

A systematic review of outcome reporting, definition and measurement heterogeneity in Non-Muscle Invasive Bladder Cancer effectiveness trials of adjuvant, prophylactic treatment after transurethral resection

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Abstract

Background: Heterogenous outcome reporting in non-muscle-invasive bladder cancer (NMIBC) effectiveness trials of adjuvant intervention after transurethral resection (TURBT) has been noted in systematic reviews (SRs). This hinders comparing results across trials, combining them in meta-analyses, and evidence-based decision-making for patients and clinicians.

Objective: We aimed to systematically review the extent of reporting and definition heterogeneity.

Methods: We included randomized controlled trials (RCTs) identified from SRs comparing adjuvant treatments after TURBT or TURBT alone in patients with NMIBC (with or without carcinoma in situ) published between 2000-2020. Abstracts and full texts were screened independently by two reviewers. Data were extracted by one reviewer and checked by another.

Results: We screened 807 abstracts; from 15 SRs, 57 RCTs were included. Verbatim outcome names were coded to standard outcome names and organised using the Williamson and Clarke taxonomy. Recurrence (98%), progression (74%), treatment response (in CIS studies) (40%), and adverse events (77%) were frequently reported across studies. However, overall (33%) and cancer-specific (33%) survival, treatment completion (17%) and treatment change (37%) were less often reported. Quality of Life (3%) and economic outcomes (2%) were rarely reported. Heterogeneity was evident

throughout, particularly in the definitions of progression and recurrence, and how CIS patients were handled in the analysis of studies with predominantly papillary patients, highlighting further issues with the definition of recurrence and progression vs treatment response for CIS patients. Data reporting was also inconsistent, with some trials reporting event rates at various time-points and others reporting time-to-event with or without Hazard Ratios. Adverse events were inconsistently reported. QoL data was absent in most trials.

Conclusions: Heterogenous outcome reporting is evident in NMIBC effectiveness trials. This has profound implications for meta-analyses, SRs and evidence-based treatment decisions. A core outcome set is required to reduce heterogeneity.

Patient Summary: ~~Patients with non-muscle-invasive bladder cancer benefit from adjuvant instillation therapies.~~ This systematic review found inconsistencies in outcome definitions and reporting, pointing out the urgent need for a core outcome set to help improve evidence-based treatment decisions.

1. Introduction

Description of the condition

Bladder cancer is the 6th commonest male, and 17th commonest female cancer globally, with the highest incidence rates being observed in Europe and North America.¹ The disease is categorised into two broad stage groupings, non-muscle invasive (NMIBC) and muscle-invasive (MIBC) bladder cancer. Most cases (75-85%) present as NMIBC and these patients typically have a higher long-term survival and a lower cancer specific mortality compared to those with MIBC.²

NMIBC is defined as tumour(s) confined to the mucosa or invading the lamina propria.³ Using the TNM staging system, they are classified as Ta-T1 or Tis (or Cis) N0 M0.⁴ NMIBC tumours may be graded using the WHO 1973 or WHO 2004 grading systems – both indicating worse prognosis with increasing grade. Most patients diagnosed with NMIBC is initially treated conservatively (sparing the bladder) with curative intent by transurethral resection of bladder tumour (TURBT). NMIBC is seen as a chronic disease requiring frequent follow-up and repeated TURBTs, making it the most expensive of all cancers to treat from diagnosis to death⁵⁻⁸ with additional productivity losses and informal care costs.⁹ Cumulative costs of care are especially high in intermediate- and high-risk NMIBC due to higher risk of progression to MIBC requiring definitive treatment.⁷

Given the high recurrence rates and the risk of progression to MIBC, NMIBC treatment usually involves adjuvant intravesical instillations with chemotherapy or immunotherapy. The timing, treatment duration, and choice of agent for intravesical therapy is guided by a risk categorisation system which is based upon clinical and pathological factors.³ For instance, evidence from high quality systematic reviews and meta-analyses shows that a single immediate post-operative instillation of chemotherapy (IPOIC) is well tolerated and clinically effective in reducing recurrences in low risk patients.¹⁰⁻¹² The European Association of Urology (EAU)³ and the National Institute for Clinical and Healthcare Excellence (NICE)¹³ both recommend that eligible patients receive IPOIC. It is considered cost effective for the NHS.¹³ Intermediate risk patients may also be given repeated chemotherapy instillations, but their timing and frequency remains undefined¹⁴. It is recommended that high risk patients are treated with intravesical bacillus Calmette-Guerin (BCG) immunotherapy or be considered for immediate cystectomy.³ Five-year recurrence and progression rates for patients with stage Ta-T1 bladder cancer treated with 1 to 3 years maintenance BCG are 28-51% and 7-20%, respectively.¹⁵

Why it is important to do this review

Inconsistent outcome reporting (different outcomes in different trials) and variability in outcome reporting (same outcomes reported, but different definitions used) become acutely evident when many bladder cancer trials are included in systematic reviews of intervention effectiveness.^{16–18} Outcome reporting heterogeneity has been highlighted as a concern within evidence-based medicine generally,^{19–22} and has been emphasised as an area for improvement in NMIBC trials by the International Bladder Cancer Group.²³ Heterogeneous outcome reporting and the potential for selective outcome reporting bias in NMIBC trials hinder comparing and contrasting the results of individual trials as well as the publication of unbiased systematic reviews and meta-analyses of the evidence base. As a consequence, making evidence-based recommendations in clinical practice guidelines, translating them into health care policy, and decision-making by clinicians and patients are all hampered.

