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Original Article

Intravesical Chemotherapy versus Bacillus Calmette-Guérin as First-Line Adjuvant Therapy in BCG-Naïve Non-Muscle-Invasive Bladder Cancer: A Systematic Review and Meta-Analysis of Randomised Controlled Trials

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ABSTRACT

Background: BCG is the standard adjuvant treatment for intermediate- and high-risk non-muscle-invasive bladder cancer (NMIBC), but shortages and toxicity have renewed interest in intravesical chemotherapy as a first-line alternative. Recent trials of gemcitabine and gemcitabine–docetaxel have not been pooled with the older mitomycin and anthracycline trials.

Objective: To compare intravesical single-agent or combination chemotherapy with BCG in adults with BCG-naïve NMIBC. The main aim was to establish how BCG shortage can be managed with chemotherapy alone or chemotherapy combined with BCG, by (1) comparing chemotherapy with BCG and (2) judging whether chemotherapy can meet the demand created by BCG shortage.

Methods: PubMed, Scopus, and Embase was searched to 4 October 2026 for randomised controlled trials (RCTs) comparing intravesical chemotherapy with BCG. Trials in which BCG-naïve status was not reported, or in which patients were not strictly BCG-naïve, were excluded. The primary outcome was recurrence, expressed as a hazard ratio (HR; values above 1 favour BCG) taken from the report or derived from published summary statistics. Secondary outcomes were progression, complete response in carcinoma in situ (CIS), adverse events and treatment discontinuation. Random-effects (DerSimonian–Laird) models were used.

Results: Fourteen RCTs (3,227 participants) contributed to the primary analysis; seven further eligible trials reported no extractable effect size. Overall, chemotherapy was associated with a higher hazard of recurrence than BCG (HR 1.38 (95% CI 1.05–1.82); I^2 = 81%, τ^2 = 0.20; Hartung–Knapp interval 0.98–1.96). The effect differed by agent (p for subgroup difference = 0.002): epirubicin HR 2.07 (95% CI 1.36–3.13), doxorubicin 2.49 (95% CI 1.16–5.38), mitomycin C 1.05 (95% CI 0.76–1.45), gemcitabine 0.81 (95% CI 0.35–1.87) and gemcitabine–docetaxel 0.38 (95% CI 0.12–1.18), each of the last two in a single trial. BCG was superior when given with maintenance (HR 1.53 (95% CI 1.20–1.95)), whereas induction-only BCG

was less effective than MMC (HR 0.77 (95% CI 0.62–0.96)). Progression did not differ significantly (RR 1.49 (95% CI 0.98–2.26); three trials). Adverse events tended to be less frequent with chemotherapy (RR 0.73 (95% CI 0.52–1.05); three trials).
Conclusions: In BCG-naïve NMIBC, maintenance BCG prevents recurrence better than anthracyclines and, less consistently, mitomycin C. Gemcitabine-based regimens gave recurrence estimates compatible with BCG and tended to be better tolerated, but the trials are small, short and at high risk of bias. The evidence is of low to very low certainty, and gemcitabine–docetaxel should be regarded as promising rather than proven until phase 3 data are available. Across 14 trials chemotherapy carried a higher recurrence hazard than BCG (HR 1.38, 95% CI 1.05–1.82), but this estimate was borderline. Chemotherapy may ease BCG shortage mainly in intermediate-risk disease, allowing scarce BCG to be kept for high-risk patients.

Keywords: non-muscle-invasive bladder cancer; BCG; intravesical chemotherapy; gemcitabine; docetaxel; mitomycin; meta-analysis.

INTRODUCTION

About three quarters of bladder cancers are non-muscle-invasive at diagnosis, and recurrence after transurethral resection (TURBT) is common. Intravesical BCG with maintenance is the recommended adjuvant treatment for high-risk disease and an option for intermediate-risk disease. An individual-patient-data meta-analysis of nine trials found that BCG reduced recurrence by 32% compared with mitomycin C (MMC) only when maintenance was given [1], and Cochrane reviews reached similar, low-certainty conclusions for MMC and epirubicin [2,3].

Two problems limit BCG in practice. Local and systemic toxicity leads many patients to stop treatment, which has prompted work on dose reduction and prophylaxis [4,5], and recurring global shortages mean that some patients cannot receive a full course. Recent reviews of first-line options in BCG-naïve disease have concentrated on adding immune checkpoint inhibitors or other agents to BCG [6,7]; these combinations improve recurrence-related outcomes at the cost of more severe adverse events, and they still depend on BCG supply.

Chemotherapy that replaces BCG is a different question. Earlier syntheses covered MMC, anthracyclines and single-agent gemcitabine [8,9,10], but newer randomised trials, including the first randomised comparison of sequential gemcitabine–docetaxel with BCG in a BCG-naïve population [11], have not been considered together with the older evidence. We therefore pooled RCTs comparing intravesical chemotherapy with BCG in BCG-naïve NMIBC, with recurrence as the primary outcome. The review had two objectives: first, to compare intravesical chemotherapy (single-agent or combination) with BCG; and second, to determine whether chemotherapy can be used to meet the demand created by BCG shortage. Regimens that combine chemotherapy with BCG were identified but not pooled with the chemotherapy-alone comparison (see Methods).

