from bladder cancer

We found no studies that reported time to death from bladder cancer.

Time to death from any cause

Gontero 2013 reported one death from any cause, but we could not extract HR since the study did not report which intervention the participant received (i.e. gemcitabine or one-third BCG).

Grade I or II adverse events

We are very uncertain about the effect of gemcitabine on CTCAE grade I or II adverse events compared to one-third dose BCG (RR 0.84, 95% CI 0.49 to 1.46; studies = 1, participants = 88; very low-certainty evidence; Analysis 5.4). We downgraded the certainty of the evidence due to study limitations (downgraded one level) and imprecision (downgraded two levels); the CI was consistent both with an appreciable reduction as well as an appreciable increase in CTCAE grade I or II adverse events (i.e. wide CIs).

Disease-specific quality of life

Gemcitabine may result in similar disease-specific quality of life compared to one-third dose BCG (MD 4.50, 95% CI –1.60 to 10.60; studies = 1, participants = 88; low-certainty evidence; Analysis 5.5). We downgraded the certainty of the evidence due to study limitations and imprecision, given the CI was also consistent with the improvement of quality of life.

Subgroup analysis

We were unable to perform any of the predefined subgroup analyses.

Sensitivity analysis

We were unable to perform a sensitivity analysis because there was only one study.

DISCUSSION

Summary of main results

This latest update of a prior Cochrane Review (Jones 2012) includes seven studies with 1222 randomized participants across five comparisons for evaluating the effect of gemcitabine compared to other agents in the NMIBC.

Gemcitabine versus saline

In people with primary and recurrent NMIBC, gemcitabine may reduce the risk of recurrence and may have a similar effect on the risk of progression over time compared to saline. We are very uncertain about the effects of gemcitabine on the risk of death from bladder cancer and death from any cause overtime. In terms of adverse events, gemcitabine may have similar CTCAE grade I to V adverse events compared to saline. Based on the preplanned subgroup analysis, we are uncertain about the effect of gemcitabine according to the tumor grade. This result should be interpreted with caution because the included study was not designed to assess subgroup effects.

Based on the predefined sensitivity analysis of the one study judged at low risk of bias (Messing 2018), findings were similar. We found no information about the disease-specific quality of life.

Gemcitabine versus mitomycin

In people with recurrent NMIBC previously treated with BCG or epirubicin (one of the intravesical chemotherapeutic drug which is used in NMIBC), gemcitabine may reduce the risk of recurrence over time and may reduce the risk of progression over time. In terms of adverse events, gemcitabine may reduce CTCAE grade I or II adverse events compared to mitomycin, but we are very uncertain about the effect of gemcitabine on CTCAE grade III to V adverse events. We found no information about time to death from bladder cancer, time to death from any cause, and disease-specific quality of life.

Gemcitabine versus BCG

In participants with primary high-risk NMIBC, gemcitabine may increase the risk of recurrence over time, but we are very uncertain about the effect on the risk of progression compared to BCG. We found no information about other outcomes.

Gemcitabine versus BCG for recurrent high-risk NMIBC after one-course BCG failure

After one-course BCG failure, gemcitabine may reduce the risk of recurrence and progression over time compared to BCG. However, we are very uncertain about the effect on grade I to V CTCAE adverse events and the risk of death from bladder cancer. We found no information about time to death from any cause and disease-specific quality of life.

Gemcitabine versus one-third dose BCG

In participants with primary and recurrent intermediate-risk NMIBC, we are very uncertain about the effect of gemcitabine on the risk of recurrence and grade I to V CTCAE adverse events. Gemcitabine may have a similar effect on the risk of progression over time and disease-specific quality of life compared to one-third dose BCG. We found no information about time to death from bladder cancer and time to death from any cause.

Overall completeness and applicability of evidence

The studies included in this review may deserve the following consideration.

- The findings of this review were based on fairly narrow evidence base on seven unique trials. Only one or two trials informed each of the five comparisons and all trials were conducted in Europe (four studies from Italy) or the US. Similar studies performed by other investigators in other countries would be valuable in validating these findings.
- Although our review intended to evaluate the effect of intravesical gemcitabine in NMIBC, two studies included a small subset of patients who were ultimately found to have muscle-invasive disease (Böhle 2009 7.7% and Messing 2018; 3.7%). Since we were unable to exclude this group of patients from the analysis. their contribution was small and this also resembles routine clinical practice we included these studies (available analysis data set) in our review and also did not downgrade for indirectness. .
- There are multiple factors that affect the effect of intravesical instillation therapy such as the dose of anti-tumor agents, dwell time of anti-tumor agents, and instillation schedule. In addition, tumor factors such as the number of tumors, tumor size, stage, presence of CIS, and grade can influence the effectiveness of treatment. In this review, each study used a different dose and schedule, and some of the studies did not provide relevant information, thus we could not conduct preplanned subgroup analysis except for one comparison (Analysis 1.7).
- There was moderate heterogeneity between the studies in terms of time to recurrence and time to progression (Analysis 1.1; Analysis 1.2). This probably results from different dwell times of gemcitabine and saline. However, despite the different dwell times of gemcitabine, the effect estimate favored gemcitabine, and we could apply this result to clinical practice.
- Based on current evidence-based guidelines (Babjuk 2019), after TUR of bladder tumor, people should undergo immediate postoperative instillation of mitomycin C followed by an induction course of anti-tumor agents, namely BCG, with or without maintenance therapy according to their risk of recurrence. As none of the included studies used this comparison, which is considered the standard of care, these issues limit clinical applicability.
- Our ability to assess the longer-term outcomes of gemcitabine compared to other agents was limited given that the follow-up duration in some of the studies was 12 weeks or less than two years (mean or median). The evidence to assess the efficacy and safety of gemcitabine over such a short term appears insufficient to provide assurance of long-term outcomes.
- The findings of this systematic review were limited to evidence from RCTs of low to very low certainty. The consideration of non-randomized studies may have provided some evidence for additional outcomes such as adverse events (Schünemann 2013). Also, while we believe this to be unlikely, it is possible that they could have provided complementary results with higher certainty than those from RCTs.

Quality of the evidence

We judged the overall risk of bias of the included trials as unclear except for one trial (Messing 2018). Some studies raised concerns about performance and detection bias, and others have reporting and other biases (e.g. baseline imbalance and different treatment schedules). We judged the certainty of the evidence as low to very low for most outcomes due to these study limitations as well as wide CIs that crossed assumed clinically important thresholds resulting in the imprecision of the results. Moreover, several outcomes based on only a single study of a small number of participants.

Potential biases in the review process

Despite a comprehensive search strategy with no publication or language restrictions, we may have missed additional RCTs that may be unpublished or were published in languages other than English (or both). We translated all Chinese literature into English using Google translator; therefore, the lack of human double-data abstraction may be considered a potential source of bias. The small number of studies included in this review was insufficient to generate funnel plots; therefore, the risk of publication bias may have been underestimated.

Böhle 2009 and Messing 2018 included some people with clinical stage T2 disease (i.e. muscle invasive bladder tumor). Since the T2 tumors are more aggressive than NMIBC, this could be a source of bias, possibly resulting in an underestimate of the effect size.

For the interpretation of clinically important effect sizes, we used absolute effect estimates that were informed by the input of expert clinicians on our team; unless there were publish thresholds (as was the case for quality-of-life instruments), we used 5% for the most patient-important primary outcomes and 3% for the secondary outcomes of time to death from bladder cancer and time to death from any cause. We recognize that different thresholds might lead to different interpretations and have, therefore, made all our judgments as transparent as possible.

Agreements and disagreements with other studies or reviews

We found only two systematic reviews that investigated the effect of gemcitabine compared to BCG (Ye 2018) and mitomycin (Li 2020a). Ye 2018 included 365 participants from five trials, both randomized and non-randomized, and concluded that intravesical gemcitabine may have a similar effect on the recurrence (RR 1.17, 95% CI 0.83 to 1.67), progression (RR 1.02, 95% CI 0.42 to 2.56), and any adverse events (RR 0.55, 95% CI 0.25 to 1.20) compared to

BCG. However, this review did not consider clinical heterogeneity of included studies (i.e. meta-analysis with regard to primary high-risk and intermediate-risk bladder cancer) and used RR for time to event outcomes, thereby questioning the appropriateness of pooling. Moreover, it provided no information of a priori registered protocol and risk of bias of included studies. Li 2020a reported that gemcitabine was more effective than mitomycin in terms of recurrence and adverse events. Although, the author explicitly mentioned that they included RCTs only, some studies were not RCTs. With regard to analysis, it had the same issues identified with Ye 2018. They did not consider clinical heterogeneity between included studies. Recently, two systematic reviews which included participants with NMIBC not responsive to intravesical BCG were published (Kamat 2020; Li 2020b). They included all studies regardless of the study design, however, they found no additional RCTs to the ones that we included. These two reviews can help the reader understand the current best body of evidence; however, our confidence must be very low about the results from study designs other than RCTs given the inherent study limitations of non-randomized studies.

In addition, none of the existing systematic reviews (including the previous version of this Cochrane Review) provided a GRADE rating, which we consider critical to any systematic review (Jones 2012; Li 2020a; Ye 2018). This updated Cochrane Review used rigorous methodology, exhaustive literature search, and assessment of the certainty of the evidence using GRADE, thereby providing the most reliable evidence summary. Furthermore, our interpretation focused on clinically relevant (rather and statistically significant) findings and provided absolute effect size estimates for all dichotomous and time-to-event outcomes.

AUTHORS' CONCLUSIONS

Implications for practice

Based on the findings of low- to very-low certainty evidence, gemcitabine may reduce recurrence over time in primary and recurrent non-muscle invasive bladder cancer (NMIBC) compared to saline and mitomycin. Gemcitabine may have similar Common Terminology Criteria for Adverse Events (CTCAE) grade III to V adverse events compared to saline. Gemcitabine may be inferior in terms of recurrence compared to BCG, but in people who have recurred after BCG treatment, it may be superior in terms of risk of recurrence and progression over time. Compared to one-third dose BCG, we are very uncertain about the effect of gemcitabine on the recurrence and CTCAE grade III to V adverse events, but may have similar effects on the risk of progression.

Implications for research

More adequately powered and high-quality trials using the same treatment schedule between gemcitabine and other intravesical agent including one-third dose of BCG (NCCN guideline 2019), reporting outcomes in subgroups according to the risk classification system, patient-reported quality of life data and long-term outcomes such as mortality would be useful. Moreover, in the era of BCG shortage, there is a need for trials of gemcitabine versus other novel intravesical agents (Sari 2020).

ACKNOWLEDGEMENTS

We acknowledge the support received from the authors of included and excluded studies – Andreas Böhle, Riccardo Autorino, and Paolo Gontero – who provided additional, unpublished data.

REFERENCES

References to studies included in this review

Addeo 2010 *{published data only}*

* Addeo R, Caraglia M, Bellini S, Abbruzzese A, Vincenzi B, Montella L, et al. Randomized phase III trial on gemcitabine versus mytomicin in recurrent superficial bladder cancer: evaluation of efficacy and tolerance. *Journal of Clinical Oncology* 2010;**28**(4):543-8. [PMID: 19841330]

Faiola V, Montella L, Addeo R, Bellini S, Miragliulo A, Cennamo G, et al. Intravesical gemcitabine versus mitomycin for recurrent superficial bladder tumours (stages pTa and pT1): a randomized prospective study. *European Journal of Cancer Supplements* 2008;**6**(14):124. [DOI: 10.1016/j.ejcsup.2008.06.049]

Montella L, Addeo R, Bellini S, Faiola V, Tarantino L, Pizza C, et al. Intravesical gemcitabine versus mitomycin for recurrent superficial bladder tumors (stages pTa and pT1): a randomized prospective study. *Journal of Clinical Oncology* 2008;**26**(15 Suppl):5075. [DOI: 10.1200/jco.2008.26.15_suppl.5075]

Bendary 2011 *{published data only}*

Bendary L, Khalil S, Shahin A, Nawar N. Intravesical gemcitabine versus Bacillus Calmette-Guerin (BCG) in treatment of non-muscle invasive bladder cancer: short term comparative study. *Journal of Urology* 2011;**185**(4s):e664-5. [DOI: 10.1016/j.juro.2011.02.1765]

Böhle 2009 *{published and unpublished data}*

Böhle A, Helsberg K, Soldatenkova V, Lubben B, Stoffregen C, Buttner H, S274 Study Group. Single postoperative instillation of gemcitabine in patients with superficial transitional cell carcinoma of the bladder: a randomised, double-blind, placebo-controlled phase 3 multicenter study. *Journal of Urology* 2009;**181**(4s):689. [DOI: 10.1016/S0022-5347(09)61930-3]

* Böhle A, Leyh H, Frei C, Kühn M, Tschada R, Pottek T, et al. Single postoperative instillation of gemcitabine in patients with non-muscle-invasive transitional cell carcinoma of the bladder: a randomised, double-blind, placebo-controlled phase III multicentre study. *European Urology* 2009;**56**(3):495-503. [PMID: 19560257]

NCT00191477. Instillation of gemcitabine in patients with superficial bladder cancer. clinicaltrials.gov/ct2/show/NCT00191477 (first received 19 September 2005). [NCT00191477]

Di Lorenzo 2010 *{published data only}*

Autorino R, Cantiello F, Damiano R, De Sio M, Di Lorenzo G, Rubino D, et al. Gemcitabine versus BCG after initial BCG failure in non muscle-invasive bladder cancer: a prospective randomized trial. *European Urology Supplements* 2009;**8**(4):283. [DOI: 10.1016/S1569-9056(09)60644-8]

* Di Lorenzo G, Perdona S, Damiano R, Faiella A, Cantiello F, Pignata S, et al. Gemcitabine versus Bacille Calmette-Guerin after initial Bacille Calmette-Guerin failure in non-muscle-invasive bladder cancer: a multicenter prospective randomized trial. *Cancer* 2010;**116**(8):1893-900. [PMID: 20162706]

Gontero 2013 *{published data only}*

Gontero P, Gurioli A, Mehnert A, Schmid M, Kluth L, Pappagallo G, et al. Is there a difference in quality of life between BCG and intravesical chemotherapy? Results of a randomized phase II study. *European Urology Supplements* 2012;**11**(1):e966-6a. [DOI: 10.1016/S1569-9056(12)60963-4]

Gontero P, Gurioli A, Oderda M, Mehnert A, Rink M, Schmid M, et al. Is there a difference in quality of life between BCG and intravesical chemotherapy? Results of a randomized phase II study. *Journal of Urology* 2012;**187**(4s):e218. [DOI: 10.1016/j.juro.2012.02.604]

Gontero P, Oderda M, Gurioli A, Marson F, Mehnert A, Rink M, et al. Is there a difference in quality of life between intravesical chemotherapy and BCG? Results of a randomized phase II trial. *Anticancer Research* 2012;**32**(5):1908-9.

* Gontero P, Oderda M, Mehnert A, Gurioli A, Marson F, Lucca I, et al. The impact of intravesical gemcitabine and 1/3 dose Bacillus Calmette-Guérin instillation therapy on the quality of life in patients with non-muscle invasive bladder cancer: results of a prospective, randomized, phase II trial. *Journal of Urology* 2013;**190**(3):857-62. [PMID: 23545101]

NCT01697306. The impact of intravesical gemcitabine and 1/3 dose Bacillus Calmette-Guerin on the quality of life in superficial bladder cancer. clinicaltrials.gov/ct2/show/study/NCT01697306 (first received 2 October 2012). [NCT01697306]

Messing 2018 *{published data only}*

Messing E, Tangen C, Lerner S, Sahasrabudhe D, Koppie T, Wood D, et al. A phase III blinded study of immediate post-TURBT instillation of gemcitabine versus saline in patients with newly diagnosed or occasionally recurring grade I/II non-muscle invasive bladder cancer: SWOG S0337. *Journal of Urology* 2017;**197**(4s):e914-5. [DOI: 10.1016/j.juro.2017.03.036]

* Messing EM, Tangen CM, Lerner SP, Sahasrabudhe DM, Koppie TM, Wood DP Jr, et al. Effect of intravesical instillation of gemcitabine vs saline immediately following resection of suspected low-grade non-muscle-invasive bladder cancer on tumor recurrence: SWOG S0337 randomized clinical trial. *JAMA* 2018;**319**(18):1880-8. [PMID: 29801011]

NCT00445601. S0337, Gemcitabine after surgery in treating patients with newly diagnosed or recurrent bladder cancer. clinicaltrials.gov/ct2/show/study/NCT00445601 (first received 9 March 2007). [NCT00445601]

Porena 2010 *{published data only}*

NCT00696579. Bacillus of calmette and guerin (BCG) versus gemcitabine for intravesical therapy in high risk superficial bladder cancer. clinicaltrials.gov/ct2/show/study/NCT00696579 (first received 12 June 2008). [NCT00696579]

* Porena M, Del Zingaro M, Lazzeri M, Mearini L, Giannantoni A, Bini V, et al. Bacillus Calmette-Guerin versus gemcitabine for intravesical therapy in high-risk superficial bladder cancer: a randomised prospective study. *Urologia Internationalis* 2010;**84**(1):23-7. [PMID: 20173364]

References to studies excluded from this review

Böhle 2010 *{published data only}*

Böhle A, Leyh H, Frei C, Kuhn M, Tschada R, Pottek T, et al. Single postoperative instillation of gemcitabine in patients with non-muscle-invasive transitional cell carcinoma of the bladder: a randomised, double-blind, placebo-controlled phase III multicentre study. *Journal of Urology* 2010;**184**(3):897-8. [DOI: 10.1016/j.juro.2010.05.060]

Brausi 2011 *{published data only}*

Brausi MA, Gontero P, Altieri V, Colombo R, Conti I, Bono AV. Can gemcitabine instillation ablate solitary low-risk non-muscle-invasive bladder cancer? Results of a phase II marker lesion study. *Urologia Internationalis* 2011;**87**(4):470-4. [PMID: 22086229]