Developing core outcome set (COS) a solution to reduce outcome heterogeneity, selective outcome reporting bias, and helps to ensure that all trials contribute useable information to the evidence base. A COS is an agreed standardised collection of outcomes which should be measured and reported, as a minimum, in all trials for a specific clinical area.²² ~~Developing a COS is a solution to reduce outcome heterogeneity, selective outcome reporting bias, and helps to ensure that all trials contribute useable information to the evidence base.~~ Our group has registered a bladder cancer COS development project (B-COS) with the Core Outcome Measures for Effectiveness Trials initiative COS register (<http://www.comet-initiative.org/studies/details/1135>), with the intent to create separate COS for three broad categories of disease: NMIBC, MIBC, and metastatic BC. Within each COS we define the scope with regards to the applicable populations and treatments. After defining the scope of a COS, the next step is to identify existing knowledge regarding outcomes. To meet this requirement, we have aimed to systematically review the outcomes reported in NMIBC effectiveness trials. Our systematic review protocol was registered with PROSPERO (https://www.crd.york.ac.uk/prospéro/display_record.php?RecordID=91820). The reviews for the other parts of the project will be reported separately as will the subsequent phases of the COS development projects, involving qualitative interview studies with patients, and consensus studies with key stakeholders such as patients and healthcare professionals using Delphi methods to come to consensus on the core outcomes to be measured in future bladder cancer effectiveness trials and audits.

2. Methods

Aims and objectives

The aim was to systematically review outcomes reported in NMIBC effectiveness trials of adjuvant, prophylactic treatment after TURBT.

The objectives were to systematically review:

1. Outcomes reported
2. Outcome definitions (including time points)
3. Outcome assessment methods

Eligibility Criteria

Types of studies

We included phase III randomised controlled trials (RCTs) comparing different adjuvant instillation treatments after TURBT or trials with TURBT alone as a control arm. We limited to RCTs included in systematic reviews of intervention effectiveness as a pragmatic and efficient way to identify studies

and overview potentially important outcomes. This is a strategy that has been used in published systematic reviews of outcome reporting heterogeneity where the aim is to overview outcome reporting heterogeneity rather than to find every outcome previously reported.^{22,24} All pre phase III trials and all non-randomised designs were excluded. Studies reported only as abstracts were excluded a priori because it was unlikely that all outcomes would be reported in the abstract, and that they would also not provide enough information on the definition and measurement of outcomes reported.

Types of participants

We included studies with adult (≥ 18 years) males and females with histologically confirmed urothelial NMIBC, stage Ta or T1 N0 M0, with or without *carcinoma in situ (CIS)*, and all tumour grades (using any grading system). Studies including paediatric patients and patients with MIBC, clinical N+ or M+ were excluded unless outcomes were separately reported and defined for NMIBC patients.

Types of interventions and comparators

We included RCTs comparing any type of intravesical adjuvant prophylactic treatments after TURBT and RCTs comparing intravesical treatment after TURBT versus TURBT alone. Studies of oral vitamins or mineral supplements were excluded.

Types of Outcomes

We report on all outcomes related to clinical effectiveness including, for example, outcomes related to recurrence, progression, survival and cause of death, local and systemic adverse events and quality of life/patient reported outcomes. Outcome definitions, timepoints, and assessment methods are also reported.

We do not report any estimates of treatment effect for any individual trials and there was no attempt to synthesise aggregated quantitative data.

Literature Search

The literature search was undertaken by an experienced information specialist (CY) using the search criteria specified in Appendix 1. Medline, Embase and Cochrane Database of Systematic Reviews (CDSR) were searched for relevant systematic reviews. We also hand-searched the reference sections of relevant international clinical practice guidelines. We restricted to systematic reviews and RCTs published after 2000 to reflect outcomes reported in the current clinical practice. We excluded non-English studies as a pragmatic consideration due to resource restrictions.

An update search was done on 15th January 2020.

Data collection and analysis

Selection of studies

Following de-duplication, at least two review authors (DC, SM, SS, IO, EV, RC) independently screened the titles and abstracts of identified systematic reviews for eligibility. The full texts of all potentially eligible publications were retrieved and screened independently by two review authors (DC, SM, SS, IO, EV, RC) using a standardised form, linking together multiple records of the same

study in the process. Any disagreements were resolved by discussion or by consulting a senior review author (RS). Once the list of systematic reviews meeting the inclusion criteria were finalised, a second screening process was initiated whereby the studies included in the systematic reviews were screened against our inclusion criteria. Where lists of studies excluded from the systematic reviews were available, we also screened these in case the studies had been excluded for not reporting on outcomes of interest. In such instances the trial may still have met inclusion criteria for our review. The study selection process is described in the PRISMA flow diagram (Figure 1).²⁵

Data extraction and management

A standardised data extraction form was developed and piloted. One review author extracted data and a second review author checked data extractions for accuracy (DC, SM, SS, IO, EV, RC). Any disagreements were resolved by discussion or by consulting a third review author.

Data that were extracted included: the study design; countries and institutions where the data were collected; dates defining start and end of patient recruitment and follow-up; how intervention comparator groups were formed; participant demographic and clinical characteristics; eligibility criteria for participants; the numbers of participants who were included in the study, assigned to each intervention comparator group; description of interventions; study funding sources; and ethical approval. All primary and secondary effectiveness outcomes reported, their definitions, and any outcome measurement instruments used were extracted verbatim.