METHODS

The review follows the PRISMA 2020 statement [12].

2.1 Eligibility criteria

Trials in which the experimental arm also contained BCG (sequential or alternating chemo-immunotherapy) or interferon, and trials in BCG-failure populations, were excluded. These chemotherapy-plus-BCG trials were not pooled with the chemotherapy-alone comparison; they are considered in the Discussion as a possible BCG-sparing approach. Because older reports rarely describe prior BCG exposure, BCG-naïve status was classed as explicit (stated in eligibility criteria) or presumed (first-line adjuvant design with no mention of prior BCG); trials restricted to patients with prior BCG were excluded. Trials in which BCG-naïve status was not reported, or in which patients were not strictly BCG-naïve, were excluded from the primary analysis.

2.2 Search and selection

PubMed and Scopus was searched on 4 October 2026 without language limits, combining terms for BCG, bladder cancer, intravesical administration, the individual agents (mitomycin, epirubicin, doxorubicin, thiotepa, pirarubicin, gemcitabine, docetaxel, valrubicin), device-assisted delivery and randomised design. Reference lists of earlier systematic reviews were checked. Four structured queries and three author-targeted queries returned 364 records before de-duplication. Titles and abstracts were screened and potentially eligible reports were assessed against the criteria above.

2.3 Data extraction and effect measures

For each trial we recorded design, risk group, regimens, BCG schedule, follow-up, numbers randomised and outcome data. The effect measure for recurrence was the HR of chemotherapy versus BCG. When the HR and its confidence interval were not reported, ln(HR) and its standard error were derived by the methods of Parmar and Tierney [13,14], in this order of preference: reported HR with standard error from total events; log-rank or Cox p-value with total events; Kaplan–Meier survival at a fixed time with its confidence interval or p-value; and crude events per arm using the complementary log-log transformation. The method used for every trial is listed in Table 1 and in the data file. For multi-arm trials, BCG arms of different strains or schedules were combined; where two chemotherapy arms shared one BCG arm they were merged for the overall estimate and shown separately in agent-specific analyses.

2.4 Risk of bias

Risk of bias was judged with the RoB 2 tool [15] at the level of the recurrence outcome. Judgements are provisional because several trials were assessed from abstracts only.

2.5 Statistical analysis

Estimates were pooled on the log scale with the DerSimonian–Laird random-effects model [16]. Heterogeneity was described with I^2 and τ^2 [17], and Hartung–Knapp confidence intervals and 95% prediction intervals were calculated as a check. Pre-specified subgroup analyses covered chemotherapy agent, BCG maintenance in the comparator arm, explicit versus presumed BCG-naïve status and risk group. Sensitivity analyses excluded estimates that rested on assumptions or interim data (arm sizes assumed equal in two trials and a 12-month interim analysis in one), restricted the analysis to estimates derived from time-to-event statistics, substituted the 3-year MMC arm of one three-arm trial, and omitted each trial in turn. Dichotomous secondary outcomes were pooled as risk ratios (RR). Small-study effects were examined with a funnel plot and Egger's test [18]. All trials compared chemotherapy with BCG and none compared agents with each other, so the network is star-shaped; a network meta-analysis would add nothing to the agent-specific pairwise estimates and was not done. Analyses were run in Python 3 (NumPy, SciPy); forest plots are presented in Review Manager 5 layout, and an R script (meta package) that reproduces the primary analysis is provided with the data file.

RESULTS

3.1 Included trials

Thirty-four randomised trials met the design criteria. Thirteen were excluded because BCG-naïve status was not reported or not strict (eight trials of conventional chemotherapy, two of device-assisted MMC and three in CIS), leaving twenty-one eligible trials. Fourteen trials of conventional chemotherapy (3,227 participants) gave an extractable recurrence estimate: six of MMC, four of epirubicin, two of doxorubicin, one of thiotepa (the same trial as one of the doxorubicin trials, which had both doxorubicin and thiotepa arms), one of gemcitabine and one of gemcitabine–docetaxel (Table 1). Seven eligible trials could not be pooled because the accessible report gave no event counts or variance (Table 2). Trials combining chemotherapy with BCG [19,20,21] or with interferon [22,23] and a trial in BCG failure [24] were excluded.

BCG-naïve status was explicit in four trials and presumed in ten. The comparator was BCG with maintenance in eight trials and induction only in three; the schedule was mixed or unclear in three. Median follow-up ranged from 12 months to about 20 years. In the ten trials with presumed status, BCG-naïve status was inferred from a first-line adjuvant design.