Cao 2011 *{published data only}*

Cao M, Ma CK, Ma J, Chen HG, Xue W. Evaluation of the efficacy and safety of intravesical instillation with gemcitabine after first-line intravesical chemotherapy failure in the treatment of non-muscle-invasive bladder cancer [吉西他滨膀胱灌注治疗复发性浅表性膀胱肿瘤的安全性与有效性]. *Zhonghua Zhong Liu za Zhi [Chinese Journal of Oncology]* 2011;**33**(5):385-7. [PMID: 21875472]

Dalbagni 2006 *{published data only}*

Dalbagni G, Russo P, Bochner B, Ben-Porat L, Sheinfeld J, Sogani P, et al. Phase II trial of intravesical gemcitabine in bacille Calmette-Guerin-refractory transitional cell carcinoma of the bladder. *Journal of Clinical Oncology* 2006;**24**(18):2729-34. [PMID: 16782913]

Dong 2017 *{published data only}*

Dong X, Song L, Zhang F. Curative effect analysis of different chemotherapeutics at intravesical instillation in the prevention of tumor recurrence after TUR-Bt [TUR-Bt术后不同化疗药物膀胱灌注预防肿瘤复发的效果分析]. *Zhejiang Journal of Traumatic Surgery* 2017;**1**:109-10. [caod.oriprobe.com/articles/50688689/tur_bt_shu_hou_bu_tong_hua_liao_yao_wu_bang_zuo_gu.htm]

Gantz 2018 *{published data only}*

Gantz J, Noyes E, Tangen C, Lerner S, Thompson I, Madeb R, et al. Immediate post TURB intravesical gemcitabine: a cost comparison based on SWOG S0337. *Journal of Urology* 2018;**199**(4s):e1230. [DOI: 10.1016/j.juro.2018.02.2997]

Gardmark 2005 *{published data only}*

Gardmark T, Carringer M, Beckman E, Malmstrom P U. Randomized phase II marker lesion study evaluating effect of scheduling on response to intravesical gemcitabine in recurrent stage Ta urothelial cell carcinoma of the bladder. *Urology* 2005;**66**(3):527-30. [PMID: 16140071]

Lin 2016 *{published data only}*

Lin T, Sun L. Comparison of the efficacy of different chemotherapy drugs in the prevention of postoperative recurrence in superficial bladder cancer by intravesical instillation. *China Foreign Medical Treatment* 2016;**34**:118-9. [caod.oriprobe.com/articles/50430850/Different_Intravesical_Chemotherapy_Drugs_Prevention_Efficacy_of_Super.htm]

Sun 2016 *{published data only}*

Sun S, Liu R, Zhao H, Wang B, Liu Y, Wen K. Comparison of intravesical perfusion of gemcitabine and mitomycin after non-muscle invasive bladder cancer [非肌层浸润性膀胱癌电切术后吉西他滨与丝裂霉素膀胱灌注疗效对比]. *Journal of Medical Theory and Practice* 2016;**29**:3238-9. [caod.oriprobe.com/articles/50444480/fei_ji_ceng_jin_run_xing_bang_zuo_ai_dian_qie_shu_hou_ji_xi_ta_bin_yu_.htm]

Xia 2019 *{published data only}*

Xia H, Liang C, Yang C, Chen J. Effect of gemcitabine intravesical instillation in patients with bladder cancer and its influence on survival [吉西他滨膀胱灌注在膀胱癌患者中的疗效观察及对生存期的影响研究]. *Anti-Tumor Pharmacy* 2019;**9**(5):789-92. [DOI: 10.3969/j.issn.2095-1264.2019.05.18]

References to studies awaiting assessment

Xiaohong 2015 *{published data only}*

Xiaohong Z, Tan J, Wei Y, et al. Clinical effect of antineoplastic drug perfusion in preventing postoperative recurrence of superficial bladder cancer. *J Chin Physician* 2015;**17**:1043-5.

References to ongoing studies

ChiCTR1900026643 *{unpublished data only}*

ChiCTR1900026643. The randomized controlled study for intravesical instillation of Pseudomonas aeruginosa and gemcitabine in the prevention of postoperative recurrence of non-muscle invasive bladder cancer [铜绿假单胞菌和吉西他滨膀胱灌注预防非肌层浸润性膀胱癌术后复发的随机对照研究]. chictr.org.cn/showproj.aspx?proj=44307 (first received 17 October 2019). [ChiCTR1900026643]

NCT00192049 *{unpublished data only}*

NCT00192049. A randomized study comparing single agent gemcitabine intravesical therapy versus mitomycin C in patients with intermediate risk superficial bladder cancer. clinicaltrials.gov/ct2/show/NCT00192049 (first received 19 September 2005). [NCT00192049]

NCT02695771 *{unpublished data only}*

NCT02695771. The bladder instillation comparison study (BIC). clinicaltrials.gov/ct2/show/NCT02695771 (first received 1 March 2016). [NCT02695771]

NCT04172675 *{unpublished data only}*

* NCT04172675. A study of erdafitinib versus investigator choice of intravesical chemotherapy in participants who received Bacillus Calmette-Guérin (BCG) and recurred with high risk non-muscle-invasive bladder cancer (NMIBC). clinicaltrials.gov/ct2/show/NCT04172675 (first received 20 November 2019). [NCT04172675]

Steinberg GD, Palou-Redorta J, Gschwend JE, Tran B, Loriot Y, Daneshmand S, et al. A randomized phase II study

of erdafitinib (ERDA) versus intravesical chemotherapy (IC) in patients with high-risk nonmuscle invasive bladder cancer (HR-NMIBC) with FGFR mutations or fusions, who recurred after Bacillus Calmette-Guerin (BCG) therapy. *Journal of Clinical Oncology* 2020;**38**(6 Suppl):TPS603. [DOI: 10.1200/JCO.2020.38.6_suppl.TPS603]

Additional references

Babjuk 2019

Babjuk M, Burger M, Comperat EM, Gontero P, Mostafid AH, Palou J, et al. European Association of Urology Guidelines on non-muscle-invasive bladder cancer (TaT1 and carcinoma in situ) – 2019 update. *European Urology* 2019;**76**(5):639-57. [PMID: 31443960]

Bray 2018

Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: a Cancer Journal for Clinicians* 2018;**68**(6):394-424. [PMID: 30207593]

Burger 2008

Burger M, van der Aa MN, van Oers JM, Brinkmann A, van der Kwast TH, Steyerberg EC, et al. Prediction of progression of non-muscle-invasive bladder cancer by WHO 1973 and 2004 grading and by FGFR3 mutation status: a prospective study. *European Urology* 2008;**54**(4):835-43. [PMID: 18166262]

Chang 2016

Chang S S, Boorjian S A, Chou R, Clark P E, Daneshmand S, Konety B R, Pruthi R, Quale D Z, Ritch C R, Seigne J D, Skinner E C, Smith N D, McKiernan J M. Diagnosis and Treatment of Non-Muscle Invasive Bladder Cancer: AUA/SUO Guideline. *J Urol* 2016;**196**(4):1021-9.

Covidence [Computer program]

Veritas Health Innovation Covidence. Version accessed 18 January 2019. Melbourne, Australia: Veritas Health Innovation, 2017. Available at www.covidence.org.

Cozzi 1999

Cozzi PJ, Bajorin DF, Tong W, Nguyen H, Scott J, Heston WD, et al. Toxicology and pharmacokinetics of intravesical gemcitabine: a preclinical study in dogs. *Clinical Cancer Research* 1999;**5**(9):2629-37. [PMID: 10499642]

CTCAE

National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf (accessed 17 January 2019).

Deeks 2017

Deeks JJ, Higgins JP, Altman DG, Cochrane Statistical Methods Group. Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JP, Churchill R, Chandler J, Cumpston MS, editor(s), Cochrane Handbook for Systematic Reviews of Interventions Version 5.2.0 (updated June 2017), Cochrane, 2017. Available from training.cochrane.org/handbook/archive/v5.2.

DeGeorge 2017

DeGeorge KC, Holt HR, Hodges SC. Bladder cancer: diagnosis and treatment. *American Family Physician* 2017;**96**(8):507-14. [PMID: 29094888]

EndNote [Computer program]

EndNote. Version 7.5. Boston (MA): Clarivate Analytics, 2016. Available at: www.endnote.com/.

Epstein 1998

Epstein JI, Amin MB, Reuter VR, Mostofi FK. The World Health Organization/International Society of Urological Pathology consensus classification of urothelial (transitional cell) neoplasms of the urinary bladder. Bladder Consensus Conference Committee. *American Journal of Surgical Pathology* 1998;**22**(12):1435-48. [PMID: 9850170]

Griffin 2013

Griffin JG, Holzbeierlein J. Side effects of perioperative intravesical treatment and treatment strategies for these side effects. *Urologic Clinics of North America* 2013;**40**(2):197-210. [PMID: 23540778]

Guyatt 2008

Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schunemann HJ. What is "quality of evidence" and why is it important to clinicians? *BMJ* 2008;**336**(7651):995-8. [PMID: 18456631]

Guyatt 2011

Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction – GRADE evidence profiles and summary of findings tables. *Journal of Clinical Epidemiology* 2011;**64**(4):383-94. [PMID: 21195583]

Hansel 2013

Hansel DE, Amin MB, Comperat E, Cote RJ, Knuchel R, Montironi R, et al. A contemporary update on pathology standards for bladder cancer: transurethral resection and radical cystectomy specimens. *European Urology* 2013;**63**(2):321-32. [PMID: 23088996]

Helenius 2015

Helenius M, Brekkan E, Dahlman P, Lönnemark M, Magnusson A. Bladder cancer detection in patients with gross haematuria: computed tomography urography with enhancement-triggered scan versus flexible cystoscopy. *Scandinavian Journal of Urology* 2015;**49**(5):377-81. [PMID: 25793362]

Higgins 2002

Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Statistics in Medicine* 2002;**21**(11):1539-58. [PMID: 12111919]

Higgins 2003

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**(7414):557-60. [PMID: 12958120]

Higgins 2011

Higgins JP, Deeks JJ, Altman DG, Cochrane Statistical Methods Group. Chapter 16: Special topics in statistics. In: Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from training.cochrane.org/handbook/archive/v5.1/.

Higgins 2017a

Higgins JP, Churchill R, Chandler J, Cumpston MS, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.2.0 (updated June 2017), Cochrane, 2017. Available from training.cochrane.org/handbook/archive/v5.2.

Higgins 2017b

Higgins JP, Altman DG, Sterne JA. Chapter 8: Assessing risk of bias in included studies. In: Higgins JP, Churchill R, Chandler J, Cumpston MS, editor(s), Cochrane Handbook for Systematic Reviews of Interventions Version 5.2.0 (updated June 2017), Cochrane, 2017. Available from training.cochrane.org/handbook/archive/v5.2.

Hozo 2005

Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Medical Research Methodology* 2005;**5**:13. [PMID: 15840177]

Humphrey 2016

Humphrey PA, Moch H, Cubilla AL, Ulbright TM, Reuter VE. The 2016 WHO classification of tumours of the urinary system and male genital organs – Part B: prostate and bladder tumours. *European Urology* 2016;**70**(1):106-19. [PMID: 26996659]

Kamat 2016

Kamat AM, Hahn NM, Efstathiou JA, Lerner SP, Malmström PU, Choi W, et al. Bladder cancer. *Lancet* 2016;**388**(10061):2796-810. [PMID: 27345655]

Kamat 2020

Kamat AM, Lerner SP, O'Donnell M, Georgieva MV, Yang M, Inman BA, et al. Evidence-based assessment of current and emerging bladder-sparing therapies for non-muscle-invasive bladder cancer after Bacillus Calmette-Guerin therapy: a systematic review and meta analysis. *European Urology Oncology* 2020;**3**(3):318-40.

Kilani 2002

Kilani RT, Tamimi Y, Karmali S, Mackey J, Hanel EG, Wong KK, et al. Selective cytotoxicity of gemcitabine in bladder cancer cell lines. *Anticancer Drugs* 2002;**13**(6):557-66. [PMID: 12172501]

Lamm 2014

Lamm D, Persad R, Brausi M, Buckley R, Witjes JA, Palou J, et al. Defining progression in non-muscle invasive bladder cancer: it is time for a new, standard definition. *Journal of Urology* 2014;**191**(1):20-7. [PMID: 23973937]

Laufer 2003

Laufer M, Ramalingam S, Schoenberg MP, Haisfield-Wolf ME, Zuhowski EG, Trueheart IN, et al. Intravesical gemcitabine therapy for superficial transitional cell carcinoma of the bladder: a phase I and pharmacokinetic study. *Journal of Clinical Oncology* 2003;**21**(4):697-703. [PMID: 2586808]

Li 2020a

Li R, Li Y, Song J, Gao K, Chen K, Yang X, et al. Intravesical gemcitabine versus mitomycin for non-muscle invasive bladder cancer: a systematic review and meta-analysis of randomized controlled trial. *BMC Urology* 2020;**20**(1):97. [PMID: 32660456]

Li 2020b

Li R, Sundi D, Zhang J, Kim Y, Sylvester RJ, Spiess PE, et al. Systematic review of the therapeutic efficacy of bladder-preserving treatments for non-muscle-invasive bladder cancer following intravesical Bacillus Calmette-Guérin. *European Urology* 2020;**78**(3):387-99.

Liberati 2009

Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Medicine* 2009;**6**(7):e1000100. [PMID: 19621070]

Maffezzini 2009

Maffezzini M, Campodonico F, Puntoni M, Martelli A, Mattioli F. Systemic absorption and pharmacokinetics of single-dose intravesical gemcitabine after transurethral resection of the bladder in non-muscle-invasive bladder cancer. *Urology* 2009;**74**(5):1078-83. [PMID: 19773039]

MedCalc Statistical Software [Computer program]

MedCalc Statistical Software. Version 18.11.3. Ostend, Belgium: MedCalc Software bvba, accessed 20 February 2019. Available at www.medcalc.org.

Mini 2006

Mini E, Nobili S, Caciagli B, Landini I, Mazzei T. Cellular pharmacology of gemcitabine. *Annals of Oncology* 2006;**17 Suppl 5**:v7-12. [PMID: 16807468]

NCCN guideline 2019

National Comprehensive Cancer Network. Bladder cancer, NCCN clinical practice guidelines in oncology. www.nccn.org/professionals/physician_gls/default.aspx#site (accessed 3 May 2019).

Osoba 1998

Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. *Journal of Clinical Oncology* 1998;**16**(1):139-44. [PMID: 9440735]

Parmar 1998

Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Statistics in Medicine* 1998;**17**(24):2815-34. [PMID: 9921604]

Perlis 2013

Perlis N, Zlotta AR, Beyene J, Finelli A, Fleshner NE, Kulkarni GS. Immediate post-transurethral resection of bladder tumor intravesical chemotherapy prevents non-muscle-invasive

bladder cancer recurrences: an updated meta-analysis on 2548 patients and quality-of-evidence review. *European Urology* 2013;**64**(3):421-30. [PMID: 23830475]

Peyton 2019

Peyton CC, Chipollini J, Azizi M, Kamat AM, Gilbert SM, Spiess PE. Updates on the use of intravesical therapies for non-muscle invasive bladder cancer: how, when and what. *World Journal of Urology* 2019;**37**(10):2017-29. [PMID: 30535583]

Review Manager 2014 [Computer program]

Nordic Cochrane Centre, The Cochrane Collaboration Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Sari 2020

Sari Motlagh R, Pradere B, Mori K, Miura N, Abufaraj M, Shariat SF. Bladder-preserving strategies for Bacillus Calmette-Guérin unresponsive non-muscle invasive bladder cancer; where are we and what will be expected? *Current Opinion in Urology* 2020;**30**(4):584-93. [PMID: 32304379]

Schünemann 2013

Schünemann HJ, Tugwell P, Reeves BC, Akl EA, Santesso N, Spencer FA, et al. Non-randomized studies as a source of complementary, sequential or replacement evidence for randomized controlled trials in systematic reviews on the effects of interventions. *Research Synthesis Methods* 2013;**4**(1):49-62. [PMID: 26053539]

Schünemann 2017

Schünemann HJ, Oxman AD, Higgins JP, Vist GE, Glasziou P, Akl E, et al, Cochrane GRADEing Methods Group and the Cochrane Statistical Methods Group. Chapter 11: Completing 'Summary of findings' tables and grading the confidence in or quality of the evidence. In: Higgins JP, Churchill R, Chandler J, Cumpston MS, editor(s),Cochrane Handbook for Systematic Reviews of Interventions Version 5.2.0 (updated June 2017). Cochrane, 2017. Available from training.cochrane.org/handbook/archive/v5.2.