Assessment of risk of bias in included studies

Risk of bias assessment is not necessary for systematic reviews undertaken for COS development. Some outcomes may be at risk of detection bias depending on whether they are relatively subjective or objective. Although these aspects were extracted under the 'definition' or 'measurement' fields in the data extraction form, this is out of the scope of this phase of our project. They will be investigated in a subsequent phase whereby we will assess the psychometric properties of the various outcome measurements and seek consensus on the most appropriate and feasible definitions and measurements.^{26,27}

Data synthesis

Verbatim outcome names were recoded to common names. This was done by categorising outcomes referring to the same underlying constructs under a common term. For example, "survival rates", "overall survival", "number of deaths at median follow up" and "mortality rate" all refer to the concept of 'overall survival' and were coded as such. The outcome and domain coding process was inductive and iterative. Coded outcomes were further grouped in broader domains using the standardised Williamson and Clarke Taxonomy (W/C Taxonomy).²⁸

3.0 Evidence synthesis

Characteristics of the included studies

Our initial search for relevant systematic reviews yielded 807 abstracts, of which 639 remained after removing duplicates. In total, 100 full-text SRs were assessed and 19 SRs, including 14 meta-analyses, were included. Four SRs included only previously identified RCTs and these SRs were not utilised further (Supplemental table 1). From 15 SRs published between years 2010-2018, 106 full-texts of RCTs were screened and 57 eligible RCTs were finally included (see PRISMA flow diagram, Fig. 1).

An overview of the included studies' populations, stage and grade, instillation treatments and number of outcome domains reported is shown in Table 1. Overall, 32 studies included patients with papillary only tumors, while 25 studies included a mixed population of patients with CIS with/without papillary tumors. There were 11 "single-instillation" trials, 12 "single instillation followed by induction course" trials, 27 "maintenance instillation" trials and 7 trials comparing instillations with different schedules.

In all studies, patients were followed up at regular intervals in the same and largely accepted manner: urinary cytology, cystoscopy and if necessary, by taking biopsies from the urinary bladder.³

Heterogeneity in outcome reporting, detection, and definitions

The outcomes were organised into the 10 domains in the W/C taxonomy [27]: "recurrence", "progression", "treatment response" (for CIS), "cancer-specific survival", "overall survival", "adverse events", "completion/adherence", "treatment failure/change of treatment", "quality of life" and "health economics" (Table2).

As seen in Table 2, tumor related outcomes such as recurrence (98%), progression (74%), treatment response (in CIS studies) (40%), and adverse events (77%) were frequently reported across studies. However, overall (33%) and cancer specific (33%) survival, treatment completion (17%) and treatment change (37%) were less often reported. Quality of Life (3%) and economic outcomes (2%) were rarely reported.

Tumor related outcomes

The heterogeneity in the definition and reporting of recurrence and progression in studies that recruited patients with papillary tumors only, and also treatment response in patients with CIS with or without papillary tumors, are shown in Tables 3 and 4, respectively.

Recurrence

Recurrence was reported in 56 (98%) of 57 trials (Tables 1,3,4), with 35 different verbatim names (Table 5), often related to the definition. The definition of recurrence was missing in 8/56 (14%) studies and in the others, variations of the percent of recurrences at a given time point or as a time to event outcome were used, but no consistent way of defining and measuring recurrence was used overall. Furthermore, in studies that reported both progression and recurrence, progression as the first event was regarded as a recurrence event in 12 studies and in 34 others it was not.

Progression

Of 57 studies, 42 (74 %) reported bladder cancer progression. Definition for progression was given in 41/42 (97%) studies with a large variability in definition. A common threshold for "progression" was $\geq pT2$ in 16 (38%) studies, with 2 of them also classifying CIS as a progression. As an example of inconsistency in verbatims used, "progression to MIBC" was used in the definition in 31/42 (74%) studies, with 22 of those further including metastases. Ta->T1 and T1->MIBC were considered progression in 4/42 (9%) studies (Tables 3 and 4).

Treatment response

Treatment response in patients with CIS was reported in 10 (40%) of 25 studies (Table 2). There was heterogeneity in what time-point was considered to assess the response to treatment. de Reijke et al defined and reported "complete response", "partial response", "no change" and "progression".²⁹ The rest of the studies reported only complete response to treatment.

The time-point to assess complete response varied largely, ranging from 3 months from enrollment up to 12 months.

Eight different outcomes were included in the “Treatment response (for CIS)” domain (Tables 4 and 5).

Treatment relapse after complete response was described in three trials (Table 4).

Death

A survival outcome was reported in 44/57 (40%) of studies; equally common were cancer-specific survival and overall survival, each reported in 19 (33%) studies. Ten and eleven different verbatim names were used to report overall survival and cancer-specific survival, respectively (Tables 2, 5).

Adverse events

Adverse events (AEs) were heterogeneously defined. In 12 of the 44 studies (27%) reporting AEs, there was no definition of an AE, and overall 24 different definitions/instruments were used. Studies reporting AEs used unique systems to categorise the type of AE or grade the severity of the AEs, and made no reference to a standardised reporting system. Across 10 studies, 3 standardised AE reporting instruments were used, but these did not include some of the most relevant AEs for intravesical instillations:

- NCI-CTCAE (Common Terminology Criteria of Adverse Events),
- WHO toxicity grading scale,
- WHO-ART (1979 WHO Adverse Reaction Terminology)

Adverse events were further grouped in numerous ways, e.g. local or systemic toxicity, constitutional symptoms, laboratory abnormality, death, and treatment interruption due to AEs (Table 5). Detailed lists of how AEs were described and reported are provided in Supplementary table 2.

In 25 of the 44 studies (57%) specific AEs were not listed; instead, authors reported either only local toxicities, or major/severe/more common side-effects or AEs that resulted in treatment interruption. Five of these 25 studies did not report the list of individual toxicities at all; instead, authors presented only the frequency and percentage [n (%)] of any AEs which occurred. Furthermore, poor treatment compliance related to AEs was not consistently reported.