Study	Agent	n chemo / BCG	Risk group	BCG maintenance	BCG-naïve	HR (95% CI)	Effect size from
Rintala 1991 / Järvinen 2009 (FinnBladder I) [25,26]	MMC	45 / 44	Recurrent TaT1	Yes	Presumed	2.04 (1.24–3.36)	P-value + total events (62)
Debruyne 1988 / Witjes 1998 (EORTC–Dutch SE) [27,28]	MMC	160 / 148	Mixed Ta/T1/CIS	No	Presumed	0.82 (0.53–1.25)	Crude events (12-month interim)
Vegt 1995 (Dutch SE, 3-arm) [29]	MMC	129 / 258	Mixed pTa–pT1	No	Presumed	0.70 (0.51–0.95)	Crude % (arm sizes assumed equal)

Lundholm 1996 / Malmström 1999 (Swedish–Norwegian) [30,31]	MMC	125 / 125	High	Yes	Presumed	1.40 (1.02–1.93)	P-value + total events (149)
Friedrich 2007 (6-week MMC arm) [32]	MMC	165 / 165	Intermediate/high	No	Presumed	0.89 (0.57–1.38)	3-y KM RFS with 95% CI
Mangiarotti 2008 [33]	MMC	46 / 46	Intermediate	Yes	Presumed	1.00 (0.56–1.78)	Crude events
Melekos 1996 [34]	Epirubicin	66 / 66	Recurrent/multiple	Yes	Presumed	1.36 (0.84–2.20)	Crude % (arm sizes assumed equal)
EORTC 30911 (van der Meijden 2001 / Sylvester 2010) [35,36]	Epirubicin	279 / 558	Intermediate/high	Yes	Explicit	1.61 (1.30–2.01)	Reported HR; SE from total events (~360)
Cheng 2005 [37]	Epirubicin	107 / 102	Mixed Ta/T1	Unclear	Presumed	2.31 (1.45–3.66)	10-y KM RFS + log-rank p
Hinotsu 2011 [38]	Epirubicin	32 / 83	Recurrent/multiple	Mixed	Presumed	4.35 (2.41–7.86)	KM-derived events (2 y)
Lamm 1991 (SWOG 8216, Ta/T1 stratum) [39]	Doxorubicin	66 / 65	Recurrent Ta/T1	Yes	Explicit	1.78 (1.12–2.84)	5-y KM disease-free + p
Martínez-Piñeiro 1990 (doxorubicin arm) [40]	Doxorubicin	53 / 67	Mixed	Yes	Presumed	3.95 (1.83–8.53)	Crude events
Martínez-Piñeiro 1990 (thiotepa arm) [40]	Thiotepa	56 / 67	Mixed	Yes	Presumed	3.06 (1.39–6.73)	Crude events
Bendary 2011 [41]	Gemcitabine	40 / 40	Intermediate	Unclear	Explicit	0.81 (0.35–1.87)	Crude events
Srivastava 2026 [11]	Gemcitabine–docetaxel	43 / 48	Intermediate/high	Yes	Explicit	0.38 (0.12–1.18)	KM-derived events (12 mo)

Table 1. Trials contributing a recurrence estimate. HR is chemotherapy versus BCG (above 1 favours BCG).

Study	Comparison	Reported result	Why not pooled
Lamm 1995 (SWOG 8795) [42]	MMC 20 mg vs BCG Tice, both with 1-year maintenance; n=377	RFS longer with BCG (Cox p=0.017)	No event counts or HR in accessible report
Krege 1996 [43]	MMC vs BCG vs TUR alone; n=337	No significant MMC–BCG difference (RR vs TUR 0.51 and 0.62)	No arm-level events/variance

Ojea 2007 (CUETO 95011) [44]	MMC 30 mg vs BCG 27 mg vs BCG 13.5 mg; n=430	BCG 27 mg better than MMC (p=0.006); BCG 13.5 mg vs MMC p=0.183	Reduced-dose BCG; no arm-level data in abstract
Melekos 1993 [45]	Epirubicin vs BCG vs TUR; n=161	Recurrence-free 60% vs 68%	Arm sizes not reported in abstract; possible overlap with Melekos 1996
Hinotsu 2006 [46]	Doxorubicin vs BCG Tokyo; n=80	Lower recurrence with BCG (log-rank p=0.017)	No event counts
Gontero 2013 [47]	Gemcitabine vs one-third dose BCG; n=120	No significant difference in recurrence at 1 year	No event counts in abstract; reduced-dose BCG
Sachan 2024 [48]	Chemohyperthermia MMC vs MMC vs BCG; n=135	No difference in recurrence (p=0.375)	No arm-level events

Table 2. Eligible trials without an extractable effect size.

3.2 Risk of bias

No trial was blinded, and allocation concealment was rarely described. On provisional assessment, all trials were at high risk of bias or raised some concerns, and none was at low risk. The main reasons for a high-risk judgement were single-centre conduct with unclear randomisation, short follow-up, interim data, and effect sizes that had to be derived with assumptions.

3.3 Recurrence

Across all conventional regimens, chemotherapy was associated with a higher hazard of recurrence than BCG (HR 1.38 (95% CI 1.05–1.82), p = 0.02; Figure 2). Heterogeneity was substantial (I^2 = 81%, τ^2 = 0.20), the Hartung–Knapp interval was 0.98–1.96 and included 1, and the 95% prediction interval ran from 0.49 to 3.87, so the pooled figure is imprecise and should not be read as applying to every agent.