Siegel 2020

Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA: a Cancer Journal for Clinicians* 2020;**70**(1):7-30. [PMID: 31912902]

Sternberg 2000

Sternberg CN. Gemcitabine in bladder cancer. *Seminars in Oncology* 2000;**27**(1 Suppl 2):31-9. [PMID: 10697034]

Sylvester 2006

Sylvester RJ, van der Meijden AP, Oosterlinck W, Witjes JA, Bouffioux C, Denis L, et al. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. *European Urology* 2006;**49**(3):466-77. [PMID: 16442208]

Tierney 2007

Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials* 2007;**8**:16. [PMID: 17555582]

Ye 2018

Ye Z, Chen J, Hong Y, Xin W, Yang S, Rao Y. The efficacy and safety of intravesical gemcitabine vs Bacille Calmette-Guerin for adjuvant treatment of non-muscle invasive bladder cancer: a meta-analysis. *OncoTargets and Therapy* 2018;**11**:4641-9. [PMID: 30122955]

References to other published versions of this review

Jones 2011

Jones G, Cleves A, Wilt TJ, Mason M, Kynaston HG, Shelley M. Intravesical gemcitabine for non-muscle invasive bladder cancer. *Cochrane Database of Systematic Reviews* 2011, Issue 10. Art. No: CD009294. [DOI: 10.1002/14651858.CD009294]

Jones 2012

Jones G, Cleves A, Wilt TJ, Mason M, Kynaston HG, Shelley M. Intravesical gemcitabine for non-muscle invasive bladder cancer. *Cochrane Database of Systematic Reviews* 2012, Issue 1. Art. No: CD009294. [DOI: 10.1002/14651858.CD009294.pub2]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Addeo 2010

Study characteristics	
Methods	**Study design:** randomized phase III trial (1:1)
	Setting/country: single center in Italy
	Dates when study was conducted: March 2003 to November 2005
Participants	**Ethnicity:** NA
	Inclusion criteria

Addeo 2010 *(Continued)*

- People with superficial bladder cancer (Ta and T1 of any grade) whose disease had progressed or relapsed after BCG intravesical infusion or were ineligible for BCG treatment

Exclusion criteria

- Prior radiation to the pelvis and intractable urinary tract infections

Total number of participants randomly assigned

- Screened: 120
- Eligible: 109

Disease type: recurrent disease

Intervention: gemcitabine

- Number of all participants randomly assigned: 54
- Mean age: 64.9 (SD 10.55) years
- Gender (men/women): 46/8
- Tumor T stage
  - Ta: 37; T1: 17
- Tumor grade (G1/G2/G3)
  - 11/28/15
- Tumor size (< 3 cm/≥ 3 cm)
  - NA but < 2 cm/> 2 cm = 36/18
- Number of tumors (1/> 1): 29/25
- Prior intravesical therapy: 54 (BCG: 46, epirubicin: 8)

Comparator: mitomycin C

- Number of all participants randomly assigned: 55
- Mean age: 67.9 (SD 10.2) years
- Gender (men/women): 47/8
- Tumor T stage
  - Ta: 35; T1: 20
- Tumor grade (G1/G2/G3)
  - 14/27/14
- Tumor size (< 3 cm/≥ 3 cm)
  - NA but < 2 cm/> 2 cm = 33/22
- Number of tumors (1/> 1): 34/21
- Prior intravesical therapy: 55 (BCG: 45, epirubicin: 10)

Interventions	**Intervention:** gemcitabine • Gemcitabine 2000 mg/50 mL saline • 6-week induction course of infusion after TURBT. For the initial responders who remained free of recurrences, maintenance therapy consisted of 10 monthly treatments during first year **Comparator:** mitomycin C • Mitomycin C 40 mg/50 mL saline • Early infusion of the diluted drug within 2 days after TURBT, followed by 4 weekly treatments. For the initial responders who remained free of recurrences, maintenance therapy consisted of 10 monthly treatments during first year **Follow-up:** median 36 months
Outcomes	Study did not separate the outcomes as primary and secondary **Main endpoints**

Addeo 2010 *(Continued)*

- Time of first recurrence (disease-free survival)
- Relative risk of recurrence estimated by the life-table method
- Recurrence rate per 100 patient-months
- Cumulative rates of tumor progression
- How measured: recurrence; cystourethroscopy
- Time point measured: every 6 months
- Time point reported: cumulative

Subgroup analysis

- Recurrence-free survival in high-grade disease (G3)

Funding Sources	Supported by grants from Lega Italiana per la Lotta contro i Tumori (LILT; Italian League for the Fight against Cancer; non-profit organization and has oncologic prevention as its primary institutional task): organization information is available at www.lilt.it
Declarations of interest	None
Notes	**Protocol:** NA **Language of publication:** English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote from publication:** "Random" only. **Comment:** randomization stated, but no information on method used; therefore, unclear risk of selection bias.
Allocation concealment (selection bias)	Unclear risk	**Comment:** no information given.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	**Comment:** no information given.
Blinding of outcome assessment (detection bias) Subjective outcomes	Unclear risk	**Comment:** no information given.
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	**Comment:** objective outcomes not likely affected by lack of blinding.
Incomplete outcome data (attrition bias) Time to recurrence	Low risk	**Comment:** no loss to follow-up; all randomized participants were included in the analysis.
Incomplete outcome data (attrition bias) Time to progression	Low risk	**Comment:** study did not investigate this outcome, but reported several progressions from all randomized participants in each arm. We approximated the effect estimates (HR) using an indirect method (Parmar 1998). Thus, low risk of bias.
Incomplete outcome data (attrition bias)	Low risk	**Comment:** no loss to follow-up; all randomized participants were included in the analysis.

Addeo 2010 *(Continued)*
Grade III–V adverse events

Incomplete outcome data (attrition bias) Grade I or II adverse events	Low risk	**Comment:** no loss to follow-up; all randomized participants were included in the analysis.
Selective reporting (reporting bias)	Unclear risk	**Comment:** no protocol available, but all objectives defined in the method section were reported.
Other bias	High risk	**Comment:** treatment schedule differed between groups; mitomycin C was given within 2 days of TURBT followed by 4 weekly treatment, but gemcitabine was given as a 6-week induction course. If the schedule of mitomycin C was considered as standard treatment at that time, should we rate this domain as high.

Bendary 2011

Study characteristics	
Methods	**Study design:** randomized trial **Setting/country:** single center in Egypt **Dates when study was conducted:** January 2006 to June 2008
Participants	**Ethnicity:** NA **Inclusion criteria** • Primary Ta-T1 TCC of the bladder without CIS **Exclusion criteria** • NA **Total number of participants randomly assigned** • Screened: NA • Eligible: 80 **Disease type:** primary disease **Intervention:** gemcitabine • Number of all participants randomly assigned: 40 • Age: overall mean 56.2 (SD 11.18) years • Gender (men/women): NA • Tumor T stage: NA • Tumor grade (G1/G2/G3) or tumor grade (low/high): NA • Tumor size (< 3 cm/≥ 3 cm): NA • Number of tumors (1/> 1): NA • Prior intravesical therapy: 0 **Comparator:** BCG • Number of all participants randomly assigned: 40 • Age: overall mean 56.2 (SD 11.18) years • Gender (men/women): NA

Bendary 2011 *(Continued)*

- Tumor T stage: NA
- Tumor grade (G1/G2/G3) or tumor grade (low/high): NA
- Tumor size (< 3 cm/≥ 3 cm): NA
- Number of tumors (1/> 1): NA
- Prior intravesical therapy: 0

Interventions	**Intervention:** gemcitabine • Gemcitabine 2000 mg/50 mL saline • 6 weekly intravesical instillation after 2 weeks from TURBT **Comparator:** BCG • BCG 6 × 10^8 CFU (strain: NA)/50 mL saline • 6 weekly intravesical instillation after 2 weeks from TURBT **Follow-up:** 3–18 months (mean 10.8 (SD 27) months)
Outcomes	Study did not separate the outcomes as primary and secondary. **Efficacy** • Recurrence • Progression • How measured: NA • Time point measured: NA • Time point reported: NA **Safety** • How measured: NA • Time point measured: NA • Time point reported: NA **Subgroup analysis:** NA
Funding Sources	None
Declarations of interest	NA
Notes	**Protocol:** NA **Language of publication:** English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote from publication:** "Random" only; abstract only. **Comment:** randomization stated, but no information on method used; therefore, unclear risk of selection bias.
Allocation concealment (selection bias)	Unclear risk	**Comment:** no information given; abstract only.
Blinding of participants and personnel (performance bias)	Unclear risk	**Comment:** no information given; abstract only.

Bendary 2011 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) Subjective outcomes	Unclear risk	**Comment:** no information given; abstract only.
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	**Comment:** no information given; abstract only, but objective outcomes not likely affected by lack of blinding.
Incomplete outcome data (attrition bias) Time to recurrence	Unclear risk	**Comment:** no information given; abstract only.
Incomplete outcome data (attrition bias) Time to progression	Unclear risk	**Comment:** no information given; abstract only.
Incomplete outcome data (attrition bias) Grade III–V adverse events	Unclear risk	**Comment:** no information given; abstract only.
Incomplete outcome data (attrition bias) Time to death from bladder cancer	Unclear risk	**Comment:** no information given; abstract only.
Incomplete outcome data (attrition bias) Time to death from any cause	Unclear risk	**Comment:** no information given; abstract only.
Incomplete outcome data (attrition bias) Grade I or II adverse events	Unclear risk	**Comment:** no information given; abstract only.
Incomplete outcome data (attrition bias) Disease-specific quality of life	Unclear risk	**Comment:** no information given; abstract only.
Selective reporting (reporting bias)	Unclear risk	**Comment:** no information given; abstract only.
Other bias	Unclear risk	**Comment:** no information given; abstract only

Böhle 2009

Study characteristics	
Methods	**Study design:** randomized, double-blind, placebo-controlled multicenter study **Setting/country:** multicenter (24 centers) in Germany and Turkey **Dates when study was conducted:** January 2004 to June 2005
Participants	**Ethnicity:** white

Böhle 2009 *(Continued)*

Inclusion criteria

- Clinical evidence of papillary, non-muscle-invasive TCC of the bladder and indication for TURBT (stage Ta/T1, G1–G3; no concomitant bladder CIS)
- Men or women ages ≥ 18 years
- Karnofsky performance status ≥ 70% with adequate bone marrow reserve (white blood cells: ≥ 4 × 10^9/L; platelets: ≥ 140 × 10^9/L; hemoglobin: 10 g/dL), and adequate renal and hepatic function (serum creatinine: < 2.0 mg/dL; bilirubin: < 2.0 mg/dL; alanine transaminase and aspartate transaminase < 2.5 × upper limit of normal)
- Patient compliance and geographic proximity that allowed adequate follow-up
- Women with reproductive potential must have used a reliable contraceptive method if appropriate (e.g. intrauterine device, birth control pills, or barrier device) during study
- Women with reproductive potential must have had a negative serum pregnancy test within 7 days of study enrollment
- Signed informed consent

Exclusion criteria

- Weight loss > 15% during the last 6 months, prior chemotherapy within the last 6 month, > 3 prior TURBT, history of CIS
- Clinical evidence of muscle-invasive or locally advanced bladder cancer
- Clinical evidence of upper urinary tract tumor
- Distant metastases
- Other malignancies within the last 2 years, except non-melanotic skin tumors, CIS of the cervix or organ-confined prostate cancer after curative therapy
- Severe concomitant psychiatric disease
- Febrile, active infection
- Other serious concomitant disorders that would compromise the safety of the patient or his/her ability to complete the study according to the protocol, at the discretion of the investigator (e.g. unstable angina pectoris, uncontrolled diabetes mellitus)

Total number of participants randomly assigned

- Screened: NA
- Eligible: 355

Disease type: primary and recurrent disease

Intervention: gemcitabine

- Number of all participants randomly assigned: 179
- Age: mean 63.2 (SD 11.9) years
- Gender (men/women): 127/39
- Tumor T stage
  - Tx: 3; T0: 0; Tis: 5; Ta: 93; T1: 31; T2: 12
- Tumor grade (G1/G2/G3)
  - 59/50/25
- Tumor size (< 3 cm/≥ 3 cm): NA
- Number of tumors (1/> 1): 87/75
- Primary disease: 123; recurrent disease: 43
- Prior intravesical therapy: NA

Comparator: saline

- Number of all participants randomly assigned: 176
- Age: mean 66.3 (SD 11) years
- Gender (men/women): 136/26

Böhle 2009 *(Continued)*

- Tumor T stage
  - Tx: 0; T0: 0; Tis: 6; Ta: 88; T1: 36; T2: 10
- Tumor grade (G1/G2/G3)
  - 66/48/24
- Tumor size (< 3 cm/≥ 3 cm): NA
- Number of tumors (1/> 1): 96/61
- Primary disease: 122; recurrent disease: 40
- Prior intravesical therapy: NA

Interventions	**Intervention:** gemcitabine • Gemcitabine 2000 mg/100 mL saline • Instilled over 30–40 minutes immediately after TURBT followed by continuous irrigation with saline for 20 hours **Comparator:** saline • 100 mL saline • Instilled over 30–40 minutes immediately after TURBT followed by continuous irrigation with saline for 20 hours **Follow-up:** median 23.6 months (range 0–46)

Outcomes	**Primary outcomes**
	• Protocol: recurrence-free survival
	• Report: recurrence-free survival in people with histologically confirmed NMIBC (pTa/pT1, G1–G3)
	• How measured: histologically confirmed recurrence (biopsy, TUR)
	• Time point measured: 3 and 6 months after the first TURBT, and every 6 months thereafter, until recurrence/progression of disease, or until the end of study, up to 24 months
	• Time point reported: 24 months
	
	Secondary outcomes
	• Protocol: time to recurrence; recurrence-free survival in subgroups; tumor recurrence type
	• Report: type of recurrence and toxicity (serious and other adverse events)
	• How measured
	  ◦ Recurrence in subgroup: histologically confirmed recurrence (biopsy, TUR)
	  ◦ Toxicity: NA
	• Time point measured
	  ◦ Recurrence in subgroup: 3 and 6 months after the first TURBT, and every 6 months thereafter, until recurrence/progression of disease, or until the end of study, up to 24 months
	  ◦ Toxicity: up to 3 months
	• Time point reported:
	  ◦ Recurrence: 24 months
	  ◦ Toxicity: likely cumulative
	
	Subgroup analysis; recurrence-free survival only
	• Low-grade vs high-grade tumor
	• Primary vs recurrent disease
	• Single vs multiple disease
	• Second TUR vs without second TUR
	• BCG vs without BCG
	• German centers vs Turkish centers

Böhle 2009 *(Continued)*

Funding Sources	The study was funded and sponsored by Eli Lilly and Company, Indianapolis, IN, USA. The sponsor assisted in the design and conduct of the study; contributed to the management, analysis, interpretation, preparation, and review of the data; and approved the manuscript.
Declarations of interest	H Buttner, K Helsberg, B Lubben, V Soldatenkova, and C Stoffregen are employees of Lilly Deutschland GmbH, the German affiliate of Eli Lilly and Company, Indianapolis, IN, USA. H Buttner, K Helsberg, B Lubben, and C Stoffregen also own Eli Lilly stocks or stock options (or both). A Böhle has received honoraria for lectures from Cytochemia, Apogepha, Bard, and Hexal.
Notes	**Protocol:** NCT00191477 **Language of publication:** English Data extraction and risk of bias assessment were performed using the NCT00191477 result section (gemcitabine: n = 166, saline: n = 162 including pT2, CIS, no malignancy, pathologic specimen lost participants included).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote from publication:** "Random" only. **Comment:** randomization stated and we received the author response "computer generate random number"; therefore, low risk of selection bias.
Allocation concealment (selection bias)	Low risk	**Comment:** we received the author response "central randomisation"; therefore, low risk of selection bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Quote from publication:** "Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)." **Comment:** participants and personnel were blinded.
Blinding of outcome assessment (detection bias) Subjective outcomes	Low risk	**Quote from publication:** "Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)" **Comment:** outcome assessor was blinded; therefore, low risk of detection bias.
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	**Comment:** outcome assessor was blinded; therefore, low risk of detection bias.
Incomplete outcome data (attrition bias) Time to recurrence	Low risk	**Comment:** 166/179 (92.7%) in gemcitabine arm and 162/176 (92.1%) in saline arm were included in the analysis. Owing to the small number of participants excluded from the analysis and balanced in both groups, we considered this a low risk of attrition bias.
Incomplete outcome data (attrition bias) Time to progression	Low risk	**Comment:** the study did not investigate this outcome, but reported several progressions from per-protocol participants in each arm (124/179 [69.2%]). Attrition rates were balanced in each arm. We approximated the effect estimates (HR) using an indirect method (Parmar 1998). Thus, low risk of attrition bias.
Incomplete outcome data (attrition bias) Grade III–V adverse events	Low risk	**Comment:** 166/179 (92.7%) in gemcitabine arm and 162/176 (92.1%) in saline arm were included in the analysis. Owing to the small number of participants excluded from the analysis and balanced in both groups, we considered this a low risk of attrition bias.

Böhle 2009 *(Continued)*

Incomplete outcome data (attrition bias) Time to death from bladder cancer	Low risk	**Comment:** the study did not investigate this outcome, but reported several progressions from 166/179 (92.7%) in gemcitabine arm and 162/176 (92.1%) in saline arm. We approximated the effect estimates (HR) using an indirect method (Parmar 1998). Thus, low risk of incomplete outcome bias.
Incomplete outcome data (attrition bias) Time to death from any cause	Low risk	**Comment:** the study did not investigate this outcome, but reported several progressions from 166/179 (92.7%) in gemcitabine arm and 162/176 (92.1%) in saline arm. We approximated the effect estimates (HR) using an indirect method (Parmar 1998). Thus, low risk of incomplete outcome bias.
Incomplete outcome data (attrition bias) Grade I or II adverse events	Low risk	**Comment:** 166/179 (92.7%) in gemcitabine arm and 162/176 (92.1%) in saline arm were included in the analysis. Owing to the small number of participants excluded from the analysis and balanced in both groups, we considered this a low risk of attrition bias.
Selective reporting (reporting bias)	High risk	**Comment:** the protocol (NCT00191477) was provided, but was changed during the study period due to lower events rates. All predefined outcomes were provided, but the results of primary and secondary outcomes were different between protocol and report. Owing to lower events rates (recurrence), recurrence-free survival was calculated in subgroups as a post hoc analysis.
Other bias	High risk	**Quote from publication:** "Concomitant BCG was used in 34 (13.7%) of efficacy eligible patients (GEM [gemcitabine]: 10.5%; PBO [placebo]: 16.9%); 14 patients (5.6%; GEM: n = 5; PBO: n = 9) received more than six BCG." **Comment:** possible differences in concomitant treatment instillations. Baseline imbalance: age (recalculated using MedCalc Statistical Software).