Completion/adherence

Adherence to completion of all planned instillations was at least partially reported in 10/57 (17%) studies: six studies concerning maintenance instillations, two “induction course” studies, and two studies comparing induction to maintenance. None of the single-instillation studies reported completion rates. Four studies gave a comprehensive overview of the reasons for treatment discontinuation. The author definitions for instillation treatment completion are reported in Table 5.

Treatment failure/change of treatment

21/57 studies (37%) reported treatment failure and/or the need to change from instillations to a different treatment. 21 studies specified the treatment that was given after instillations were discontinued:

- radical cystectomy (RC) (14/21 studies)
- RC and/or radiotherapy (RT) (4/12 studies)

- TURBT (1/21)
- RC, TURBT+RT, chemotherapy (1/21)
- “non-allowed instillations” (1/21)

Global quality of life

Two studies measured and reported patient experience during the instillations; Koga et al by measuring QoL, and Huang et al by evaluating instillation related pain/irritation.^{30,31}

In the study by Koga et al, QoL was assessed according to the Japanese version of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) v2.0. QoL was assessed before induction therapy, after the 5th instillation of induction therapy, 4 weeks after the completion of induction therapy, and 14 months after randomization.³⁰

Huang et al evaluated the effect of hyaluronic acid in reducing pirarubicin instillation related side-effects. A visual analog scale (VAS) was used daily to evaluate pain.³¹

Resource use (health economics)

Only one study evaluated the costs related to the treatment. Berrum-Svennung et al randomized BC patients to one instillation of epirubicin or placebo after TURBT and evaluated cancer recurrences. They also calculated the cost of delivering a single instillation during the initial treatment and as first recurrences occurred.³²

Discussion

This is the first study to systematically and comprehensively overview the extent of outcome reporting, measurement, and definition heterogeneity in the setting of adjuvant treatments for NMIBC.

Recurrence was frequently reported in the included RCTs; yet, some studies did not define it. In those that did, there was variability in the names that were used ~~(for example “disease-free interval”, “disease-free survival”, “time to recurrence”, and “recurrence free survival”)~~, the definitions and the reporting, ~~with some reporting hazard ratios or median time to event, or event rates at inconsistent time points (e.g. 1,2,3,5,10 years)~~. Most concerning, however, was the variation in how progression was handled in the analysis of recurrence. In studies where progression as the first event was counted as a recurrence, the measure provided is qualitatively and quantitatively different from those where recurrence was more narrowly defined as the re-appearance of a non-muscle invasive tumour. To overlook this subtlety runs the risk of not comparing like with like across studies, or statistically pooling aggregated results in a potentially misleading way.

Progression was also frequently reported, but again the definitions were inconsistent across trials, ~~with some using progression to MIBC as the threshold, while others considered an increase in stage from Ta-T1 and/or an increase in grade as progression~~. Worsening of the disease leads to a change in treatment strategy, and that was also inconsistently reported. It is also crucial to point out whether assessment of progression has been made based on imaging (e.g. CT or MRI), TURBT or radical cystectomy. As only four studies gave a comprehensive overview of reasons to change the treatment strategy, there is a high risk of getting misleading results. If prior to progression, patients die due to an unrelated cause, or undergo cystectomy (for example due to recurrent high grade T1 disease),

then the progression rates at specific time points will be different according to whether the death and cystectomy have been counted as a competing risk (cumulative incidence function) or simply as censored (Kaplan-Meier curve). Equally important is to highlight how patients are followed for the efficacy outcomes in case the treatment has been stopped due to side-effects. There may also be a difference in outcomes according to whether the results are reported in all randomized patients (intent to treat analysis) or only in eligible patients who have been treated according to the protocol (per protocol analysis).

Treatment response in patients with CIS in specific was evaluated and reported in only 40% of studies. The rest of the studies recruiting patients with CIS considered CIS as papillary tumors, and reported only recurrence or/and progression. However, CIS additional diagnostic challenges and may have a very different disease course than papillary tumors do: as such, separate approaches to measure and define their outcomes should be applied.²³

The most heterogenous outcome was AEs, evident in the many categorizations and instruments used to record AEs, and in the system level subgroupings chosen by trialists. Unfortunately, many of these were not optimal for instillation-related AEs. Whilst in some instances it may be possible for systematic reviewers to recode lists of AEs (if they are provided) to a common standardized toxicity classification system, this is a poor excuse for lack of standardization in primary trials and needlessly adds time and complexity to the critical interpretation of the evidence base. Poor treatment compliance reporting is likely to confound other cancer related outcomes such as recurrence, progression and overall survival.

Perhaps the most alarming finding is that QoL is conspicuously missing. Instillation treatments are demanding for patients and it would be very important to understand all the consequences (both oncological and QoL-related) for patients before the decision about treatment is made. A recent investigation of QoL in bladder cancer patients compared to a matched sample of older adults without bladder cancer in a US population found significant declines in health-related QoL (HRQoL) scores over time in the physical, mental and social components of the SF-36.³³ The EORTC Quality of Life Group also developed an externally validated QLQ-BLS24 questionnaire for NMIBC.³⁴ In a systematic review, Mason and colleagues used the COSMIN checklist to evaluate the psychometric properties of PROMs used in bladder cancer populations, of which two of the 15 included PROMs were NMIBC-specific (QLQ-BLS24 and CAVICAVEMNI).^{35,36} Of note, they found that no existing PROM stood out as the most appropriate measure of QoL in any bladder cancer populations and although further validation studies are required generic PROMs, cancer-generic PROMs and bladder cancer-specific PROMs will currently provide the most robust picture. This is a very important study to a subsequent phase of our COS development as most existing cancer COS have included QoL and it is anticipated NMIBC patients will also prioritise this, encompassing urinary, bowel and sexual function, as a critically important outcome domains.