Results differed by agent (test for subgroup differences p = 0.002). BCG was clearly better than epirubicin (HR 2.07 (95% CI 1.36–3.13); I^2 = 75%, τ^2 = 0.13; four trials) and doxorubicin (HR 2.49 (95% CI 1.16–5.38)). For MMC the pooled estimate did not differ significantly from BCG (HR 1.05 (95% CI 0.76–1.45); I^2 = 73%, τ^2 = 0.12; six trials). The thiotepa arm of the trial that also tested doxorubicin favoured BCG (HR 3.06 (95% CI 1.39–6.73)) [40]. Single-agent gemcitabine was represented by one intermediate-risk trial, which gave a hazard similar to BCG with a wide interval (HR 0.81 (95% CI 0.35–1.87)) [41]. In the only randomised trial of gemcitabine–docetaxel, 12-month recurrence-free survival was 90.7% with gemcitabine–docetaxel and 77.1% with BCG [11], giving a derived HR of 0.38 (95% CI 0.12–1.18). The two gemcitabine-containing trials together gave HR 0.61 (95% CI 0.30–1.26).

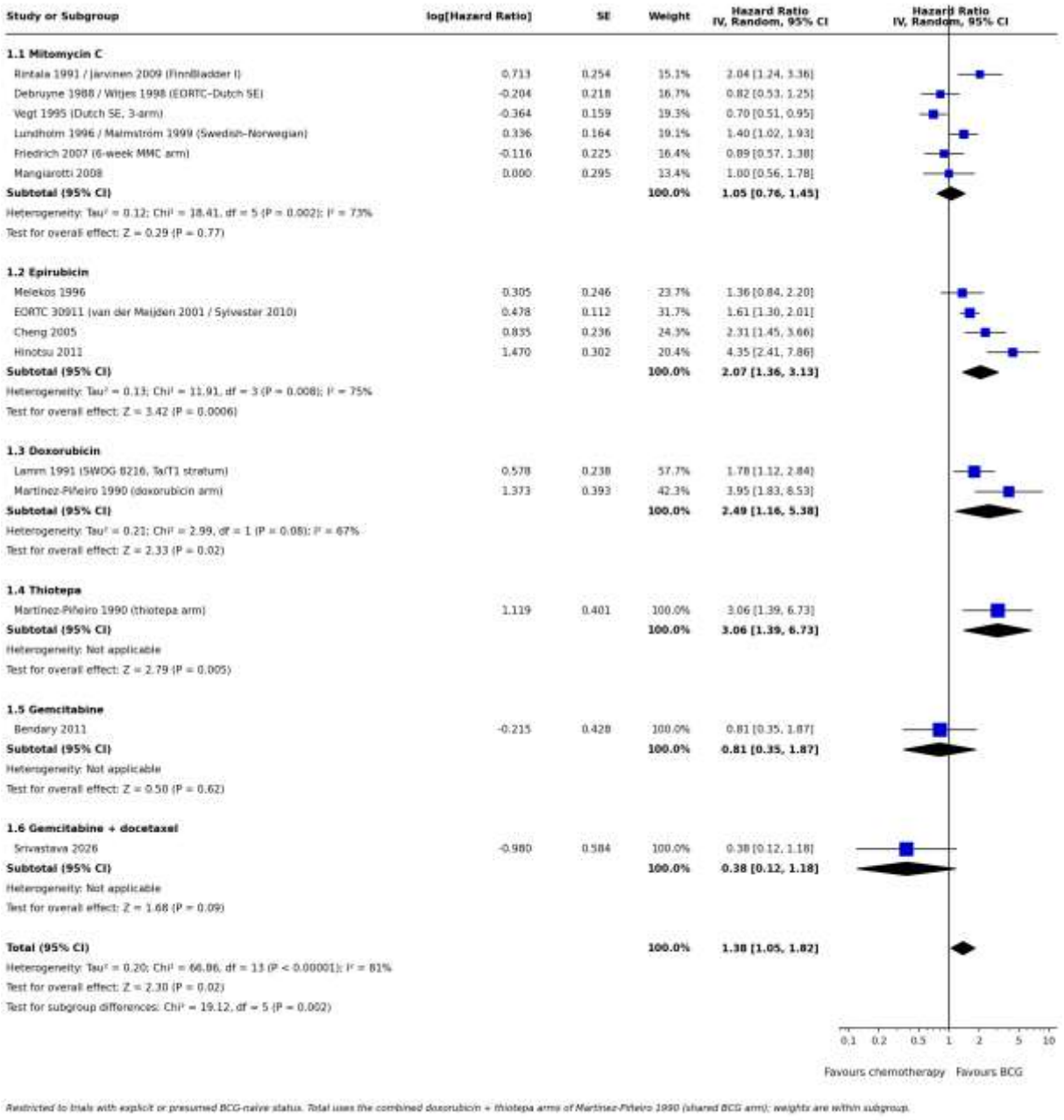


Figure 2. Recurrence with conventional intravesical chemotherapy versus BCG, by agent. Random-effects model. The overall estimate uses the combined chemotherapy arms of Martínez-Piñeiro 1990.