Di Lorenzo 2010

Study characteristics	
Methods	**Study design:** multicenter, prospective, randomized, phase 2 trial **Setting/country:** multicenter in Italy **Dates when study was conducted:** June 2006 to May 2008
Participants	**Ethnicity:** NA **Inclusion criteria** • High-risk NMIBC, based on the European Organization for Research and Treatment of Cancer scoring system, failing BCG therapy, for whom radical cystectomy was indicated, but not conducted because of refusal or ineligibility because of age or comorbidities and high anesthesiologic risk **Exclusion criteria** • Concurrent or previous muscle-invasive disease • Concurrent or previous tumor in the upper urinary tract or prostatic urethra • Chronic urinary tract infection, cured or active tuberculosis • Any other malignancy except basal cell carcinoma of skin • Previous pelvic irradiation • Creatinine, glutamate oxaloacetic transaminase, and glutamate pyruvic transaminase higher than twice the standard • Pregnancy or lactation, and any other disease with immunodeficiency

Di Lorenzo 2010 *(Continued)*

Total number of participants randomly assigned

- Screened: 92
- Eligible: 80

Disease type: recurrent (1-course BCG failure) high-risk disease

Intervention: gemcitabine

- Number of all participants randomly assigned: 40
- Age: mean 69.3 (SD 8.4) years
- Gender (men/women): 27/13
- Tumor T stage
  - Ta: 10; T1: 30
- Tumor grade (low/high)
  - 11/29
- Tumor size (< 3 cm/≥ 3 cm): 15/25
- Number of tumors (1/> 1): 30/10

Comparator: BCG

- Number of all participants randomly assigned: 40
- Age: mean 71.4 (SD 7.9) years
- Gender (men/women): 22/18
- Tumor T stage
  - Ta: 8; T1: 32
- Tumor grade (low/high)
  - 13/27
- Tumor size (< 3 cm/≥ 3 cm): 17/23
- Number of tumors (1/> 1): 8/32

Interventions	**Intervention:** gemcitabine • Gemcitabine 2000 mg/50 mL saline • Treatment after 4–6 weeks from the last TUR, twice weekly (days 1 and 4) for 6 consecutive weeks (induction course), and then weekly for 3 consecutive weeks at 3, 6, and 12 months **Comparator:** BCG • BCG: Connaught strain, 81 mg/50 mL saline • Treatment after 4–6 weeks from the last TUR, 6-week induction course and then each week for 3 weeks, at 3, 6, and 12 months. **Follow-up:** gemcitabine: median 15.2 months (range 6–22); BCG: median 15.8 months (range 7–21)

Outcomes	**Primary outcomes**
	• Recurrence rate (percentage of participants with recurrence) at 1-year follow-up
	• How measured: cystoscopy and pathologically confirmed after TUR
	• Time point measured: cytology and cystoscopy performed at 3-month intervals
	• Time point reported: 1 year
	Secondary outcomes
	• Time to recurrence; progression rate; time to progression; toxicity
	• How measured
	  ◦ Time to recurrence; progression rate; time to progression: cystoscopy and pathologically confirmed after TUR
	  ◦ Toxicity: CTCAE version 3.0

Di Lorenzo 2010 *(Continued)*

- Time point measured: 3-month intervals after initial treatment
- Time point reported: likely cumulative

Subgroup analysis: none

Funding Sources	NA
Declarations of interest	None
Notes	**Protocol:** NA **Language of publication:** English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote from publication:** "By using a central computer-generated randomisation list." **Comment:** we considered this method of random sequence generation to have low risk of bias.
Allocation concealment (selection bias)	Low risk	**Quote from publication:** "By using a central computer-generated randomisation list." **Comment:** central randomization; this method may ensure allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	High risk	**Quote from publication:** "An open label study design was used, that is, patients and investigators were not masked as to the drugs they were assigned."
Blinding of outcome assessment (detection bias) Subjective outcomes	High risk	**Quote from publication:** "An open label study design was used, that is, patients and investigators were not masked as to the drugs they were assigned."
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	**Comment:** objective outcomes not likely affected by lack of blinding.
Incomplete outcome data (attrition bias) Time to recurrence	Low risk	**Comment:** no loss to follow-up; all randomized participants were included in the analysis.
Incomplete outcome data (attrition bias) Time to progression	Low risk	**Comment:** the study did not investigate this outcome, but reported several progressions from all randomized participants. We approximated the effect estimates (HR) using an indirect method (Parmar 1998). Thus, low risk of attrition bias.
Incomplete outcome data (attrition bias) Grade III–V adverse events	Low risk	**Comment:** no loss to follow-up; all randomized participants were included in the analysis.
Incomplete outcome data (attrition bias) Time to death from bladder cancer	Low risk	**Comment:** the study did not investigate this outcome, but reported several bladder cancer death from all randomized participants. We approximated the effect estimates (HR) using an indirect method (Tierney 2007). Thus, low risk of attrition bias.

Di Lorenzo 2010 *(Continued)*

Incomplete outcome data (attrition bias) Grade I or II adverse events	Low risk	**Comment:** no loss to follow-up; all randomized participants were included in the analysis.
Selective reporting (reporting bias)	Unclear risk	**Comment:** the protocol was not published (author response); time to first recurrence was not defined in the method section.
Other bias	High risk	**Comment:** treatment schedule differed between groups; gemcitabine was given twice weekly for 6 weeks, then weekly for 3 consecutive weeks at 3, 6, and 12 months; BCG was given weekly for 6 weeks, then 3 weekly instillations at 3, 6, 9, and 12 months.

Gontero 2013

Study characteristics	
Methods	**Study design:** multicenter, prospective, randomized, phase II study **Setting/country:** multicenter (3 centers) in Italy, Germany, and the US **Dates when study was conducted:** 2006–2010

Participants	**Ethnicity:** NA
	
	Inclusion criteria
	
	• People with clinical evidence of intermediate-risk NMIBC (namely Ta-1, G1–G2, multifocal or unique and recurrent, > 3 cm in diameter)
	• WHO performance status ≤ 2
	• Age ≤ 85 years
	• BCG naive, people not treated with intravesical chemotherapy in the last 3 months
	
	Exclusion criteria
	
	• Presence of T1G3 or CIS
	• Preoperative urinary cytology positive for high-grade atypia
	• Inadequate bone marrow reserve (white blood cells < 3×10^9/L, platelets < 100×10^9/L)
	• History of genitourinary tuberculosis
	• Presence of uncontrolled urinary infections
	
	Total number of participants randomly assigned
	
	• Screened: 120
	• Eligible: 118
	
	Disease type: primary and recurrent intermediate-risk disease
	
	Intervention: gemcitabine
	
	• Number of all participants randomly assigned: 59
	• Age: mean 67.4 (SD 9.4) years
	• Gender (men/women): 53/8
	• Tumor T stage
	  ○ Ta: 42; T1: 19
	• Tumor grade (G1/G2)
	  ○ 17/44
	• Tumor size (< 3 cm/≥ 3 cm): NA

Gontero 2013 *(Continued)*

- Number of tumors (1/> 1): 25/36
- Primary disease: 38; recurrent disease: 23
- Prior intravesical therapy: 8 (mitomycin: 4; epirubicin: 4)

Comparator: 1/3 dose BCG

- Number of all participants randomly assigned: 59
- Age: mean 67.5 (SD 9.8) years
- Gender (men/women): 50/9
- Tumor T stage
  - Ta: 42; T1: 17
- Tumor grade (G1/G2)
  - 20/39
- Tumor size (< 3 cm/≥ 3 cm): NA
- Number of tumors (1/> 1): 29/30
- Primary disease: 31; recurrent disease: 28
- Prior intravesical therapy: 14 (mitomycin: 6; epirubicin: 8)

Interventions	**Intervention:** gemcitabine • Gemcitabine 2000 mg/50 mL saline • 7 to 15 days after TUR, participants received 6 weekly instillations and maintenance consisted of monthly instillations up to 1 year **Comparator:** 1/3 dose BCG • 1/3 dose BCG (Connaught strain (ImmuCyst), 27 mg/50 mL saline) • 7–15 days after TUR, participants received an induction cycle of 6 weekly instillations, and maintenance consisted of 3 weekly instillations at 3, 6, and 12 months **Follow-up:** 1 year

Outcomes	**Primary outcomes**
	• Quality of life
	• How measured: EORTC QLQ-C30 and EORTC QLQ-BLS 24 questionnaires
	• Time point measured: baseline, after induction (after 6 weeks), at 1 year
	• Time point reported: baseline, after induction (after 6 weeks), at 1 year
	Secondary outcomes
	• Recurrence and progression at 1 year; toxicity
	• How measured
	  ◦ Recurrence: urinary cytology and cystoscopy performed every 3 months
	  ◦ Progression: biopsy or TUR
	  ◦ Toxicity: CTCAE version 3.0
	• Time point measured and time point reported
	  ◦ Recurrence, progression: at each event
	  ◦ Toxicity: baseline, after induction (after 6 weeks), at 1 year
	Subgroup analysis: none

Funding Sources	NA
Declarations of interest	NA
Notes	**Protocol:** NCT01697306 **Language of publication:** English

Gontero 2013 *(Continued)*

Baseline characteristics were based on eligible participants.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote from publication:** "Simple 1:1 randomisation was used." **Comment:** randomization stated and we received the author response "computer generate random number;" therefore, low risk of selection bias.
Allocation concealment (selection bias)	Low risk	**Comment:** we received the author response "central randomisation"; therefore, low risk of selection bias.
Blinding of participants and personnel (performance bias) All outcomes	High risk	**Quote from publication:** in the protocol "None (open lable)" [sic: open label].
Blinding of outcome assessment (detection bias) Subjective outcomes	High risk	**Quote from publication:** in the protocol "None (open lable)" [sic: open label].
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	**Comment:** objective outcomes not likely affected by lack of blinding.
Incomplete outcome data (attrition bias) Time to recurrence	Low risk	**Comment:** no loss to follow-up; all randomized participants were included in the analysis.
Incomplete outcome data (attrition bias) Time to progression	Low risk	**Comment:** no loss to follow-up; all randomized participants were included in the analysis.
Incomplete outcome data (attrition bias) Grade III–V adverse events	High risk	**Comment:** 41/59 (69.4%) participants in gemcitabine arm and 47/59 (79.6%) participants in 1/3 dose BCG arm were included in the analysis. The reasons for attrition were reported, but attrition rates were not balanced.
Incomplete outcome data (attrition bias) Time to death from any cause	Unclear risk	**Quote from publication:** "At 1-year follow up only 1 patient died of a non-cancer specific cause." **Comment:** author reported 1 participant died due to non-cancer cause, but they did not report the denominator.
Incomplete outcome data (attrition bias) Grade I or II adverse events	High risk	**Comment:** 41/59 (69.4%) participants in gemcitabine arm and 47/59 (79.6%) participants in 1/3 dose BCG arm were included in the analysis. The reasons for attrition were reported, but attrition rates were not balanced.
Incomplete outcome data (attrition bias) Disease-specific quality of life	High risk	**Comment:** 41/59 (69.4%) participants in gemcitabine arm and 47/59 (79.6%) participants in 1/3 dose BCG arm were included in the analysis. The reasons for attrition were reported, but attrition rates were not balanced.
Selective reporting (reporting bias)	Low risk	**Comment:** the protocol was provided (NCT01697306), but toxicity was not predefined. However, this is unlikely to introduce a bias.
Other bias	Low risk	**Comment:** treatment schedule differed between groups, but it was the same as protocol.

Messing 2018

Study characteristics	
Methods	**Study design:** randomized double-blind clinical trial **Setting/country:** multicenter (23 centers) in the US **Dates when study was conducted:** January 2008 to August 2012

Participants	**Ethnicity:** white: 371; black: 15; Asian: 9; American Indian: 2; unknown: 9
	
	Inclusion criteria
	
	• Clinically appeared to have newly diagnosed or recurrent G1 or G2, Ta or T1 urothelial (transitional cell) cancer of the bladder
	• Participants had had no more than 2 recurrences (other than the index tumor) in the 18 months preceding the index tumor's TURBT which are also G1 or G 2, stage Ta or T1 without any previous Tis or G3 cancers within 2 years preceding the index tumor TURBT or any history of muscularis propria invading (Stage ≥ T2), in their urologist's opinion not currently be a candidate for treatment other than a TURBT (e.g. a series of BCG instillations)
	• Serum creatinine < 2.2 mg/dL (194 mmol/L) and serum bilirubin, alkaline phosphatase, aspartate aminotransferase, and alanine aminotransferase levels below 2 times the institution's upper limits of normal
	• Adequate hematologic function (hematocrit > 35% and < 52%; white blood cell count ≥ 3000/µL; platelet count > 75 000/µL and < 500 000/µL)
	• Eastern Cooperative Oncology Group performance status score ≤ 1
	• No urine infection
	• Normal upper urinary tract imaging findings (for malignancy) within 1 year before the index TURBT
	
	Exclusion criteria
	
	• If within 18 months before the index TURBT, participants had any high-grade or > 2 low-grade non-muscle-invasive urothelial cancer episodes or had received intravesical therapy within 6 months
	• Previous or concurrent upper urinary tract or prostatic urethral urothelial cancer
	• Previous pelvic radiotherapy for any malignancy
	• Prior treatment for any malignancy within 5 years other than non-melanoma skin cancer or non-muscle-invasive bladder urothelial cancer
	
	Total number of participants randomly assigned
	
	• Screened: NA
	• Eligible: 416
	
	Disease type: primary and recurrent disease
	
	Intervention: gemcitabine
	
	• Number of all participants randomly assigned: 207
	• Age: median 66 (IQR 59–74) years
	• Gender (men/women): 163/38
	• Tumor T stage
	  ◦ Tx, T0: 17; Tis, Ta, T1: 146; T2: 5
	• Tumor grade (low/high)
	  ◦ 102/44
	• Tumor size (< 3 cm/≥ 3 cm): NA
	• Number of tumors (1/> 1): 135/66
	• Primary disease: 128; recurrent disease: 73
	• Prior intravesical therapy: 39 (BCG: 18; doxorubicin: 1; mitomycin C: 1; not specified: 19)

Messing 2018 *(Continued)*

Comparator: saline

- Number of all participants randomly assigned: 209
- Age: median 66 (IQR 59–75) years
- Gender (men/women): 181/24
- Tumor T stage
  - Tx, T0: 14; Tis, Ta, T1: 155; T2: 8
- Tumor grade (low/high)
  - 113/42
- Tumor size (< 3 cm/≥ 3 cm): NA
- Number of tumors (1/> 1): 140/65
- Primary disease: 128; recurrent disease: 77
- Prior intravesical therapy: 39 (BCG: 25; doxorubicin: 0; mitomycin C: 2; not specified: 12)

Interventions	**Intervention:** gemcitabine • Gemcitabine 2000 mg/100 mL saline • Single instillation within 3 hours after OP (1 hour retained) **Comparator:** saline • 100 mL saline • Single instillation within 3 hours after OP (1 hour retained) **Follow-up:** median 4 years

Outcomes	**Primary outcomes**
	• Time to recurrence
	• How measured: confirmed by histology
	• Time point measured: cystoscopies every 3 months for 2 years and then every 6 months for an additional 2 years
	• Time point reported: 4 years
	Secondary outcomes
	• Time to progression; toxicity; time to death due to any cause
	• How measured
	  ◦ Progression: confirmed by histology
	  ◦ Toxicity: CTCAE version 3.0 and version 4.0
	• Time point measured
	  ◦ at scheduled times during a trial
	• Time point reported:
	  ◦ Time to progression; time to death due to any cause: 4 years
	  ◦ Toxicity: within 28 days
	Subgroup analysis: time to recurrence only
	• Low-grade vs high-grade tumor
	• Primary vs recurrent disease
	• Single vs multiple

Funding Sources	National Cancer Institute of the National Institutes of Health under award numbers CA180888, CA180819, CA180846, CA180834, CA180858, CA128567, CA180801, CA189953, CA189854, CA180830, CA180818, CA22433, CA35995, CA12644, CA68183, CA11083, CA46282, CA58416, CA46113, CA37981, and CA04919 and in part by Eli Lilly (which provided gemcitabine for the study). Role of the funders/sponsors: the National Cancer Institute approved the study design and through its grants to Southwest Oncology Group, supported the conduct of the study and collection, management, analysis, and interpretation of the data, and, through the genitourinary committee of Southwest Oncology Group, supported

Messing 2018 *(Continued)*

	the preparation, review, and approval of the manuscript and the decision to submit the manuscript for publication. Eli Lilly had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, and approval of the manuscript; or decision to submit the manuscript for publication.
Declarations of interest	Dr Lerner reported receipt of personal fees for advisory board membership from BioCancell, Incyte, Nucleix, and UroGen and for consultancy from Vaxiion and clinical trial grants from UroGen, Endo, FKD, Viventia, JBL, and Roche/Genentech. Dr Koppie reported receipt of personal fees from Convergent Genomics. Dr Karsh reported receipt of personal fees for consulting or speaking or research funding to his institution (or a combination) from Astellas, Bayer, Janssen, Sanofi, Spectrum, Precision Biopsy, 3D Biopsy, Augmenix, Dendreon, Pfizer, Abbvie, Myriad Genetics, AstraZeneca, Vaxiion, and Arivan Research. No other disclosures were reported.
Notes	**Protocol:** NCT00445601; supplement in the original report **Language of publication:** English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote from publication:** in the protocol, "Patients will be centrally randomized at the Southwest Oncology Group Statistical Center. At the time of registration, patients will be randomly assigned to either Arm 1 or Arm 2 in a blinded fashion according to a dynamic allocation scheme." **Comment:** we considered this method of random sequence generation to have low risk of bias.
Allocation concealment (selection bias)	Low risk	**Quote from publication:** in the protocol, "Phone or Web registration." **Comment:** this method may ensure allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Quote from publication:** in the protocol, "The investigator, treating urologist and patient will be blinded to treatment, but the local institutional pharmacist will not." **Comment:** lack of blinding of the pharmacist may not introduce a bias; therefore, low risk of performance bias.
Blinding of outcome assessment (detection bias) Subjective outcomes	Low risk	**Quote from publication:** in the protocol, "The investigator, treating urologist and patient will be blinded to treatment, but the local institutional pharmacist will not." **Comment:** lack of blinding of the pharmacist is unlikely to introduce a bias; therefore, low risk of performance bias.
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	**Comment:** outcome assessor was blinded; therefore, low risk of detection bias.
Incomplete outcome data (attrition bias) Time to recurrence	Low risk	**Comment:** 201/207 (97.1%) participants in gemcitabine arm and 205/209 (98%) participants in saline arm were included in the analysis. Owing to the small number of participants excluded from the analysis and balanced in both groups, we considered risk of attrition bias to be low.
Incomplete outcome data (attrition bias) Time to progression	Low risk	**Comment:** 201/207 (97.1%) participants in gemcitabine arm and 205/209 (98%) participants in saline arm were included in the analysis. Owing to the small number of participants excluded from the analysis and balanced in both groups, we considered risk of attrition bias to be low.