Without having included NMIBC patients in a qualitative study of their experiences of bladder cancer and its treatments, it cannot yet be known which outcomes are of most importance to them, or if they are adequately captured in current trials, but it is discouraging that so few trials routinely include patient reported outcome measures (PROMs).

Health economics was considered in only one RCT, which calculated costs of single instillation.³² Bladder cancer, especially NMIBC, contributes significantly to healthcare costs due to intense surveillance strategies and its potential to recur and progress.^{8,37} This should be considered when treatments and outcomes are compared.

Kamat et al provided recommendations on NMIBC intervention trial designs, eligibility criteria, and 'clinically meaningful' effect size thresholds for outcomes.²³ Likewise, Lamm et al suggested a change in definition for progression in NMIBC.³⁸ These initiatives are important to bear in mind for

subsequent phases of our project. Once the outcomes considered core by all stakeholders (e.g. patients, urologists, oncologists, nurses, payers, methodologists) are known (i.e. *what* to measure)²² then we will turn attention to definitions and measurement tools (i.e. *how* to measure)³⁹ whilst again including key stakeholders. Importantly, these initiatives, in conjunction with ours, show that there is an acknowledgement of problems with the evidence base and a desire to do improvements.

Limitations

The decision to exclude phase I and II trials (phases before determining the therapeutic effect of the drug) and to exclude all non-randomised designs may have limited the chance to capture longer-term and patient reported outcomes relating to function and QoL. However, in subsequent phases of the project, such as in Delphi survey and consensus meetings, participants will have an opportunity to propose 'new' outcomes not already considered for prioritisation, therefore we consider that the risk of having missed outcomes is minimal, and that we have carried out a pragmatic trade-off against the resource implication of including all study designs.

Conclusions

We have shown that there is inconsistency in outcome reporting and variation in definitions in randomized trials comparing adjuvant treatments in NMIBC patients. This situation makes comparing the results of individual studies difficult, and makes their statistical combination challenging, impossible, or inappropriate; hence, providing summaries of the evidence which are, at best, unwieldy and at worst misleading, making evidence-based treatment recommendations difficult. A core outcome set, incorporating the views of a variety of stakeholders such as urologists, oncologists, methodologists and, most importantly, patients, is urgently required.

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Erik Veskimae - performance of work; interpretation or analysis of data; writing the article.

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Conflict of interest statements

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References

1. Richters A, Aben KKH, Kiemenev LALM. The global burden of urinary bladder cancer: an update. *World J Urol.* 2020;38(8):1895-1904. doi:10.1007/s00345-019-02984-4
2. van Rhijn BWG, Burger M, Lotan Y, et al. Recurrence and Progression of Disease in Non-Muscle-Invasive Bladder Cancer: From Epidemiology to Treatment Strategy. *Eur Urol.* 2009;56(3):430-442. doi:10.1016/j.eururo.2009.06.028
3. Babjuk M, Burger M, Compérat EM, et al. European Association of Urology Guidelines on Non-muscle-invasive Bladder Cancer (TaT1 and Carcinoma In Situ) - 2019 Update. *Eur Urol.* 2019;76(5):639-657. doi:10.1016/j.eururo.2019.08.016

4. Brierley J, Gospodarowicz M, Wittekind C. *TNM Classification of Malignant Tumours, 8th Edition*. Wiley-Blackwell; 2017.
5. Botteman MF, Pashos CL, Redaelli A, Laskin B, Hauser R. The health economics of bladder cancer: A comprehensive review of the published literature. *Pharmacoeconomics*. 2003;21(18):1315-1330. doi:10.1007/BF03262330
6. Riley GF, Potosky AL, Lubitz JD, Kessler LG. Medicare payments from diagnosis to death for elderly cancer patients by stage at diagnosis. *Med Care*. 1995;33(8):828-841. doi:10.1097/00005650-199508000-00007
7. Mossanen M, Wang Y, Szymaniak J, et al. Evaluating the cost of surveillance for non-muscle-invasive bladder cancer: an analysis based on risk categories. *World J Urol*. 2019;37(10):2059-2065. doi:10.1007/s00345-018-2550-x
8. Svatek RS, Hollenbeck BK, Holmäng S, et al. The Economics of Bladder Cancer: Costs and Considerations of Caring for This Disease. *Eur Urol*. 2014;66(2):253-262. doi:10.1016/j.eururo.2014.01.006
9. Leal J, Luengo-Fernandez R, Sullivan R, Witjes JA. Economic Burden of Bladder Cancer Across the European Union. *Eur Urol*. 2016;69(3):438-447. doi:10.1016/j.eururo.2015.10.024
10. Sylvester RJ, Oosterlinck W, Holmang S, et al. Systematic Review and Individual Patient Data Meta-analysis of Randomized Trials Comparing a Single Immediate Instillation of Chemotherapy After Transurethral Resection with Transurethral Resection Alone in Patients with Stage pTa-pT1 Urothelial Carcinoma of the Bladder: Which Patients Benefit from the Instillation? *Eur Urol*. 2016;69(2):231-244. doi:10.1016/j.eururo.2015.05.050
11. 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. *Eur Urol*. 2013;64(3):421-430. doi:10.1016/j.eururo.2013.06.009
12. Abern MR, Owusu RA, Anderson MR, Rampersaud EN, Inman BA. Perioperative intravesical chemotherapy in non-muscle-invasive bladder cancer: a systematic review and meta-analysis. *J Natl Compr Cancer Netw JNCCN*. 2013;11(4):477-484. doi:10.6004/jnccn.2013.0060
13. Bladder cancer: diagnosis and management of bladder cancer: © NICE (2015) Bladder cancer: diagnosis and management of bladder cancer. *BJU Int*. 2017;120(6):755-765. doi:10.1111/bju.14045
14. Sylvester RJ, Oosterlinck W, Witjes JA. The Schedule and Duration of Intravesical Chemotherapy in Patients with Non–Muscle-Invasive Bladder Cancer: A Systematic Review of the Published Results of Randomized Clinical Trials. *Eur Urol*. 2008;53(4):709-719. doi:10.1016/j.eururo.2008.01.015
15. Cambier S, Sylvester RJ, Collette L, et al. EORTC Nomograms and Risk Groups for Predicting Recurrence, Progression, and Disease-specific and Overall Survival in Non-Muscle-invasive Stage Ta-T1 Urothelial Bladder Cancer Patients Treated with 1-3 Years of Maintenance Bacillus Calmette-Guérin. *Eur Urol*. 2016;69(1):60-69. doi:10.1016/j.eururo.2015.06.045
16. Hernández V, Espinos EL, Dunn J, et al. Oncological and functional outcomes of sexual function–preserving cystectomy compared with standard radical cystectomy in men: A systematic