3.4 Subgroup and sensitivity analyses

The BCG schedule explained much of the heterogeneity (p for subgroup difference < 0.001; Figure 3). Where BCG was given with maintenance, chemotherapy was inferior (HR 1.53 (95% CI 1.20–1.95); $I^2 = 54\%$, $\tau^2 = 0.06$; eight trials). Where BCG was given as a 6-week induction only, the estimate favoured chemotherapy; all three trials tested MMC (HR 0.77 (95% CI 0.62–0.96); $I^2 = 0\%$, $\tau^2 = 0.00$). Three trials with mixed or unclear schedules were not included in this comparison. The estimate was HR 1.23 (95% CI 0.77–1.97) in the four explicitly BCG-naïve trials and HR 1.47 (95% CI 1.03–2.11) in the ten trials with presumed BCG-naïve status (p for difference = 0.55). The single trial confined to high-risk disease gave HR 1.40 (95% CI 1.02–1.93) and the two trials confined to intermediate-risk disease HR 0.93 (95% CI 0.58–1.50).

Excluding the three estimates that rested on assumptions or interim data (arm sizes assumed equal in two trials, a 12-month interim analysis in one) gave HR 1.59 (95% CI 1.20–2.11). Restricting to the six estimates derived from hazard ratios, log-rank statistics or Kaplan–Meier data gave HR 1.58 (95% CI 1.26–1.98) with less heterogeneity ($I^2 = 54\%$, $\tau^2 = 0.04$). Using

the 3-year MMC arm of Friedrich 2007, which had far fewer recurrences than 6-week BCG (HR 0.35, 95% CI 0.19–0.65) [32], gave an overall HR of 1.30 (95% CI 0.95–1.77). Omitting one trial at a time (Figure 6) moved the pooled HR between 1.28 and 1.48, and the lower confidence limit fell to 0.99 when EORTC 30911, Cheng 2005, Hinotsu 2011 or Martínez-Piñeiro 1990 was omitted. The funnel plot was roughly symmetrical (Egger p = 0.92; Figure 5), although with only fourteen trials the test has little power.

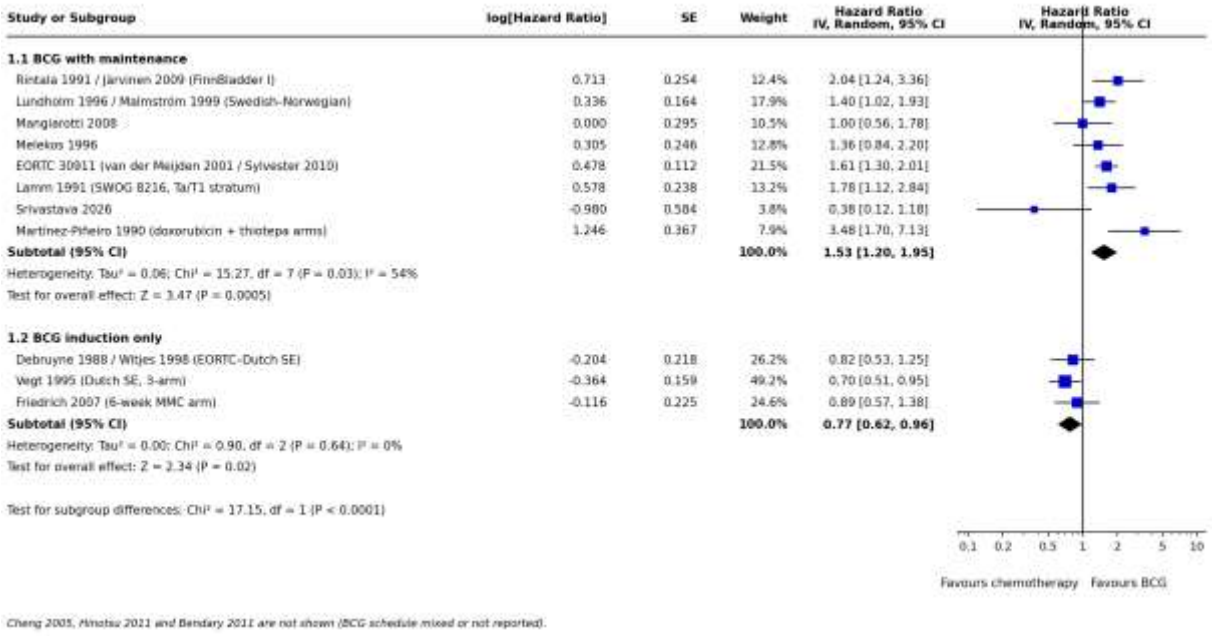


Figure 3. Recurrence by BCG schedule in the comparator arm. Cheng 2005, Hinotsu 2011 and Bendary 2011 are not shown because their BCG schedule was mixed or unclear.

3.5 Secondary outcomes

Progression was reported with counts in three trials [11,26,49] and did not differ significantly, although it tended to be more frequent with chemotherapy (RR 1.49 (95% CI 0.98–2.26); I^2 = 0%, τ^2 = 0.00; Figure 4a). In the CIS stratum of SWOG 8216 [39], failure to achieve a complete response was more likely with doxorubicin than with BCG (RR 2.21 (95% CI 1.46–3.35)), in line with an earlier meta-analysis [50].