Messing 2018 *(Continued)*

Incomplete outcome data (attrition bias) Grade III–V adverse events	Low risk	**Comment:** 165/207 (79.7%) participants in gemcitabine arm and 175/209 (83.7%) participants in saline arm were included in the analysis, but attrition rates were balanced and the reasons for attrition were reported. We considered risk of attrition bias to be low.
Incomplete outcome data (attrition bias) Time to death from any cause	Low risk	**Comment:** 201/207 (97.1%) participants in gemcitabine arm and 205/209 (98%) participants in saline arm were included in the analysis. Owing to the small number of participants excluded from the analysis and balanced in both groups, we considered risk of attrition bias to be low.
Incomplete outcome data (attrition bias) Grade I or II adverse events	Low risk	**Comment:** 165/207 (79.7%) participants in gemcitabine arm and 175/209 (83.7%) participants in saline arm were included in the analysis, but attrition rates were balanced and the reasons for attrition were reported. We considered risk of attrition bias to be low.
Selective reporting (reporting bias)	Low risk	**Comment:** the protocol (NCT00445601 and supplement in the original report) was provided and all predefined analyses were reported. Post hoc analysis for 1 subgroup outcome (time to recurrence in participants with high-grade disease) was provided, but this was unlikely to introduce bias.
Other bias	Low risk	**Quote from publication:** "Although subsequent treatment was evenly distributed between groups but not reliably collected which might affect the tumor progression. No central pathology review." **Comment:** this may affect the effect estimates of progression. However, given time to progression is a secondary outcome, this is unlikely to affect the whole study results.

Porena 2010

Study characteristics	
Methods	**Study design:** randomized controlled trial **Setting/country:** single center in Italy **Dates when study was conducted:** January 2004 to December 2006
Participants	**Ethnicity:** NA **Inclusion criteria** • Ages 18–75 years • Primary diagnosis of high-risk superficial bladder cancer according to EAU guidelines • Participants having never been treated with other intravesical chemotherapeutic agents, and consenting to participate in the study **Exclusion criteria** • Concomitant tumors • Urinary tract infections • Altered function of the liver, kidneys, bone marrow, or a combination of these; major cardiovascular diseases • Life expectancy < 1 year • Intravesical chemotherapy in the previous 3 months or immunotherapy in the previous 6 months • Systemic chemotherapy and pelvic radiation therapy prior to TURBT, and any condition that, in the judgment of the investigators, would interfere with the person's ability to provide informed consent,

Porena 2010 *(Continued)*

comply with study instructions, place the person at increased risk, or which might confound interpretation of study results

Total number of participants randomly assigned

- Screened: 74
- Eligible: 64

Disease type: primary high-risk disease

Intervention: gemcitabine

- Number of all participants randomly assigned: 32
- Age: mean 70.2 (SD 5.5) years
- Gender (men/women): 26/6
- Tumor T stage and grade
  - Ta-T1 G3: 26; T1 G3 or CIS or G3 + CIS: 6
- Tumor size (< 3 cm/≥ 3 cm): NA
- Number of tumors (1/> 1): NA

Comparator: BCG

- Number of all participants randomly assigned: 32
- Age: mean 68.7 (SD 10.2) years
- Gender (men/women): 28/4
- Tumor T stage and grade
  - Ta-T1 G3: 28; T1 G3 or CIS or G3 + CIS: 4
- Tumor size (< 3 cm/≥ 3 cm): NA
- Number of tumors (1/> 1): NA

Interventions	**Intervention:** gemcitabine • Gemcitabine 2000 mg/50 mL saline • 14 days after the second-look TUR, 6 weekly instillations of gemcitabine held in bladder for 2 hours as induction therapy. If there was no recurrence, participants received maintenance therapy 3, 6, 12, 18, 24, 30, and 36 months **Comparator:** BCG • BCG (Tice strain) 5×10^8 CFU/50 mL saline • 14 days after the second-look TUR, 6 weekly instillations of BCG held in bladder for 2 hours as induction therapy. If there was no recurrence, participants received maintenance therapy 3, 6, 12, 18, 24, 30, and 36 months **Follow-up:** mean 44 months
Outcomes	**Primary outcomes** • Recurrence and progression rates; intervals before recurrence and progression • How measured: cytology, cystoscopy, and cold-cup biopsy of any suspicious lesions • Time point measured: every 3 months for the first 2 years, every 6 months for the following 3 years, and then annually • Time point reported: NA **Secondary outcomes** • Tolerability (dropped out of the study, and safety) • How measured: recording of adverse events • Time point measured: NA • Time point reported: likely cumulative

Porena 2010 *(Continued)*

	Subgroup analysis: none
Funding Sources	NA
Declarations of interest	NA
Notes	**Protocol:** NCT00696579 **Language of publication:** English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote from publication:** "the randomisation code was developed using a computer random number generator to select random permuted blocks." **Comment:** we considered this method of random sequence generation to have low risk of bias.
Allocation concealment (selection bias)	Unclear risk	**Comment:** no information given.
Blinding of participants and personnel (performance bias) All outcomes	High risk	**Quote from publication:** "All study personnel and participants were not blinded to treatment assignment."
Blinding of outcome assessment (detection bias) Subjective outcomes	High risk	**Quote from publication:** "All study personnel and participants were not blinded to treatment assignment."
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	**Comment:** objective outcomes not likely affected by lack of blinding.
Incomplete outcome data (attrition bias) Time to recurrence	Low risk	**Comment:** no loss to follow-up; all randomized participants were included in the analysis.
Incomplete outcome data (attrition bias) Time to progression	Low risk	**Comment:** no loss to follow-up; all randomized participants were included in the analysis (no progression in both arms).
Incomplete outcome data (attrition bias) Grade III–V adverse events	Low risk	**Comment:** all randomized participants were included in the analysis, but no explicit description of grade III–V complications.
Incomplete outcome data (attrition bias) Grade I or II adverse events	Low risk	**Comment:** all randomized participants were included in the analysis, but no explicit description of grade I or II complications.
Selective reporting (reporting bias)	Low risk	**Comment:** the protocol (NCT00696579) and all predefined outcomes were provided.
Other bias	Low risk	**Comment:** not detected.

BCG: Bacillus Calmette-Guérin; CFU: colony-forming units; CIS: carcinoma in situ; EAU: European Association of Urology; EORTC QLQ-C30: European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EORTC QLQ-BLS 24: European Organization for the Research and Treatment of Cancer Quality of Life Superficial Bladder Cancer-Specific 24; G: tumor grade; HR: hazard ratio; IQR: interquartile range; NMIBC: non-muscle invasive bladder cancer; NA: not available; SD: standard deviation; TCC: transitional cell carcinoma; TUR: transurethral resection; TURBT: transurethral resection of the bladder tumor; WHO: World Health Organization.

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

Study	Reason for exclusion
Böhle 2010	Commentary.
Brausi 2011	Ineligible study design; no comparator.
Cao 2011	Ineligible comparator; different drugs were combined as a comparator.
Dalbagni 2006	Ineligible study design; no comparator.
Dong 2017	Ineligible study design; not an RCT (quasi-randomization).
Gantz 2018	Ineligible study design; not an RCT.
Gardmark 2005	Ineligible comparator; different dose and schedule of gemcitabine used as a comparator.
Lin 2016	Ineligible study design; not an RCT.
Sun 2016	Ineligible study design; not an RCT.
Xia 2019	Ineligible study design; not an RCT (quasi-randomization).

RCT: randomized controlled trial·

Characteristics of studies awaiting classification *[ordered by study ID]*

Xiaohong 2015

Methods	No information
Participants	56 participants (men: 45; women: 11)
Interventions	**Intervention** • Gemcitabine: 1000 mg weekly for 8 weeks followed by 10 monthly instillations (total 1 year) **Comparator** • Mitomycin C: 40 mg weekly for 8 weeks followed by 10 monthly instillations (total 1 year)
Outcomes	No information
Notes	We could not obtain the full text of this study. Information about participants and interventions came from Li 2020a.

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

ChiCTR1900026643

Study name	The randomized controlled study for intravesical instillation of *Pseudomonas aeruginosa* and gemcitabine in the prevention of postoperative recurrence of non-muscle invasive bladder cancer
Methods	Open-label parallel randomized study

Participants	**Estimated enrollment:** 80 participants
	Eligible ages: ages > 18 and < 75 years
	Eligible sexes: both
	Eligibility criteria
	• Inclusion criteria
	  ◦ Person informed and has given written informed consent
	  ◦ Ages 18 years to < 75 years, both men and women
	  ◦ People undergoing TURBT
	  ◦ Preoperative diagnosis is NMIBC (Ta-T1N0M0), pathologic diagnosis of urothelial carcinoma
	  ◦ No previous history of other malignant tumors
	• Exclusion criteria
	  • Tumor invading the ureter, prostate, and urethra
	  • Incapable or behavioral capacity limited
	  • Preoperative routine chest X-ray and pelvic enhancement CT examination revealed that distant metastasis or intraoperative findings of tumor invasive muscle layer
	  • Have other serious diseases, including cardiovascular, respiratory, kidney, or liver diseases, and uncontrolled hypertension and diabetes
	  • Pregnant and lactating women
	  • History of pelvic surgery or lower urinary tract surgery
	  • Preoperative history of chemotherapy
	  • Severe coagulation function, abnormal electrolyte balance disorder, hypoproteinemia corrected without obvious improvement
	  • Narcotic contraindications for the anaphylaxis of narcotic drugs
	  • Researcher considers that there are any other circumstances that are not suitable for participating in the study

Interventions	**Intervention** • Gemcitabine: dose and schedule not specified **Comparator** • *Pseudomonas aeruginosa*: dose and schedule not specified
Outcomes	Postoperative recurrence rate
Starting date	20 November 2019 **Expected date of completion:** 20 November 2021
Contact information	Applicant: Li Jiashuo; tel: +8615779750929; email: 505684933@qq.com Study leader: Shang Panfeng; tel: +8613919785295; email: shangpf@lzu.edu.cn
Notes	**Funding source:** subproject of the key research and development project in Gansu Province. Quote: "Regularization and diagnosis of cystatin cancer and promotion and application of different urinary diversion procedures." **Sponsors and collaborators:** Lanzhou University Second Hospital

NCT00192049

Study name	A randomized study comparing single agent gemcitabine intravesical therapy versus mitomycin C in patients with intermediate risk superficial bladder cancer
Methods	Open-label, parallel, randomized study

Participants	**Estimated enrollment:** 90 participants
	Eligible ages: > 18
	Eligible sexes: both
	Eligibility criteria
	• Inclusion criteria
	  ○ Histologically verified superficial transitional cell carcinoma of the bladder
	  ○ People with primary or recurrent intermediate-risk superficial bladder cancer after TUR. People with primary tumor with stage TaG1 with multiple lesions (> 3) or lesions > 3 cm or with TaG2-3 or T1G1-2
	  ○ Participants must not be pretreated with any intravesical immunotherapy (BCG) or chemotherapy
	• Exclusion criteria
	  ○ Time between TUR and start of intravesical chemotherapy will be longer than 4 weeks
	  ○ People who have received previous (BCG) or chemotherapy
	  ○ People with evidence of invasive, locally advanced, or metastatic bladder cancer or with upper urinary tract disease

Interventions	**Intervention** • Gemcitabine: dose and schedule not specified **Comparator** • Mitomycin C: dose and schedule not specified
Outcomes	**Primary outcomes** • Tumor recurrence rate at 12 months **Secondary outcomes** • Tumor recurrence rate in 6 months • Disease-free interval • Toxicity profile (local and systemic)
Starting date	December 2003 **Expected date of completion:** no date given
Contact information	Tel: +1-877-285-4559 or +1-317-615-4559
Notes	**Funding source:** not reported but probably Eli Lilly and Company **Sponsors and Collaborators:** Eli Lilly and Company

NCT02695771

Study name	The bladder instillation comparison study (BIC)
Methods	Open-label, parallel, randomized study

Participants	**Estimated enrollment:** 300 participants
	Eligible ages: > 18 years
	Eligible sexes: both
	Eligibility criteria
	• Inclusion criteria
	  ○ Sign an informed consent for the study
	  ○ Be scheduled for a TURBT for suspected non-muscle invasive bladder tumor
	• Exclusion criteria
	  ○ Unable to consent for themselves
	  ○ Age < 18 years
	  ○ Pregnant women
	  ○ Prisoners
	  ○ Known allergy or intolerance to the mitomycin C or gemcitabine
	  ○ Any other sound medical, psychiatric, or social reason as determined by the investigator

Interventions	**Intervention**
	• Mitomycin C: 40 mg/40 mL saline intravesicularly immediately following TURBT once
	Comparator
	• Active comparator
	  ○ Gemcitabine: 2000 mg/100 mL saline intravesicularly immediately following TURBT once
	• No intervention
	  ○ No intervention intravesicularly immediately following TURBT once

Outcomes	**Primary outcomes** • Tumor recurrence at 2 years • Grade III–V adverse events graded according to NCI CTCAE version 4.03 **Secondary outcomes** • Incidence of dystrophic calcification or bladder calculi at 2 years graded according to NCI CTCAE version 4.03
Starting date	April 2016 **Expected date of completion:** April 2019
Contact information	Contact: Susan M Engerman, BSN; tel: +1 616-267-8406; email: susan.engerman@spectrumhealth.org Contact: Pamela Carlon, RN; tel: +1 616-267-8406; email: pamela.carlon@spectrumhealth.org
Notes	**Funding source:** not reported **Sponsors and Collaborators:** Spectrum Health Hospitals

NCT04172675

Study name	A study of erdafitinib versus investigator choice of intravesical chemotherapy in participants who received Bacillus Calmette-Guérin (BCG) and recurred with high risk non-muscle-invasive bladder cancer (NMIBC)
Methods	Open-label, parallel, randomized study

Participants	**Estimated enrollment:** 280 participants
	
	Eligible ages: > 18 years
	
	Eligible sexes: both
	
	Eligibility criteria
	
	• Inclusion criteria
	  ○ Histologically confirmed, recurrent, non-muscle-invasive urothelial carcinoma of the bladder. Variant pathologies are allowed
	  ○ Tumor with specified fibroblast growth factor receptor mutations or fusions
	  ○ BCG-unresponsive after adequate BCG therapy or BCG experienced participants
	  ○ Refuses or is not eligible for cystectomy (Cohort 1 and Cohort 2 only)
	  ○ ECOG performance status Grade 0–1
	  ○ Must sign an informed consent form (or their legally acceptable representative must sign) indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study
	  ○ A woman of childbearing potential must have a negative pregnancy test (beta-human chorionic gonadotropin) (urine or serum) within 7 days before randomization (Cohort 1) or the first dose of study drug (Cohort 2 and Cohort 3)
	  ○ Adequate bone marrow, liver, and renal function as specified in the protocol
	• Exclusion criteria
	  ○ Histologically confirmed, muscle-invasive (≥ T2 stage) urothelial carcinoma of the bladder
	  ○ Histopathology demonstrating any small cell component, pure adenocarcinoma, pure squamous cell carcinoma, or pure squamous CIS of the bladder
	  ○ Prior treatment with a fibroblast growth factor receptor inhibitor
	  ○ Active malignancies other than the disease being treated under study. The only allowed exceptions are: skin cancer treated within the last 24 months that is considered completely cured; adequately treated lobular CIS and ductal CIS; history of localized breast cancer and receiving antihormonal agents; or history of localized prostate cancer (N0M0) and receiving androgen deprivation therapy
	  ○ Current central serous retinopathy or retinal pigment epithelial detachment of any grade

Interventions	**Intervention:** cohort 1, 2, and 3 will receive erdafitinib; orally beginning on cycle 1 day 1 until 2 years of treatment have been completed, disease recurrence, intolerable toxicity, withdrawal of consent, a decision by the investigator to discontinue treatment, or study termination, whichever occurs first. Each cycle is 28 days. • Cohort 1: participants with high-risk NMIBC presenting as papillary tumor only (CIS, absent), with disease recurrence after BCG therapy • Cohort 2: participants with high-risk, BCG-unresponsive NMIBC presenting as CIS with or without concurrent papillary tumor • Cohort 3: marker lesion study in intermediate-risk NMIBC presenting as papillary disease only. **Comparator:** cohort 1 will receive investigators choice of intravesical chemotherapy; gemcitabine or mitomycin C • Cohort 1: participants with high-risk NMIBC presenting as papillary tumor only (CIS, absent), with disease recurrence after BCG therapy will receive the investigator's choice of either intravesical gemcitabine or intravesical mitomycin C/hyperthermic mitomycin C. Participants who are randomized to gemcitabine or mitomycin C/hyperthermic mitomycin C in cohort 1 and demonstrate