review. *Urol Oncol Semin Orig Investig*. 2017;35(9):539.e17-539.e29.
doi:10.1016/j.urolonc.2017.04.013

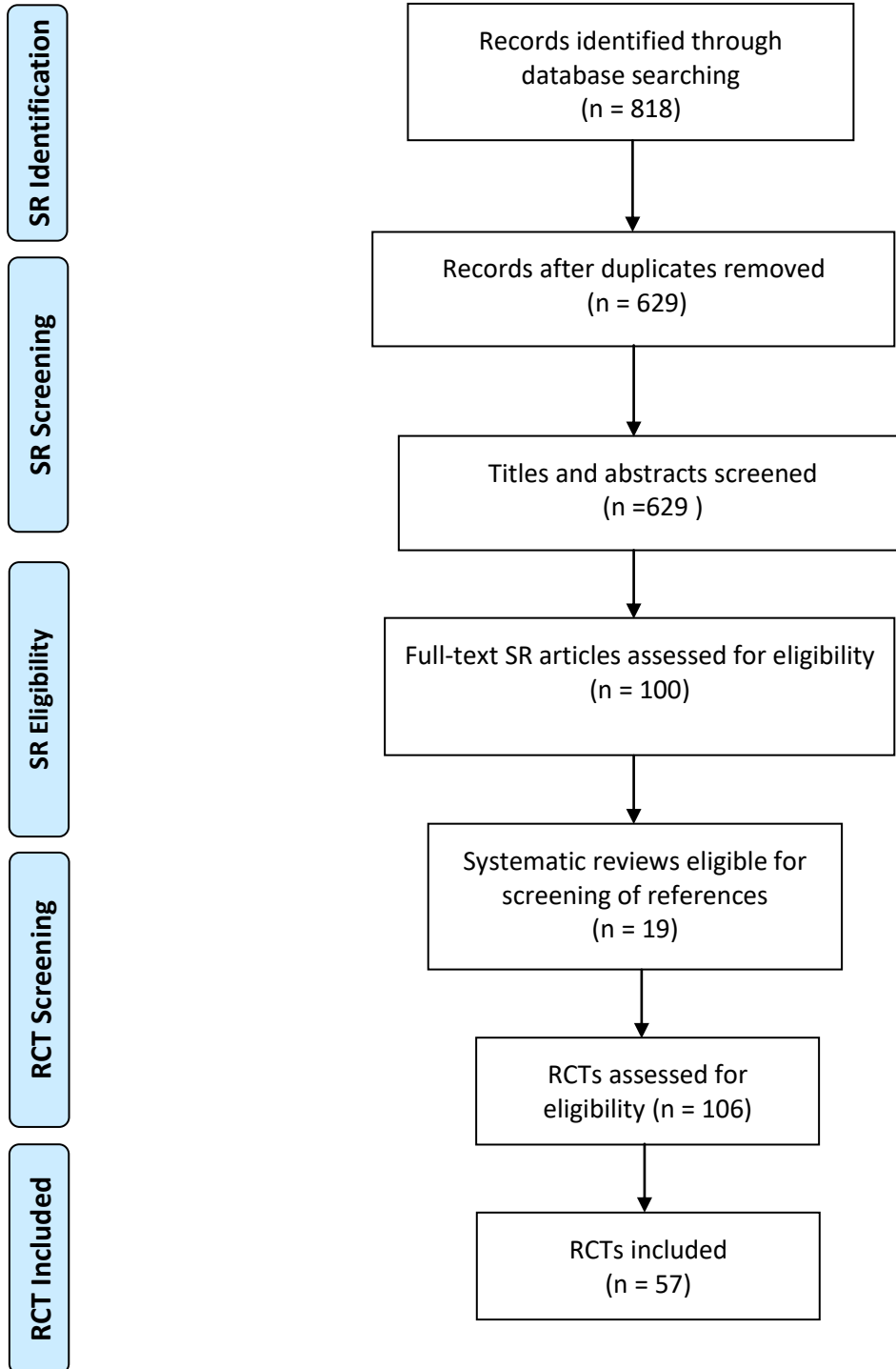
17. Veskimäe E, Neuzillet Y, Rouanne M, et al. Systematic review of the oncological and functional outcomes of pelvic organ-preserving radical cystectomy (RC) compared with standard RC in women who undergo curative surgery and orthotopic neobladder substitution for bladder cancer. *BJU Int*. 2017;120(1):12-24. doi:10.1111/bju.13819
18. Bruins HM, Veskimäe E, Hernandez V, et al. The impact of the extent of lymphadenectomy on oncologic outcomes in patients undergoing radical cystectomy for bladder cancer: a systematic review. *Eur Urol*. 2014;66(6):1065-1077. doi:10.1016/j.eururo.2014.05.031
19. Williamson PR, Altman DG, Blazeby JM, et al. Developing core outcome sets for clinical trials: issues to consider. *Trials*. 2012;13:132. doi:10.1186/1745-6215-13-132
20. Williamson P, Altman D, Blazeby J, Clarke M, Gargon E. Driving up the Quality and Relevance of Research Through the Use of Agreed Core Outcomes. *J Health Serv Res Policy*. 2012;17(1):1-2. doi:10.1258/jhsrp.2011.011131
21. Tunis SR, Clarke M, Gorst SL, et al. Improving the relevance and consistency of outcomes in comparative effectiveness research. *J Comp Eff Res*. 2016;5(2):193-205. doi:10.2217/ce-2015-0007
22. Williamson PR, Altman DG, Bagley H, et al. The COMET Handbook: version 1.0. *Trials*. 2017;18(Suppl 3):280. doi:10.1186/s13063-017-1978-4
23. Kamat AM, Sylvester RJ, Böhle A, et al. Definitions, End Points, and Clinical Trial Designs for Non-Muscle-Invasive Bladder Cancer: Recommendations From the International Bladder Cancer Group. *J Clin Oncol Off J Am Soc Clin Oncol*. 2016;34(16):1935-1944. doi:10.1200/JCO.2015.64.4070
24. Bruce I, Harman N, Williamson P, et al. The management of Otitis Media with Effusion in children with cleft palate (mOMEnt): a feasibility study and economic evaluation. *Health Technol Assess*. 2015;19(68):1-374. doi:10.3310/hta19680
25. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6(7):e1000097. doi:10.1371/journal.pmed.1000097
26. Prinsen CAC, Vohra S, Rose MR, et al. How to select outcome measurement instruments for outcomes included in a “Core Outcome Set” – a practical guideline. *Trials*. 2016;17(1):449. doi:10.1186/s13063-016-1555-2
27. Mokkink LB, Terwee CB, Patrick DL, et al. The COSMIN checklist for assessing the methodological quality of studies on measurement properties of health status measurement instruments: an international Delphi study. *Qual Life Res*. 2010;19(4):539-549. doi:10.1007/s11136-010-9606-8
28. Dodd S, Clarke M, Becker L, Mavergames C, Fish R, Williamson PR. A taxonomy has been developed for outcomes in medical research to help improve knowledge discovery. *J Clin Epidemiol*. 2018;96:84-92. doi:10.1016/j.jclinepi.2017.12.020
29. de REIJKE TM, Kurth KH, Sylvester RJ, et al. BACILLUS CALMETTE-GUERIN VERSUS EPIRUBICIN FOR PRIMARY, SECONDARY OR CONCURRENT CARCINOMA IN SITU OF THE BLADDER: RESULTS OF A EUROPEAN ORGANIZATION FOR THE RESEARCH AND TREATMENT OF CANCER—GENITO-URINARY GROUP PHASE III TRIAL (30906). *J Urol*. 2005;173(2):405-409.