Adverse events, as defined in each trial, tended to be less frequent with chemotherapy (RR 0.73 (95% CI 0.52–1.05); I^2 = 53%, τ^2 = 0.05; three trials [11,33,35]; Figure 4b). Discontinuation because of adverse events was reported in only two trials, which pointed in opposite directions: it was less frequent with epirubicin in EORTC 30911 (RR 0.32 (95% CI 0.19–0.52)) [35], but one MMC trial reported more withdrawals for chemical cystitis and hypersensitivity (RR 5.50 (95% CI 1.29–23.45)) [33]. Grade 3 or higher events were too sparsely reported to pool; in the gemcitabine–docetaxel trial there were none with chemotherapy and three with BCG [11]. Survival was rarely reported. EORTC 30911 found longer overall and disease-specific survival with BCG than with epirubicin [36], whereas the long-term MMC trials found no survival difference [26,49].

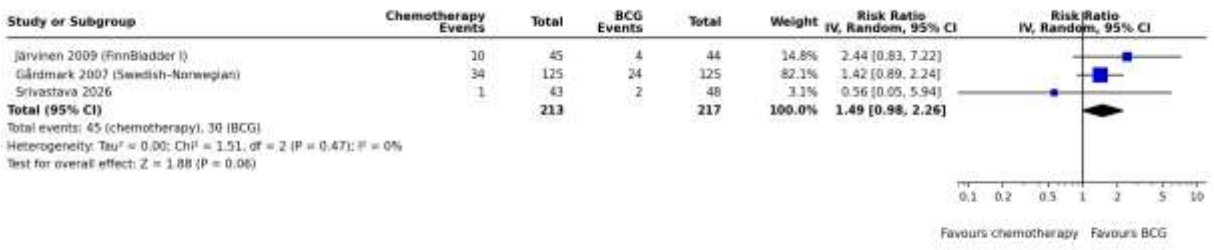


Figure 4a. Progression.

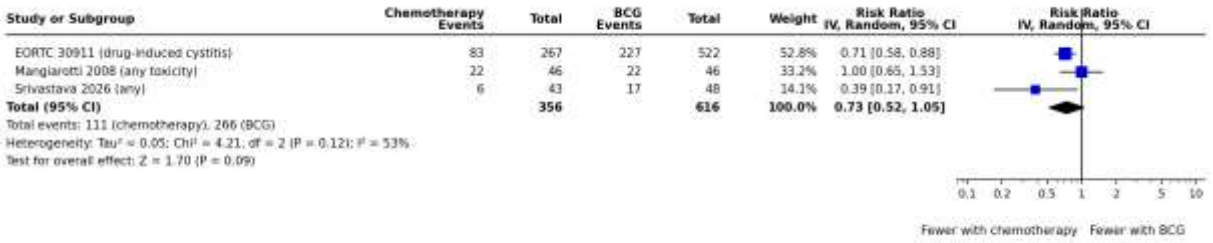


Figure 4b. Adverse events (any or local, as defined in each trial).

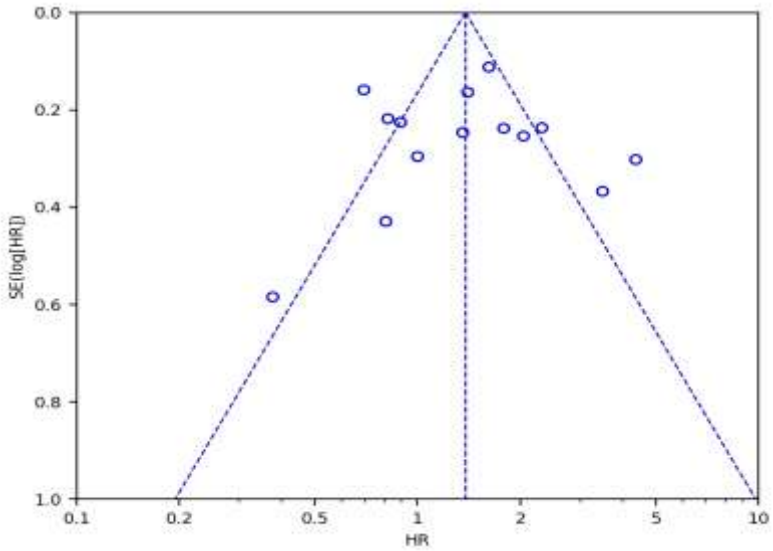


Figure 5. Funnel plot for the primary analysis.