NCT04172675 *(Continued)*

	a recurrence via investigator disease assessment will have the opportunity to cross over to treatment with erdafitinib.
Outcomes	**Primary outcomes** • Recurrence-free survival up to 4 years **Secondary outcomes** • Time to progression up to 4 years • Time to disease worsening up to 4 years • Disease-specific survival up to 4 years • Overall survival up to 4 years • Recurrence-free survival at month 6, month 12, and month 24 • Recurrence-free survival 2 up to 4 years • Recurrence-free survival by central histopathologic review up to 4 years • Plasma concentration of erdafitinib cycle 1 day 14, cycle 2 day 1 (each cycle is 28 days) • Number of participants with adverse events up to 4 years • Change from baseline in Patient's Global Impression of Severity (of cancer) (PGIS) to 4 years • Change from baseline in Patient's Global Impression of Change (of cancer) (PGIC) to cycle 2 Day 1 and end of treatment (up to 2 years) (each cycle is 28 days) • Change from baseline in European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire (EORTC QLQ) – C30 to 4 years • Change from baseline in EORTC QLQ – NMIBC24 to 4 years • Change from baseline in EuroQol European Quality of Life – 5 Dimensions-5 Levels (EQ-5D-5L) to 4 years • Maximum observed analyte concentration (Cmax) of midazolam and its metabolite (1-OH-midazolam) at predose and cycle 1 day 13 (each cycle is 28 days) • Time to reach maximum observed analyte concentration (Tmax) midazolam and its metabolite (1-OH-midazolam) at predose and cycle 1 day 13 (each cycle is 28 days) • Area under the analyte concentration vs time curve (AUC) from time zero to the time of last measurable analyte concentration of midazolam and its metabolite (1-OH-midazolam) at predose and cycle 1 day 13 (each cycle is 28 days) • Area under the analyte concentration vs time curve (AUC) from time zero to infinite time of midazolam and its metabolite (1-OH-midazolam) at predose and cycle 1 day 13 (each cycle is 28 days) • Maximum observed plasma concentration (Cmax) of metformin at predose and cycle 1 day 14 (each cycle is 28 days) • Time to reach maximum observed plasma concentration (Tmax) of metformin at predose and cycle 1 day 14 (each cycle is 28 days) • Area under the analyte concentration vs time curve (AUC) from time zero to the time of last measurable of metformin at predose and cycle 1 day 14 (each cycle is 28 days) • Area under the analyte concentration vs time curve (AUC) from time zero to infinite time of metformin at predose and cycle 1 day 14 (each cycle is 28 days)
Starting date	February 28, 2020 **Expected date of completion:** 10 June 2026
Contact information	Tel: +1 844-434-4210; email: JNJ.CT@sylogent.com
Notes	**Funding source:** Janssen Research & Development, LLC **Sponsors and Collaborators:** Janssen Research & Development, LLC

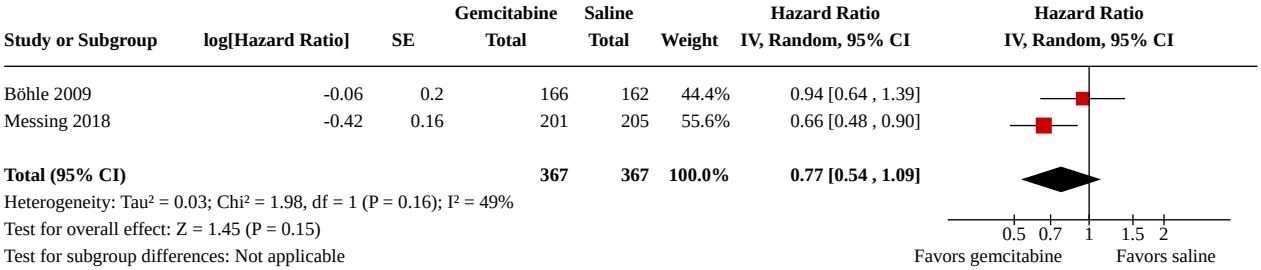
BCG: Bacillus Calmette-Guérin; CIS: carcinoma in situ; CT: computer tomography; CTCAE: Common Terminology Criteria for Adverse Events; ECOG: Eastern Cooperative Oncology Group; G: tumor grade; NCI: National Cancer Institute; NMIBC: non-muscle invasive bladder cancer; TUR: transurethral resection; TURBT: transurethral resection of the bladder tumor.

DATA AND ANALYSES

Comparison 1. Gemcitabine versus saline

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Time to recurrence	2	734	Hazard Ratio (IV, Random, 95% CI)	0.77 [0.54, 1.09]
1.2 Time to progression	2	654	Hazard Ratio (IV, Random, 95% CI)	0.96 [0.19, 4.71]
1.3 Grade III–V adverse events	2	668	Risk Ratio (M-H, Random, 95% CI)	1.26 [0.58, 2.75]
1.4 Time to death from bladder cancer	1		Hazard Ratio (IV, Random, 95% CI)	Totals not selected
1.5 Time to death from any cause	2	734	Hazard Ratio (IV, Random, 95% CI)	0.62 [0.39, 1.00]
1.6 Grade I or II adverse events	2	668	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.87, 1.45]
1.7 Time to recurrence (subgroup analysis)	2	543	Hazard Ratio (IV, Random, 95% CI)	0.74 [0.49, 1.09]
1.7.1 Low-grade tumor	2	430	Hazard Ratio (IV, Random, 95% CI)	0.75 [0.38, 1.46]
1.7.2 High-grade tumor	2	113	Hazard Ratio (IV, Random, 95% CI)	0.74 [0.43, 1.28]

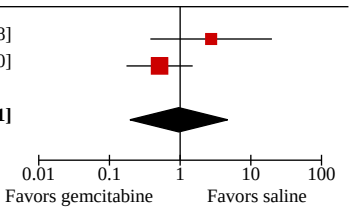
Analysis 1.1. Comparison 1: Gemcitabine versus saline, Outcome 1: Time to recurrence



Analysis 1.2. Comparison 1: Gemcitabine versus saline, Outcome 2: Time to progression

Study or Subgroup	log[Hazard Ratio]	SE	Gemcitabine Total	Saline Total	Weight	Hazard Ratio IV, Random, 95% CI
Böhle 2009	1.01	1.01	124	124	37.3%	2.75 [0.38 , 19.88]
Messing 2018	-0.67	0.55	201	205	62.7%	0.51 [0.17 , 1.50]
Total (95% CI)			**325**	**329**	**100.0%**	**0.96 [0.19 , 4.71]**

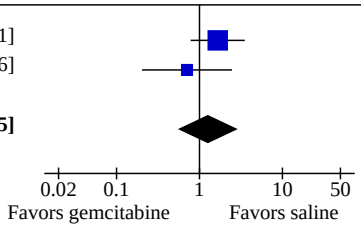
Heterogeneity: Tau² = 0.75; Chi² = 2.13, df = 1 (P = 0.14); I² = 53%
Test for overall effect: Z = 0.05 (P = 0.96)
Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1: Gemcitabine versus saline, Outcome 3: Grade III–V adverse events

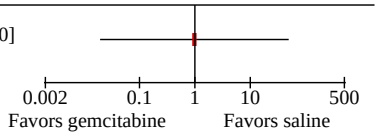
Study or Subgroup	Gemcitabine Events	Gemcitabine Total	Saline Events	Saline Total	Weight	Risk Ratio M-H, Random, 95% CI
Böhle 2009	17	166	10	162	67.7%	1.66 [0.78 , 3.51]
Messing 2018	4	165	6	175	32.3%	0.71 [0.20 , 2.46]
Total (95% CI)		**331**		**337**	**100.0%**	**1.26 [0.58 , 2.75]**
Total events:	21		16			

Heterogeneity: Tau² = 0.09; Chi² = 1.32, df = 1 (P = 0.25); I² = 24%
Test for overall effect: Z = 0.58 (P = 0.56)
Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1: Gemcitabine versus saline, Outcome 4: Time to death from bladder cancer

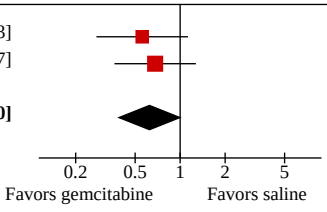
Study or Subgroup	log[Hazard Ratio]	SE	Gemcitabine Total	Saline Total	Hazard Ratio IV, Random, 95% CI
Böhle 2009	-0.02	2	166	162	0.98 [0.02 , 49.40]



Analysis 1.5. Comparison 1: Gemcitabine versus saline, Outcome 5: Time to death from any cause

Study or Subgroup	log[Hazard Ratio]	SE	Gemcitabine Total	Saline Total	Weight	Hazard Ratio IV, Random, 95% CI
Böhle 2009	-0.584	0.36	166	162	44.1%	0.56 [0.28 , 1.13]
Messing 2018	-0.385	0.32	201	205	55.9%	0.68 [0.36 , 1.27]
Total (95% CI)			**367**	**367**	**100.0%**	**0.62 [0.39 , 1.00]**

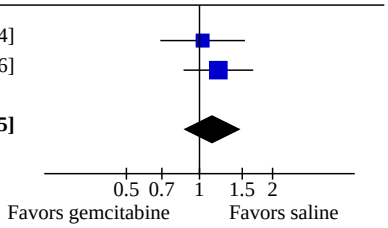
Heterogeneity: Tau² = 0.00; Chi² = 0.17, df = 1 (P = 0.68); I² = 0%
Test for overall effect: Z = 1.98 (P = 0.05)
Test for subgroup differences: Not applicable



Analysis 1.6. Comparison 1: Gemcitabine versus saline, Outcome 6: Grade I or II adverse events

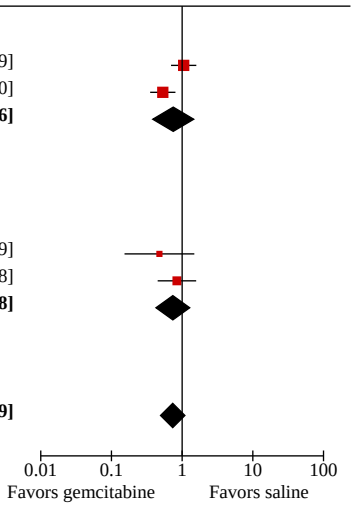
Study or Subgroup	Gemcitabine Events	Gemcitabine Total	Saline Events	Saline Total	Weight	Risk Ratio M-H, Random, 95% CI
Böhle 2009	38	166	36	162	40.4%	1.03 [0.69 , 1.54]
Messing 2018	53	165	47	175	59.6%	1.20 [0.86 , 1.66]
Total (95% CI)		**331**		**337**	**100.0%**	**1.13 [0.87 , 1.45]**
Total events:	91		83			

Heterogeneity: Tau² = 0.00; Chi² = 0.32, df = 1 (P = 0.57); I² = 0%
Test for overall effect: Z = 0.91 (P = 0.36)
Test for subgroup differences: Not applicable



Analysis 1.7. Comparison 1: Gemcitabine versus saline, Outcome 7: Time to recurrence (subgroup analysis)

Study or Subgroup	log[Hazard Ratio]	SE	Gemcitabine Total	Saline Total	Weight	Hazard Ratio IV, Random, 95% CI
1.7.1 Low-grade tumor						
Böhle 2009	0.05	0.21	106	109	33.7%	1.05 [0.70 , 1.59]
Messing 2018	-0.63	0.21	102	113	33.7%	0.53 [0.35 , 0.80]
Subtotal (95% CI)			**208**	**222**	**67.4%**	**0.75 [0.38 , 1.46]**
Heterogeneity: Tau² = 0.19; Chi² = 5.24, df = 1 (P = 0.02); I² = 81%						
Test for overall effect: Z = 0.85 (P = 0.39)						
1.7.2 High-grade tumor						
Böhle 2009	-0.74	0.58	13	14	9.9%	0.48 [0.15 , 1.49]
Messing 2018	-0.17	0.32	44	42	22.8%	0.84 [0.45 , 1.58]
Subtotal (95% CI)			**57**	**56**	**32.6%**	**0.74 [0.43 , 1.28]**
Heterogeneity: Tau² = 0.00; Chi² = 0.74, df = 1 (P = 0.39); I² = 0%						
Test for overall effect: Z = 1.08 (P = 0.28)						
Total (95% CI)			**265**	**278**	**100.0%**	**0.74 [0.49 , 1.09]**
Heterogeneity: Tau² = 0.08; Chi² = 5.98, df = 3 (P = 0.11); I² = 50%						
Test for overall effect: Z = 1.52 (P = 0.13)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.98), I² = 0%						



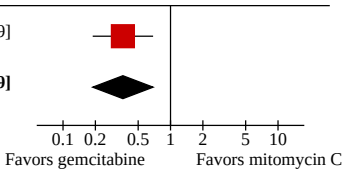
Comparison 2. Gemcitabine versus mitomycin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Time to recurrence	1	109	Hazard Ratio (IV, Random, 95% CI)	0.36 [0.19, 0.69]
2.2 Time to progression	1	109	Hazard Ratio (IV, Random, 95% CI)	0.57 [0.32, 1.01]
2.3 Grade III–V adverse events	1	109	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.13, 1.93]
2.4 Grade I or II adverse events	1	109	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.37, 0.78]

Analysis 2.1. Comparison 2: Gemcitabine versus mitomycin, Outcome 1: Time to recurrence

Study or Subgroup	log[Hazard Ratio]	SE	Gemcitabine Total	Mitomycin C Total	Weight	Hazard Ratio IV, Random, 95% CI
Addeo 2010	-1.02	0.33	54	55	100.0%	0.36 [0.19 , 0.69]
Total (95% CI)			**54**	**55**	**100.0%**	**0.36 [0.19 , 0.69]**

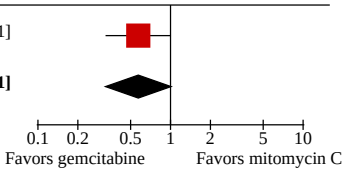
Heterogeneity: Not applicable
Test for overall effect: Z = 3.09 (P = 0.002)
Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2: Gemcitabine versus mitomycin, Outcome 2: Time to progression

Study or Subgroup	log[Hazard Ratio]	SE	Gemcitabine Total	Mitomycin C Total	Weight	Hazard Ratio IV, Random, 95% CI
Addeo 2010	-0.56	0.29	54	55	100.0%	0.57 [0.32 , 1.01]
Total (95% CI)			**54**	**55**	**100.0%**	**0.57 [0.32 , 1.01]**

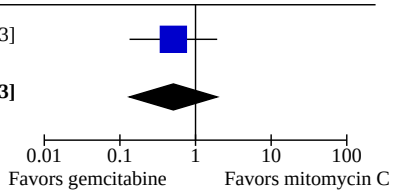
Heterogeneity: Not applicable
Test for overall effect: Z = 1.93 (P = 0.05)
Test for subgroup differences: Not applicable



Analysis 2.3. Comparison 2: Gemcitabine versus mitomycin, Outcome 3: Grade III–V adverse events

Study or Subgroup	Gemcitabine Events	Gemcitabine Total	Mitomycin C Events	Mitomycin C Total	Weight	Risk Ratio M-H, Random, 95% CI
Addeo 2010	3	54	6	55	100.0%	0.51 [0.13 , 1.93]
Total (95% CI)		**54**		**55**	**100.0%**	**0.51 [0.13 , 1.93]**
Total events:	3		6			

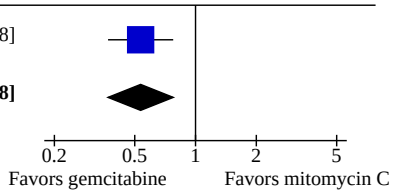
Heterogeneity: Not applicable
Test for overall effect: Z = 0.99 (P = 0.32)
Test for subgroup differences: Not applicable



Analysis 2.4. Comparison 2: Gemcitabine versus mitomycin, Outcome 4: Grade I or II adverse events

Study or Subgroup	Gemcitabine Events	Gemcitabine Total	Mitomycin C Events	Mitomycin C Total	Weight	Risk Ratio M-H, Random, 95% CI
Addeo 2010	21	54	40	55	100.0%	0.53 [0.37 , 0.78]
Total (95% CI)		**54**		**55**	**100.0%**	**0.53 [0.37 , 0.78]**
Total events:	21		40			

Heterogeneity: Not applicable
Test for overall effect: Z = 3.30 (P = 0.0010)
Test for subgroup differences: Not applicable



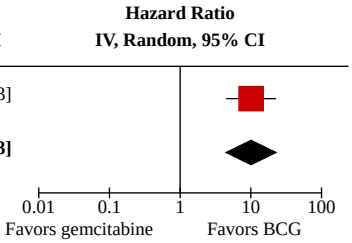
Comparison 3. Gemcitabine versus Bacillus Calmette-Guérin (BCG)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Time to recurrence	1	64	Hazard Ratio (IV, Random, 95% CI)	10.07 [4.48, 22.63]
3.2 Time to progression	1	64	Hazard Ratio (IV, Random, 95% CI)	Not estimable

Analysis 3.1. Comparison 3: Gemcitabine versus Bacillus Calmette-Guérin (BCG), Outcome 1: Time to recurrence

Study or Subgroup	log[Hazard Ratio]	SE	Gemcitabine Total	BCG Total	Weight	Hazard Ratio IV, Random, 95% CI
Porena 2010	2.31	0.413	32	32	100.0%	10.07 [4.48 , 22.63]
Total (95% CI)			**32**	**32**	**100.0%**	**10.07 [4.48 , 22.63]**

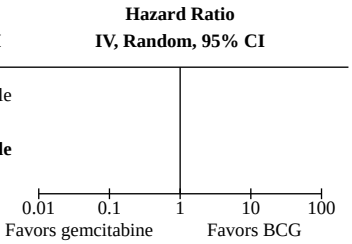
Heterogeneity: Not applicable
Test for overall effect: Z = 5.59 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 3.2. Comparison 3: Gemcitabine versus Bacillus Calmette-Guérin (BCG), Outcome 2: Time to progression

Study or Subgroup	log[Hazard Ratio]	SE	Gemcitabine Total	BCG Total	Weight	Hazard Ratio IV, Random, 95% CI
Porena 2010	0	0	32	32		Not estimable
Total (95% CI)			**32**	**32**		**Not estimable**

Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



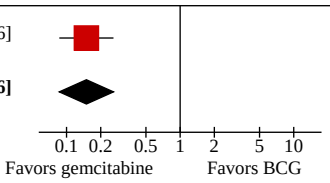
Comparison 4. Gemcitabine versus Bacillus Calmette-Guérin [BCG] for recurrent (one-course BCG failure) high-risk non-muscle invasive bladder cancer

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Time to recurrence	1	80	Hazard Ratio (IV, Random, 95% CI)	0.15 [0.09, 0.26]
4.2 Time to progression	1	80	Hazard Ratio (IV, Random, 95% CI)	0.45 [0.27, 0.76]
4.3 Grade III–V adverse events	1	80	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.21, 4.66]
4.4 Time to death from bladder cancer	1	80	Hazard Ratio (IV, Random, 95% CI)	0.04 [0.00, 2.25]
4.5 Grade I or II adverse events	1	80	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.48, 1.77]

Analysis 4.1. Comparison 4: Gemcitabine versus Bacillus Calmette-Guérin [BCG] for recurrent (one-course BCG failure) high-risk non-muscle invasive bladder cancer, Outcome 1: Time to recurrence