doi:10.1097/01.ju.0000150425.09317.67

30. Koga H, Ozono S, Tsushima T, et al. Maintenance intravesical bacillus Calmette-Guérin instillation for Ta, T1 cancer and carcinoma in situ of the bladder: Randomized controlled trial by the BCG Tokyo Strain Study Group: Maintenance intravesical BCG. *Int J Urol*. 2010;17(9):759-766. doi:10.1111/j.1442-2042.2010.02584.x
31. Huang W, Wang F, Wu C, Hu W. Efficacy and safety of pirarubicin combined with hyaluronic acid for non-muscle invasive bladder cancer after transurethral resection: a prospective, randomized study. *Int Urol Nephrol*. 2015;47(4):631-636. doi:10.1007/s11255-015-0940-1
32. Berrum-Svennung I, Granfors T, Jahnsen S, Boman H, Holmäng S. A Single Instillation of Epirubicin After Transurethral Resection of Bladder Tumors Prevents Only Small Recurrences. *J Urol*. 2008;179(1):101-106. doi:10.1016/j.juro.2007.08.166
33. Smith AB, Jaeger B, Pinheiro LC, et al. Impact of bladder cancer on health-related quality of life. *BJU Int*. 2018;121(4):549-557. doi:10.1111/bju.14047
34. Blazeby JM, Hall E, Aaronson NK, et al. Validation and Reliability Testing of the EORTC QLQ-NMIBC24 Questionnaire Module to Assess Patient-reported Outcomes in Non-Muscle-invasive Bladder Cancer. *Eur Urol*. 2014;66(6):1148-1156. doi:10.1016/j.eururo.2014.02.034
35. Mason SJ, Catto JWF, Downing A, Bottomley SE, Glaser AW, Wright P. Evaluating patient-reported outcome measures (PROMs) for bladder cancer: a systematic review using the COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) checklist. *BJU Int*. 2018;122(5):760-773. doi:10.1111/bju.14368
36. Abáigar-Pedraza I, Megías-Garrigós J, Sánchez-Payá J. Cuestionario de calidad de vida para pacientes con cáncer de vejiga no músculo invasivo. *Actas Urol Esp*. 2016;40(4):251-257. doi:10.1016/j.acuro.2015.12.001
37. Cox E, Saramago P, Kelly J, et al. Effects of Bladder Cancer on UK Healthcare Costs and Patient Health-Related Quality of Life: Evidence From the BOXIT Trial. *Clin Genitourin Cancer*. 2020;18(4):e418-e442. doi:10.1016/j.clgc.2019.12.004
38. Lamm D, Persad R, Brausi M, et al. Defining progression in nonmuscle invasive bladder cancer: it is time for a new, standard definition. *J Urol*. 2014;191(1):20-27. doi:10.1016/j.juro.2013.07.102
39. COSMIN handbook.
https://fac.ksu.edu.sa/sites/default/files/cosmin_checklist_manual_v9.pdf.