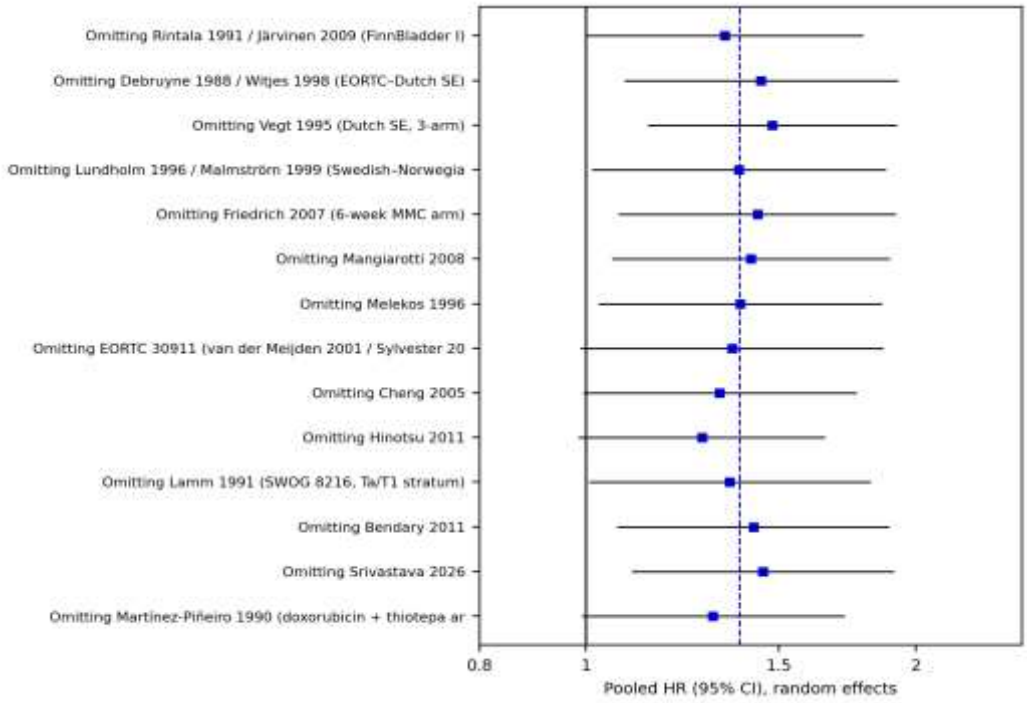


Figure 6. Leave-one-out sensitivity analysis for the primary outcome. The dashed line is the overall pooled HR.

3.6 Certainty of evidence

Outcome	Trials	Effect (95% CI)	Certainty (GRADE, provisional)	Reasons for downgrading
Recurrence, all agents	14	HR 1.38 (1.05–1.82)	Low	Risk of bias; inconsistency; imprecision
Recurrence, epirubicin	4	HR 2.07 (1.36–3.13)	Low	Risk of bias; inconsistency in size of effect
Recurrence, mitomycin C	6	HR 1.05 (0.76–1.45)	Low	Risk of bias; inconsistency; missing eligible trials
Recurrence, gemcitabine	1	HR 0.81 (0.35–1.87)	Very low	Single small trial; risk of bias; imprecision
Recurrence, gemcitabine–docetaxel	1	HR 0.38 (0.12–1.18)	Very low	Single small trial; 12-month follow-up; imprecision
Progression	3	RR 1.49 (0.98–2.26)	Very low	Risk of bias; imprecision; few trials
Adverse events	3	RR 0.73 (0.52–1.05)	Very low	Unblinded subjective outcome; varying definitions; imprecision; few trials

Table 3. Summary of findings.

DISCUSSION

Taken as a class, intravesical chemotherapy was less effective than BCG at preventing recurrence in patients who had not previously received BCG, but the class effect hides clear differences between agents. The class estimate was nevertheless borderline: the Hartung–Knapp interval included 1, and the lower confidence limit fell to 0.99 when some single trials were omitted. BCG was consistently better than epirubicin and doxorubicin. For MMC the comparison depended on the BCG schedule: maintenance BCG was superior, whereas induction-only BCG was less effective than MMC, which is the pattern described in the individual-patient-data meta-analysis [1] and in earlier work on progression [51]. The two gemcitabine-based trials gave estimates compatible with BCG, with a tendency to fewer adverse events.

The seven eligible trials that could not be pooled matter for the MMC result. SWOG 8795 [42] and CUETO 95011 [44] both favoured BCG, and their absence probably biases our MMC estimate towards the null. Our MMC estimate should therefore be read alongside the Cochrane review, which had access to these data and reported an HR of 0.88 (0.71–1.09) for BCG versus MMC [2]. The interim data used for one large trial [27,28] and the equal-arm assumption for another [29] add further uncertainty; removing assumption-based estimates did not change the direction of the overall result.

The newer evidence is the main addition here. One small trial of single-agent gemcitabine in intermediate-risk disease found a recurrence rate similar to BCG [41]. A trial of gemcitabine against one-third-dose BCG also reported no difference at one year but gave no counts [47]. The randomised trial of sequential gemcitabine–docetaxel reported fewer recurrences and fewer adverse events than BCG at 12 months [11]; with 15 recurrences in 91 patients and no description of the randomisation procedure in the accessible record, the confidence interval includes both a large benefit and no difference. These findings agree with a recent pooled analysis of gemcitabine that mixed randomised and observational studies [10], and they support the rationale for the ongoing phase 3 BRIDGE trial (ECOG-ACRIN EA8212) comparing gemcitabine–docetaxel with BCG [52], whose results were still awaited when the most recent review of first-line regimens was completed [7], but they do not establish equivalence.

For practice, the results support current guidance: maintenance BCG remains the reference for high-risk disease, anthracyclines are not an adequate substitute, and MMC with maintenance is a reasonable alternative for intermediate-risk disease. When BCG is unavailable or not tolerated, gemcitabine-based chemotherapy is a possible alternative in intermediate-risk patients, but the randomised evidence is limited to one small trial of gemcitabine and one of gemcitabine–docetaxel, follow-up is short and progression data are few.