Study or Subgroup	log[Hazard Ratio]	SE	Gemcitabine Total	BCG Total	Weight	Hazard Ratio IV, Random, 95% CI
Di Lorenzo 2010	-1.9	0.28	40	40	100.0%	0.15 [0.09 , 0.26]
Total (95% CI)			**40**	**40**	**100.0%**	**0.15 [0.09 , 0.26]**

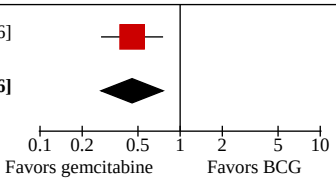
Heterogeneity: Not applicable
Test for overall effect: Z = 6.79 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 4.2. Comparison 4: Gemcitabine versus Bacillus Calmette-Guérin [BCG] for recurrent (one-course BCG failure) high-risk non-muscle invasive bladder cancer, Outcome 2: Time to progression

Study or Subgroup	log[Hazard Ratio]	SE	Gemcitabine Total	BCG Total	Weight	Hazard Ratio IV, Random, 95% CI
Di Lorenzo 2010	-0.79	0.26	40	40	100.0%	0.45 [0.27 , 0.76]
Total (95% CI)			**40**	**40**	**100.0%**	**0.45 [0.27 , 0.76]**

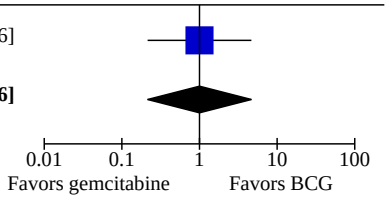
Heterogeneity: Not applicable
Test for overall effect: Z = 3.04 (P = 0.002)
Test for subgroup differences: Not applicable



Analysis 4.3. Comparison 4: Gemcitabine versus Bacillus Calmette-Guérin [BCG] for recurrent (one-course BCG failure) high-risk non-muscle invasive bladder cancer, Outcome 3: Grade III–V adverse events

Study or Subgroup	Gemcitabine Events	Gemcitabine Total	BCG Events	BCG Total	Weight	Risk Ratio M-H, Random, 95% CI
Di Lorenzo 2010	3	40	3	40	100.0%	1.00 [0.21 , 4.66]
Total (95% CI)		**40**		**40**	**100.0%**	**1.00 [0.21 , 4.66]**
Total events:	3		3			

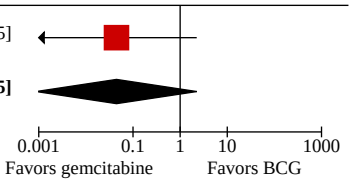
Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)
Test for subgroup differences: Not applicable



Analysis 4.4. Comparison 4: Gemcitabine versus Bacillus Calmette-Guérin [BCG] for recurrent (one-course BCG failure) high-risk non-muscle invasive bladder cancer, Outcome 4: Time to death from bladder cancer

Study or Subgroup	log[Hazard Ratio]	SE	Gemcitabine Total	BCG Total	Weight	Hazard Ratio IV, Random, 95% CI
Di Lorenzo 2010	-3.11	2	40	40	100.0%	0.04 [0.00 , 2.25]
Total (95% CI)			**40**	**40**	**100.0%**	**0.04 [0.00 , 2.25]**

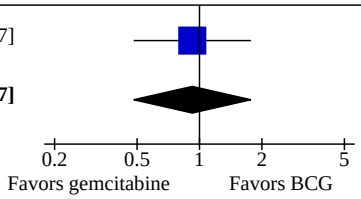
Heterogeneity: Not applicable
Test for overall effect: Z = 1.55 (P = 0.12)
Test for subgroup differences: Not applicable



Analysis 4.5. Comparison 4: Gemcitabine versus Bacillus Calmette-Guérin [BCG] for recurrent (one-course BCG failure) high-risk non-muscle invasive bladder cancer, Outcome 5: Grade I or II adverse events

Study or Subgroup	Gemcitabine Events	Gemcitabine Total	BCG Events	BCG Total	Weight	Risk Ratio M-H, Random, 95% CI
Di Lorenzo 2010	12	40	13	40	100.0%	0.92 [0.48 , 1.77]
Total (95% CI)		**40**		**40**	**100.0%**	**0.92 [0.48 , 1.77]**
Total events:	12		13			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.24 (P = 0.81)
Test for subgroup differences: Not applicable



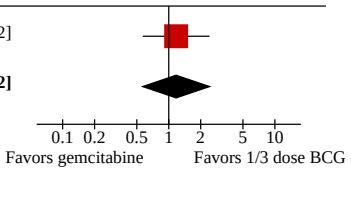
Comparison 5. Gemcitabine versus one-third dose Bacillus Calmette-Guérin (BCG)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Time to recurrence	1	118	Hazard Ratio (IV, Random, 95% CI)	1.17 [0.57, 2.42]
5.2 Time to progression	1	118	Hazard Ratio (IV, Random, 95% CI)	1.63 [0.39, 6.83]
5.3 Grade III–V adverse events	1	88	Risk Ratio (M-H, Random, 95% CI)	Not estimable
5.4 Grade I or II adverse events	1	88	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.49, 1.46]
5.5 Disease-specific quality of life	1	88	Mean Difference (IV, Random, 95% CI)	4.50 [-1.60, 10.60]

Analysis 5.1. Comparison 5: Gemcitabine versus one-third dose Bacillus Calmette-Guérin (BCG), Outcome 1: Time to recurrence

Study or Subgroup	log[Hazard Ratio]	SE	Gemcitabine Total	1/3 dose BCG Total	Weight	Hazard Ratio IV, Random, 95% CI
Gontero 2013	0.16	0.37	59	59	100.0%	1.17 [0.57 , 2.42]
Total (95% CI)			**59**	**59**	**100.0%**	**1.17 [0.57 , 2.42]**

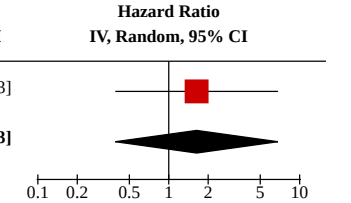
Heterogeneity: Not applicable
Test for overall effect: Z = 0.43 (P = 0.67)
Test for subgroup differences: Not applicable



Analysis 5.2. Comparison 5: Gemcitabine versus one-third dose Bacillus Calmette-Guérin (BCG), Outcome 2: Time to progression

Study or Subgroup	log[Hazard Ratio]	SE	Gemcitabine Total	1/3 dose BCG Total	Weight	Hazard Ratio IV, Random, 95% CI
Gontero 2013	0.49	0.73	59	59	100.0%	1.63 [0.39 , 6.83]
Total (95% CI)			**59**	**59**	**100.0%**	**1.63 [0.39 , 6.83]**

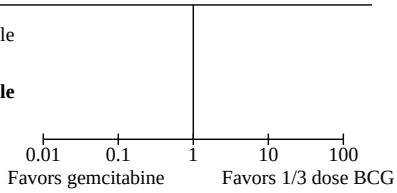
Heterogeneity: Not applicable
Test for overall effect: Z = 0.67 (P = 0.50)
Test for subgroup differences: Not applicable



Analysis 5.3. Comparison 5: Gemcitabine versus one-third dose Bacillus Calmette-Guérin (BCG), Outcome 3: Grade III–V adverse events

Study or Subgroup	Gemcitabine Events	Gemcitabine Total	1/3 dose BCG Events	1/3 dose BCG Total	Weight	Risk Ratio M-H, Random, 95% CI
Gontero 2013	0	41	0	47		Not estimable
Total (95% CI)		**41**		**47**		**Not estimable**
Total events:	0		0			

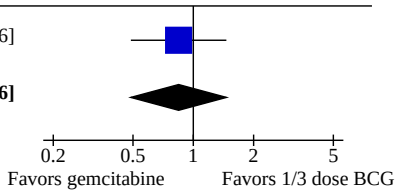
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 5.4. Comparison 5: Gemcitabine versus one-third dose Bacillus Calmette-Guérin (BCG), Outcome 4: Grade I or II adverse events

Study or Subgroup	Gemcitabine Events	Gemcitabine Total	1/3 dose BCG Events	1/3 dose BCG Total	Weight	Risk Ratio M-H, Random, 95% CI
Gontero 2013	14	41	19	47	100.0%	0.84 [0.49 , 1.46]
Total (95% CI)		**41**		**47**	**100.0%**	**0.84 [0.49 , 1.46]**
Total events:	14		19			

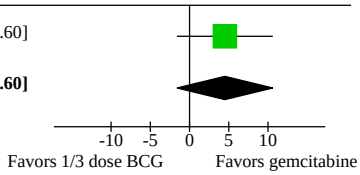
Heterogeneity: Not applicable
Test for overall effect: Z = 0.60 (P = 0.55)
Test for subgroup differences: Not applicable



Analysis 5.5. Comparison 5: Gemcitabine versus one-third dose Bacillus Calmette-Guérin (BCG), Outcome 5: Disease-specific quality of life

Study or Subgroup	Gemcitabine Mean	Gemcitabine SD	Gemcitabine Total	1/3 dose BCG Mean	1/3 dose BCG SD	1/3 dose BCG Total	Weight	Mean Difference IV, Random, 95% CI
Gontero 2013	80.9	14.1	41	76.4	15.1	47	100.0%	4.50 [-1.60 , 10.60]
Total (95% CI)			**41**			**47**	**100.0%**	**4.50 [-1.60 , 10.60]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.44 (P = 0.15)
Test for subgroup differences: Not applicable



ADDITIONAL TABLES

Table 1. Baseline characteristics of the included study

Study name	Trial period	Setting/country	Description of participants	Intervention(s) and comparator(s)	Treatment schedule	Duration of follow-up	Age (mean ± SD) (years)	Gender (men/women, %)	Disease type
Addeo 2010	2003–2005	Single center/Italy	Participants with NMIBC who underwent TURBT	Intervention: gemcitabine 2000 mg/50 mL saline	6-week induction course + maintenance 10 monthly treatments during first year	Median 36 months	64.9 ± 10.55	46 (85.2)/8 (14.8)	Recurrent disease
				Comparator: mitomycin 40 mg/50 mL saline	4-week induction course + maintenance 10 monthly treatments during first year		67.9 ± 10.2	47 (85.5)/8 (14.5)	
Bendary 2011	2006–2008	Single center/Egypt	Participants with NMIBC who underwent TURBT	Intervention: gemcitabine 2000 mg/50 mL saline	6-week induction course	Range 3–18 months (mean 10.8 ± 27 months)	Overall 56.2 ± 11.18	NA	Primary without CIS disease
				Comparator: BCG 6×10^8 CFU/50 mL saline				NA	
Böhle 2009	2004–2005	Multicenter (24 centers)/Germany and Turkey	Participants with NMIBC who underwent TURBT	Intervention: gemcitabine 2000 mg/100 mL saline	Single instillation	median 23.6 months (range 0–46 months)	63.2 ± 11.9	127 (76.5)/39 (23.5)	Primary and recurrent disease, both
				Comparator: 100 mL saline			66.3 ± 11	136 (84)/26 (16)	
Di Lorenzo 2010	2006–2008	Multicenter/Italy	Participants with NMIBC who underwent TURBT	Intervention: gemcitabine 2000 mg/50 mL saline	Twice weekly (days 1 and 4) for 6-week induction course + maintenance 3 weekly instillations at 3, 6, and 12 months.	Median 15.2 months (range 6–22 months)	69.3 ± 8.4	27 (67.5)/13 (32.5)	Recurrent disease (BCG failure; high-risk disease only)
				Comparator: BCG (Connaught strain, 81 mg/50 mL saline)	6-week induction course + maintenance 3 weekly instillations at 3, 6, and 12 months	median 15.8 months (range 7–21 months)	71.4 ± 7.9	22 (55)/18 (45)	

Table 1. Baseline characteristics of the included study *(Continued)*

Gontero 2013	2006–2010	Multicenter (3 centers)/multicountry (Italy, Germany, and the US)	Participants with NMIBC who underwent TURBT	Intervention: gemcitabine 2000 mg/50 mL saline	6-week induction course + maintenance monthly treatments up to 1 year	1 year	67.4 ± 9.4	53 (86.9)/8 (13.1)	Primary and recurrent disease, both (intermediate-risk disease only)
				Comparator: 1/3 dose BCG (Connaught strain, 27 mg/50 mL saline)	6-week induction course + maintenance 3 weekly instillations at 3, 6, and 12 months		67.5 ± 9.8	50 (84.7)/9(15.3)	
Messing 2018	2008–2012	Multicenter (23 centers)/the US	Participants with NMIBC who underwent TURBT	Intervention: gemcitabine 2000 mg/100 mL saline	Single instillation	4 years	Median: 66 (IQR 59–74)	163 (81)/38 (19)	Primary and recurrent disease, both
				Comparator: 100 mL saline			Median: 66 (IQR 59–75)	181 (88)/24 (12)	
Porena 2010	2004–2006	Single center/Italy	Participants with NMIBC who underwent TURBT	Intervention: gemcitabine 2000 mg/50 mL saline	6-week induction course + maintenance therapy 3, 6, 12, 18, 24, 30, and 36 months	Mean 44 months	70.2 ± 5.5	26 (81.3)/6 (18.7)	Primary disease (high-risk disease only)
				Comparator: BCG (Tice strain) 5×10^8 CFU/50 mL saline			68.7 ± 10.2	28 (87.5)/4 (12.5)	

BCG: Bacillus Calmette-Guérin; CFU: colony-forming units; CIS: carcinoma in situ; IQR: interquartile range; NA: not available; NMIBC: non-muscle invasive bladder cancer; SD: standard deviation; TURBT: transurethral resection of the bladder tumor.

Table 2. Participants in the included study

Study name	Interventions and comparators	Screened/ eligible (n)	Randomized (n)	Analyzed (n): efficacy	Analyzed (n): safety	Finishing trial (n (%))
Addeo 2010	Intervention: gemcitabine 2000 mg/50 mL saline	120/109	54	54	54	54 (100)
	Comparator: mitomycin 40 mg/50 mL saline		55	55	55	55 (100)
Bendary 2011	Intervention: gemcitabine 2000 mg/50 mL saline	NA/80	40	NA	NA	NA
	Comparator: BCG 6×10^8 CFU/50 mL saline		40	NA	NA	NA
Böhle 2009	Intervention: gemcitabine 2000 mg/100 mL saline	NA/355	179	Primary outcome; 166/secondary outcome; 124	166	41 (22.9)
	Comparator: 100 mL saline		176	Primary outcome; 162/secondary outcome; 124	162	47 (26.7)
Di Lorenzo 2010	Intervention: gemcitabine 2000 mg/50 mL saline	92/80	40	40	40	40 (100)
	Comparator: BCG (Connaught strain, 81 mg/50 mL saline)		40	40	40	40 (100)
Gontero 2013	Intervention: gemcitabine 2000 mg/50 mL saline	120/118	59	41	41	41 (100)
	Comparator: 1/3 dose BCG (Connaught strain, 27 mg/50 mL saline)		59	47	47	47 (100)
Messing 2018	Intervention: gemcitabine 2000 mg/100 mL saline	NA/416	207	201	165	102 (49.3)
	Comparator: 100 mL saline		209	205	175	113 (54.1)
Porena 2010	Intervention: gemcitabine 2000 mg/50 mL saline	74/64	32	32	32	32 (100)
	Comparator: BCG (Tice strain) 5×10^8 CFU/50 mL saline		32	32	32	32 (100)
Intervention: gemcitabine			611	—	—	310[a]
Comparator: mitomycin			55	—	—	55 (100)
Comparator: BCG			171	—	—	119[a]

Table 2. Participants in the included study *(Continued)*

Comparator: saline	385	—	—	160 (62.3)
Grand total	1222	—	—	644 (52.7)[b]

BCG: Bacillus Calmette-Guérin; CFU: colony-forming units; n: number of participants; NA: not available.
[a] Bendary 2011 did not report the number of participants who finished trial.
[b]Calculated without Bendary 2011.

Table 3. Gemcitabine compared to saline (sensitivity analysis based on risk of bias)

Patient or population: participants with non-muscle invasive bladder cancer (344 men, 62 women)
Country: US
Setting: multicenter (23 centers), likely inpatients
Intervention: gemcitabine
Comparison: saline

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with saline[a]	Risk difference with gemcitabine
Time to recurrence Follow-up: 4 years MCID: 5% absolute difference	406 (1 RCT)	⊕⊕⊕⊖ **Moderate** [b]	**HR 0.66** (0.48 to 0.90)	**Study population**	
				470 per 1000	128 fewer per 1000 (207 fewer to 35 fewer)
Time to progression Follow-up: 4 years MCID: 5% absolute difference	406 (1 RCT)	⊕⊕⊕⊕ **High**	**HR 0.51** (0.17 to 1.50)	**Study population**	
				48 per 1000	23 fewer per 1000 (40 fewer to 23 more)
Grade III–V adverse events assessed with: CTCAE version 3.0 and version 4.0 Follow-up: 1 month MCID: 5% absolute difference	340 (1 RCT)	⊕⊕⊕⊖ **Moderate** [b]	**RR 0.71** (0.20 to 2.46)	**Study population**	
				34 per 1000	10 fewer per 1000 (27 fewer to 50 more)
Time to death from bladder cancer	Not reported	—	—	—	
Time to death from any cause Follow-up: 4 years MCID: 3% absolute difference	406 (1 RCT)	⊕⊕⊖⊖ **Low** [c]	**HR 0.68** (0.36 to 1.27)	**Study population**	
				121 per 1000	37 fewer per 1000 (76 fewer to 30 more)
Grade I or II adverse events assessed with: CTCAE version 3.0 and version 4.0 Follow-up: 1 month MCID: 5% absolute difference	340 (1 RCT)	⊕⊕⊕⊖ **Moderate** [b]	**RR 1.20** (0.86 to 1.66)	**Study population**	
				269 per 1000	54 more per 1000 (38 fewer to 177 more)

Table 3. Gemcitabine compared to saline (sensitivity analysis based on risk of bias) *(Continued)*

Disease-specific quality of life	Not reported	—	—	—	—

*__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).

CI: confidence interval; **CTCAE:** Common Terminology Criteria for Adverse Events; **HR:** hazard ratio; **MCID:** minimal clinically important difference; **n:** number of participants; **RCT:** randomized controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: 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 certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Baseline risk came from Messing 2018.
[b]Downgraded one level for imprecision: confidence intervals crossed the assumed threshold of a clinically important difference.
[c]Downgraded two levels for imprecision: confidence intervals crossed the line of no difference and the assumed threshold of a clinically important difference: wide confidence intervals.

Table 4. Gemcitabine compared to BCG

Patient or population: participants with non-muscle invasive bladder cancer[1] (54 men, 10 women)
Country: Italy
Setting: single center, likely inpatients
Intervention: gemcitabine
Comparison: BCG

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with BCG	Risk difference with Gemcitabine
Time to recurrence Follow-up: mean 44 months MCID: 5% absolute difference	64 (1 RCT)	⊕⊕⊖⊖ **Low** [a,b]	**HR 10.07** (4.48 to 22.63)	**Study population**	
				478 per 1000	521 more per 1000 (468 more to 522 more)
Time to progression Follow-up: mean 44 months MCID: 5% absolute difference	64 (1 RCT)	⊕⊖⊖⊖ **Very low** [a,c]	Not estimable	No events	No events
Grade III–V adverse events	Not reported	—	—	—	—
Time to death from bladder cancer	Not reported	—	—	—	—
Time to death from any cause	Not reported	—	—	—	—
Grade I or II adverse events	Not reported	—	—	—	—

Table 4. Gemcitabine compared to BCG *(Continued)*

Disease-specific quality of life	Not reported	—	—	—	—

*__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; **MCID:** minimal clinically important difference; **HR: h**azard ratio; **RCT:** randomized controlled trial.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: 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 certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1]The analysis was only based on participants with primary high-risk non-muscle invasive bladder cancer; the only included study did not include participants with recurrent disease.
[a]Downgraded one level for study limitations: unclear or high risk of bias on one or more domains.
[b]Downgraded one level for imprecision: outcome based on only a single study of a small number of participants.
[c]Downgraded two levels for imprecision: no events in either arm.

Table 5. Gemcitabine compared to one-third dose BCG

Patient or population: participants with non-muscle invasive bladder cancer (103 men, 17 women)
Country: Italy, Germany, and the US
Setting: multicenter (3 centers), likely inpatients
Intervention: gemcitabine
Comparison: 1/3 dose BCG

Outcomes	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Relative effect (95% CI)**	**Anticipated absolute effects* (95% CI)**	
				Risk with 1/3 dose BCG	**Risk difference with gemcitabine**
Time to recurrence Follow-up: 1 year MCID: 5% absolute difference	118 (1 RCT)	⊕⊖⊖⊖ **Very low** [a,b]	**HR 1.17** (0.57 to 2.42)	**Study population**	
				237 per 1000	34 more per 1000 (94 fewer to 243 more)
Time to progression Follow-up: 1 year MCID: 5% absolute difference	118 (1 RCT)	⊕⊕⊖⊖ **Low** [a,c]	**HR 1.63** (0.39 to 6.83)	**Study population**	
				51 per 1000	31 more per 1000 (31 fewer to 250 more)
Grade III–V adverse events assessed with: CTCAE version 3.0 Follow-up: 1 year MCID: 5% absolute difference	88 (1 RCT)	⊕⊖⊖⊖ **Very low** [a,d]	Not estimable	No events	No events
Time to death from bladder cancer	Not reported	—	—	—	—

Table 5. Gemcitabine compared to one-third dose BCG *(Continued)*

Time to death from any cause	Not reported	—	—	—	—
Grade I or II adverse events assessed with: CTCAE version 3.0 Follow-up: 1 year MCID: 5% absolute difference	88 (1 RCT)	⊕⊖⊖⊖ **Very low** [a,b]	**RR 0.84** (0.49 to 1.46)	**Study population** 404 per 1000	65 fewer per 1000 (206 fewer to 186 more)
Disease-specific quality of life assessed with: EORTC QLQ-C30 (Global health status scale: higher score represents better functioning) Scale: 0–100 Follow-up: 1 year MCID: 10[e]	88 (1 RCT)	⊕⊕⊖⊖ **Low** [a,c]	—	The mean disease-specific quality of life was 80.9	**MD 4.5 higher** (1.6 lower to 10.6 higher)

*__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; **CTCAE:** Common Terminology Criteria for Adverse Events; **EORTC QLQ-C30:** European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30; **MD:** mean difference; **RCT:** randomized controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: 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 certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded one level for study limitations: high risk of bias on one or more domains.
[b]Downgraded two levels for imprecision: confidence intervals crossed a clinically important threshold and no effect; wide confidence intervals.
[c]Downgraded one level for imprecision: confidence intervals crossed a clinically important threshold and no effect.
[d]Downgraded two levels for imprecision: no events in either arm.
[e]MCID: came from Osoba 1998.

APPENDICES

Appendix 1. Search strategies

MEDLINE all segments (OvidSP)	
1	exp urinary bladder neoplasms/
2	((bladder* or urethra* or ureter* or urin* or urotheli*) adj3 (cancer* or carcinoma* or neoplas* or tumo?r* or superficial or adenoma* or adenocarcinoma* or squamous* or malignan*)).tw.

(Continued)

3	exp carcinoma, transitional cell/
4	(tcc or transitional cell).tw.
5	exp ureteral neoplasms/
6	bladder neoplasms/
7	urethral neoplasms/
8	or/1-7
9	exp deoxycytidine/
10	antimetabolites, antineoplastic/
11	(gemc?tabin* or Gemzar*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
12	(gem?cis or gem?cisplat or gem?carbo).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
13	(gem adj (cis or cisplat or carbo)).mp.
14	95058-81-4*.rn.
15	103882-84-4*.rn.
16	B76N6SBZ8R.rn.
17	or/9-16
18	exp administration, intravesical/
19	(intraves* or instill* or region* or install*).tw.
20	18 or 19
21	8 and 17 and 20
22	randomized controlled trial.pt.
23	controlled clinical trial.pt.
24	randomized.ab.
25	placebo.ab.
26	drug therapy.fs.
27	randomly.ab.
28	trial.ab.

(Continued)

29	groups.ab.
30	or/22-29
31	exp animals/ not humans.sh.
32	30 not 31
33	21 and 32
Embase (OvidSP)	
1	exp bladder tumor/
2	((bladder* or urethra* or ureter* or urin* or urotheli*) adj3 (cancer* or carcinoma* or neoplas* or tumo?r* or superficial or adenoma* or adenocarcinoma* or squamous* or malignan*)).tw.
3	exp transitional cell carcinoma/
4	(tcc or transitional cell).tw.
5	exp ureter tumor/
6	exp urethra tumor/
7	or/1-6
8	exp deoxycytidine/
9	exp antineoplastic antimetabolite/
10	exp gemcitabine/
11	(gemc?tabin* or Gemzar*).mp.
12	(gem?cis or gem?cisplat or gem?carbo).mp.
13	(gem adj (cis or cisplat or carbo)).mp.
14	95058-81-4*.rn.
15	103882-84-4*.rn.
16	B76N6SBZ8R.rn.
17	or/8-16
18	exp intravesical drug administration/
19	(intraves* or instill* or region* or install*).tw.
20	18 or 19
21	7 and 17 and 20
22	crossover procedure/

(Continued)

23	double blind procedure/
24	randomized controlled trial/
25	single blind procedure/
26	(random* or factorial* or crossover* or cross over* or cross-over* or placebo* or assign* or allocat* or volunteer*).mp.
27	((doubl* or singl*) adj blind*).mp.
28	or/22-27
29	21 and 28
The Cochrane Library (Wiley)	
#1	MeSH descriptor: [Urinary Bladder Neoplasms] explode all trees
#2	(bladder* or urethra* or ureter* or urin* or urotheli*) NEAR/3 (cancer* or carcinoma* or neoplas* or tumour* or tumor* or superficial or adenoma* or adenocarcinoma* or squamous* or malignan*):ti,kw,ab
#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	#1 OR #2 OR #3 OR #4 OR #5 OR #6
#8	MeSH descriptor: [Deoxycytidine Kinase] explode all trees
#9	MeSH descriptor: [Antimetabolites, Antineoplastic] explode all trees
#10	(gemcitabin* or Gemzar*):ti,kw,ab
#11	(gem NEAR (cis or cisplat or carbo)):ti,kw,ab
#12	(gem?cis or gem?cisplat or gem?carbo):ti,kw,ab
#13	(95058 81 4*)
#14	(103882 84 4*)
#15	B76N6SBZ8R
#16	#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15
#17	MeSH descriptor: [Administration, Intravesical] explode all trees
#18	(intraves* or instill* or region* or install*):ti,kw,ab
#19	#17 OR #18

(Continued)

#20	#7 AND #16 AND #19
Web of Science Core Collection (Thomson Reuters)	
#1	TS=((bladder* NEAR/3 (cancer* OR carcinoma* OR neoplas* OR tumo?r* OR superficial OR adenoma* OR adenocarcinoma* OR squamous* OR malignan*)))
#2	TS=((urethral NEAR/3 (cancer* OR carcinoma* OR neoplas* OR tumo?r* OR superficial OR adenoma* OR adenocarcinoma* OR squamous* OR malignan*)))
#3	TS=((ureteral NEAR/3 (cancer* OR carcinoma* OR neoplas* OR tumo?r* OR superficial OR adenoma* OR adenocarcinoma* OR squamous* OR malignan*)))
#4	TS=((urin* NEAR/3 (cancer* OR carcinoma* OR neoplas* OR tumo?r* OR superficial OR adenoma* OR adenocarcinoma* OR squamous* OR malignan*)))
#5	TS=((urotheli* NEAR/3 (cancer* OR carcinoma* OR neoplas* OR tumo?r* OR superficial OR adenoma* OR adenocarcinoma* OR squamous* OR malignan*)))
#6	TS=(tcc OR transitional cell)
#7	#6 OR #5 OR #4 OR #3 OR #2 OR #1
#8	TS=(deoxycytidine)
#9	TS=(gemc?tabin* OR gemzar*)
#10	TS=(gemcis*)
#11	TS=(gemcarbo*)
#12	#11 OR #10 OR #9 OR #8
#13	TS=(intraves* OR instill* OR region* OR install*)
#14	#13 AND #12 AND #7
#15	TS=(Clinical trial*)
#16	TS=(research design*)
#17	TS=(comparative stud*)
#18	TS=(evaluation stud*)
#19	TS=(controlled trial*)
#20	TS=(follow up stud*)
#21	TS=(prospective stud*)
#22	TS=(random*)
#23	TS=(placebo*)
#24	TS=(single blind*)

(Continued)

#25	TS=(double blind*)
#26	#25 OR #24 OR #23 OR #22 OR #21 OR #20 OR #19 OR #18 OR #17 OR #16 OR #15
#27	#26 AND #14
LILACS (Virtual Health Library)	
1	((bladder$ or bexiga or vejiga or ureter$ or urethr$ or "transitional cell" or "célula de transición" or "célula transicional")) and ((gemcitabin$ or gemzar or gemcis or gemcisplat or gemcarbo))
Scopus (Elsevier)	
1	(((TITLE-ABS-KEY ((bladder W/3 (cancer* OR carcinoma* OR neoplas* OR tumo?r* OR superficial OR adenoma* OR adenocarcinoma* OR squamous* OR malignan*)))) OR (TITLE-ABS-KEY ((ureteral* W/3 (cancer* OR carcinoma* OR neoplas* OR tumo?r* OR superficial OR adenoma* OR adenocarcinoma* OR squamous* OR malignan*)))) OR (TITLE-ABS-KEY ((urethral* W/3 (cancer* OR carcinoma* OR neoplas* OR tumo?r* OR superficial OR adenoma* OR adenocarcinoma* OR squamous* OR malignan*)))) OR (TITLE-ABS-KEY ((tcc OR "transitional cell")))) AND ((TITLE-ABS-KEY ((gemc?tabin* OR gemzar OR gemcis OR gemcisplat OR gemcarbo))) OR (CASREGNUMBER ((95058-81-4*))) OR (CASREGNUMBER ((103882-84-4*))) OR (CASREGNUMBER ((b76n6sbz8r)))) AND (TITLE-ABS-KEY ((intraves* OR instill* OR region* OR install*)))) AND ((TITLE-ABS-KEY ("clinical trial*")) OR (TITLE-ABS-KEY ("research design*")) OR (TITLE-ABS-KEY ("comparative stud*")) OR (TITLE-ABS-KEY ("evaluation stud*")) OR (TITLE-ABS-KEY ("controlled trial*")) OR (TITLE-ABS-KEY ("follow up stud*")) OR (TITLE-ABS-KEY ("prospective stud*")) OR (TITLE-ABS-KEY (random*)) OR (TITLE-ABS-KEY (placebo*)) OR (TITLE-ABS-KEY ("single blind*")) OR (TITLE-ABS-KEY ("double blind*")))
OpenGrey (Native Interface)	
1	Bladder AND Gemcitabin*
ClinicalTrials.gov (US National Institute of Health)	
1	**Condition:** Bladder **Other Terms:** Gemcitabine and Intravesical.
WHO International Clinical Trials Registry Search Portal (World Health Organization)	
1	Bladder AND Gemcitabin* AND Intraves*

Appendix 2. Survey of study investigators providing information on included and excluded studies

Study	Date study author contacted (first)	Date study author provided data (latest)	Data study author provided (short summary)
Böhle 2009	24 February 2019	26 February 2019	Randomization and allocation concealment method
Cao 2011	12 February 2019	22 February 2019	Study design
Di Lorenzo 2010	2 March 2019	2 March 2019	Protocol existence or not

(Continued)

Gontero 2013	24 February 2019	1 March 2019	Randomization and allocation concealment method

WHAT'S NEW

Date	Event	Description
18 April 2021	New search has been performed	In this update, we added 2 new studies and excluded 1 study included in the previous review due to an unsuitable comparator. We applied current MECIR standards and GRADE to assess the certainty of the evidence. The conclusions of this review have changed.
18 April 2021	New citation required and conclusions have changed	In this update, we added 2 new studies and excluded 1 study included in the previous review due to an unsuitable comparator. We applied current MECIR standards and GRADE to assess the certainty of the evidence. The conclusions of this review have changed.

HISTORY

Protocol first published: Issue 10, 2011
Review first published: Issue 1, 2012

CONTRIBUTIONS OF AUTHORS

MAH: drafted the review and provided GRADE methodologic input to the review.

PM: performed data abstraction and risk of bias assessments.

JHJ: provided clinical and methodologic input to the protocol and the review.

JEH: provided critical content expertise input to the review.

VN: provided critical content expertise input to the protocol and the review.

AC: created search strategies and executed the searches.

ECH: conceived, designed, and wrote the protocol and performed all aspects of data abstraction, analysis, risk of bias assessment, and certainty of evidence ratings.

PD: conceived, designed, and wrote the protocol; reviewed critical content; and gave final approval.

DECLARATIONS OF INTEREST

MAH: none.

PM: none.

JHJ: none.

JEH: none.

VN: none.

AC: none.

ECH: none.

PD: serves as Co-ordinating Editor of Cochrane Urology. However, he was not involved in the editorial processing or decision-making for this review. Other editors of Cochrane Urology managed the editorial process, including final sign-off for this review.

SOURCES OF SUPPORT

Internal sources

- Eu Chang Hwang, Korea, South

  Chonnam National University Hwasun Hospital, Hwasun, Korea, South Salary support for Eu Chang Hwang
- Philipp Dahm, USA

  Department of Urology, University of Minnesota, Minneapolis, MN, USA
  Salary support for PD

External sources

- No external support received, Korea, South

  None

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

This review was based on a published protocol (Jones 2011), and was an update of a Cochrane Review first published in 2012 (Jones 2012). Major differences between the previous review and the update include the following.

- We did not include Gardmark 2005 because this study compared different doses and schedules of gemcitabine.
- Types of outcome measures: we renamed primary and secondary outcomes and added details in 'Method and timing of outcome measurement' for all outcomes.
- We applied the GRADE approach and the Cochrane 'Risk of bias' assessment tool to assess the certainty of the evidence.
- We abstracted data from included studies and re-analyzed them in accordance with primary and secondary outcomes.
- We included two new trials (Gontero 2013; Messing 2018), which allowed one comparison to include a meta-analysis.
- Although our review intended to evaluate the effect of intravesical gemcitabine in NMIBC, since Böhle 2009 (7.7%) and Messing 2018 (3.7%) included a muscle-invasive bladder cancer in the analysis, we used this full analysis set (available analysis) in our review.
- The comparisons follow the framework of the prior protocol with the exception of the analysis that gemcitabine versus BCG in patients who were previously treated with BCG since the trial participants in the control arm can be expected to have a lesser BCG response (Chang 2016) since their inclusion into an overall analysis not only contradicts clinical practice but also would have bias the results in favor of the gemcitabine arm.

NOTES

We have based parts of the 'Methods' section of this review on a standard template developed by the Cochrane Metabolic and Endocrine Disorders Group, which has been modified and adapted for use by Cochrane Urology.

INDEX TERMS

Medical Subject Headings (MeSH)

Adjuvants, Immunologic [administration & dosage]; Administration, Intravesical; Antibiotics, Antineoplastic [administration & dosage] [adverse effects]; Antimetabolites, Antineoplastic [*administration & dosage] [adverse effects]; BCG Vaccine [administration & dosage]; Bias; Cause of Death; Confidence Intervals; Deoxycytidine [administration & dosage] [adverse effects] [*analogs & derivatives]; Disease Progression; Drug Administration Schedule; Mitomycin [administration & dosage] [adverse effects]; Neoplasm Recurrence, Local [*drug therapy] [mortality] [prevention & control]; Randomized Controlled Trials as Topic; Saline Solution [administration & dosage]; Urinary Bladder Neoplasms [*drug therapy] [mortality] [pathology] [prevention & control]

MeSH check words

Humans