Meeting the BCG shortage. Applied to the two objectives of this review, the pooled comparison shows that chemotherapy as a class tended to be less effective than BCG for preventing recurrence (HR 1.38, 95% CI 1.05–1.82), so it cannot replace BCG across the board, and that estimate was borderline. It can, however, reduce the number of patients who need BCG. The single trial confined to high-risk disease gave HR 1.40 (95% CI 1.02–1.93), whereas the two trials confined to intermediate-risk disease gave HR 0.93 (95% CI 0.58–1.50); although this comparison is underpowered (p for difference = 0.17), it fits the view that scarce BCG should be reserved for high-risk patients and that chemotherapy (MMC with

maintenance or a gemcitabine-based regimen) can be offered to intermediate-risk patients. Chemotherapy also tended to cause fewer adverse events (RR 0.73, 95% CI 0.52–1.05) and may be easier to complete in patients who tolerate BCG poorly. Regimens that combine chemotherapy with BCG [19,20,21] were excluded from the pooled analysis. In CUETO 93009, sequential mitomycin C plus BCG was more effective but more toxic than BCG alone [20]. Whether such combinations reduce the BCG needed per patient, or only add toxicity, was outside the scope of this review and needs a separate analysis. BCG supply can also be stretched rather than replaced: in a real-world cohort of 563 patients treated with adequate BCG, one-third-dose BCG was not associated with worse time to recurrence ($p = 0.449$) or progression ($p = 0.716$) than full dose, with higher-risk patients prioritised for full dose [53]. That study was retrospective, and the one-third-dose group had more low-grade, solitary tumours without carcinoma in situ.

4.1 Strengths and limitations

The review brings the 2023–2026 trials together with the older literature on a single hazard-ratio scale and separates the comparison by agent and by BCG schedule. Its limitations are substantial. Only PubMed was searched and screening was not done in duplicate. Most effect sizes were derived from summary statistics in abstracts, and three relied on assumptions or interim data; full-text verification may change individual estimates. Seven eligible trials could not be included quantitatively. The pooled evidence for gemcitabine and for gemcitabine–docetaxel rests on one trial each, and the secondary outcomes (progression and adverse events) on three trials each. Thirteen trials were excluded because BCG-naïve status was not reported or not strict, including three single-agent gemcitabine trials, so the pooled results may not reflect all of the available randomised evidence. BCG-naïve status was explicit in only four of the fourteen pooled trials, so the population in older trials is BCG-naïve by inference (the estimate in the explicit trials, HR 1.23 (95% CI 0.77–1.97), did not differ significantly from that in the presumed trials, HR 1.47 (95% CI 1.03–2.11); $p = 0.55$, but this comparison has low power); some included patients who had previously received intravesical chemotherapy. BCG strain, dose and schedule, chemotherapy dose and dwell time, the use of re-resection and the definition of recurrence all varied, and adverse-event definitions were not uniform. Risk-of-bias judgements are provisional.

CONCLUSIONS

In BCG-naïve NMIBC, BCG with maintenance gives better protection against recurrence than epirubicin or doxorubicin and, less consistently, than mitomycin C. Gemcitabine and gemcitabine–docetaxel (one trial each) produced recurrence estimates compatible with BCG and tended to cause fewer adverse events, but these results come from small, short trials at high risk of bias. Adequately powered trials with at least two years of follow-up, standard BCG maintenance in the control arm and reporting of progression are needed before chemotherapy can be recommended in place of BCG for high-risk disease.

Summary of meta-analysis results. Across 14 RCTs (3,227 participants) in which BCG-naïve status was explicit or presumed, intravesical chemotherapy carried a higher hazard of recurrence than BCG (HR 1.38, 95% CI 1.05–1.82; $I^2 = 81\%$), although the Hartung–Knapp interval (0.98–1.96) included 1. The effect depended on the agent: epirubicin HR 2.07 (95% CI 1.36–3.13), doxorubicin HR 2.49 (95% CI 1.16–5.38), mitomycin C HR 1.05 (95% CI 0.76–1.45), gemcitabine HR 0.81 (95% CI 0.35–1.87) and gemcitabine–docetaxel HR 0.38 (95% CI 0.12–1.18), the last two from one trial each. BCG with maintenance was superior (HR 1.53, 95% CI 1.20–1.95), whereas induction-only BCG was less effective than MMC (HR 0.77, 95% CI 0.62–0.96). Progression did not differ significantly (RR 1.49, 95% CI 0.98–2.26; three trials), and adverse events tended to be less frequent with chemotherapy (RR 0.73, 95% CI 0.52–1.05; three trials). The certainty of the evidence was low to very low.

Meeting the BCG shortage with chemotherapy. (1) Comparison: chemotherapy tended to be less effective than BCG overall, clearly so for epirubicin and doxorubicin, whereas mitomycin C, gemcitabine and gemcitabine–docetaxel gave estimates that were compatible with BCG. (2) Meeting the demand: when BCG is scarce, the available evidence is consistent with reserving it for high-risk disease and offering intermediate-risk patients mitomycin C with maintenance; gemcitabine and gemcitabine–docetaxel are promising but each rests on one small trial and needs phase 3 confirmation. Chemotherapy combined with BCG was not pooled here and needs its own analysis. Stretching the BCG supply with one-third-dose BCG is a complementary strategy supported by real-world evidence [53]. Because BCG-naïve status was explicit in only four of the fourteen pooled trials, these conclusions apply to BCG-naïve disease by inference in most of the evidence.

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