PRISMA 2009 Flow Diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Author	Titel of the systematic review	Study design
Shelley 2010	Intravesical therapy for superficial bladder cancer: a systematic review of randomised trials and meta-analyses	SR+MA
Shang 2011	Intravesical Bacillus Calmette-Guérin versus epirubicin for Ta and T1 bladder cancer	SR+MA
Jones 2012	Intravesical gemcitabine for non-muscle invasive bladder cancer	SR
Perlis 2013	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	SR+MA
Li 2014	Long-term versus short-term introvesical chemotherapy in patients with non-muscle-invasive bladder cancer: a systematic review and meta-analysis of the published results of randomized clinical trials	SR+MA
Zeng 2015	Low-Dose Versus Standard Dose of Bacillus Calmette-Guerin in the Treatment of Nonmuscle Invasive Bladder Cancer: A Systematic Review and Meta-Analysis	SR+MA
Cui 2016	Combination of Intravesical Chemotherapy and Bacillus Calmette-Guerin Versus Bacillus Calmette-Guerin Monotherapy in Intermediate- and High-risk Nonmuscle Invasive Bladder Cancer: A Systematic Review and Meta-analysis	SR+MA
Sylvester 2016	Systematic Review and Individual Patient Data Meta-analysis of Randomized Trials Comparing a Single Immediate Instillation of Chemotherapy After Transurethral Resection with Transurethral Resection Alone in Patients with Stage pTa-pT1	SR+IPD-MA

	Urothelial Carcinoma of the Bladder: Which Patients Benefit from the Instillation?	
Chou 2017	Intravesical Therapy for the Treatment of Nonmuscle Invasive Bladder Cancer: A Systematic Review and Meta-Analysis	SR+MA
Shepherd 2017	Intravesical Bacillus Calmette-Guérin with interferon-alpha versus intravesical Bacillus Calmette-Guérin for treating non-muscle-invasive bladder cancer	SR+MA
Jung 2017	Intravesical electromotive drug administration for non-muscle invasive bladder cancer	SR
Quan 2017	Dose, duration and strain of bacillus Calmette-Guerin in the treatment of nonmuscle invasive bladder cancer: Meta-analysis of randomized clinical trials	SR+MA
Boehm 2017	Efficacy of bacillus Calmette-Guérin Strains for Treatment of Nonmuscle Invasive Bladder Cancer: A Systematic Review and Network Meta-Analysis	SR+MA
Mahran 2018	Bladder irrigation after transurethral resection of superficial bladder cancer: a systematic review of the literature	SR+MA
Van Hemelrijck 201	Patient-reported outcomes in randomised clinical trials of bladder cancer: an updated systematic review	SR
Uhlig 2018	Gender-specific Differences in Recurrence of Non-muscle-invasive Bladder Cancer: A Systematic Review and Meta-analysis	SR+MA
Chen 2018	Maintenance versus non-maintenance intravesical Bacillus Calmette-Guerin instillation for non-muscle invasive bladder cancer: A systematic review and meta-analysis of randomized clinical trials	SR+MA
Tabayoyong 2018	Systematic Review on the Utilization of Maintenance Intravesical Chemotherapy in the Management of Non-muscle-invasive Bladder Cancer	SR
Deng 2017	Systematic Review and Cumulative Analysis of the Combination of Mitomycin C plus Bacillus Calmette-Guérin (BCG) for Non-Muscle-Invasive Bladder Cancer	SR

RCT's retrieved
Kaasinen 2000
Bilen 2000
Sekine 2001
Au 2001
De Reijke 2005
Hinotsu 2006
Van der Meijden 2001
Lamm 2000
Palou 2001
Ojea 2007
Friedrich 2007
Di Stasi 2006
Di Stasi 2003
Cheng 2005
Sylvester 2010
Porena 2010
Böhle 2009
Rajala 2002
Okamura 2002
EL-Ghobashy 2007
Berrum-Svennung 2008
Gudjonsson 2009
De Nunzio 2011
Nomata 2002
Koga 2004
Kuroda 2004
Isbarn 2008 (part1 & 2)
Hendricksen 2008
Seretta 2010
Mitsumori 2004
Inamoto 2013
Vijjan 2006
Agrawal 2007
Oddens 2013
Kaasinen 2003
Cai 2008
Gülpınar 2012
Solsona 2015
Barghi 2006

Arends 2016
Neples 2010
Di Stasi 2011
Martinez-Pinneiro 2002
Martinez-Pinneiro 2005
Sengiku 2013
Rentsch 2014
Hinotsu 2011
Martinez-Pineiro 2015
Nakai 2016
Gårdmark 2007
Hemdan 2014
Järvinen 2012
Järvinen 2009
Koga 2010
Bijalwan 2017
Onishi 2017

Huang 2015
RCTs ALREADY INCLUDED
RCTs ALREADY INCLUDED
RCTs ALREADY INCLUDED
RCTs ALREADY INCLUDED

Author	Titel of the systematic review	Study design	RCT's retrieved
Shelley 2010 ¹	Intravesical therapy for superficial bladder cancer: a systematic review of randomised trials and meta-analyses	SR+MA	Kaasinen 2000 ²
			Bilen 2000 ³
			Sekine 2001 ⁴
			Au 2001 ⁵
			De Reijke 2005 ⁶
			Hinotsu 2006 ⁷
			Van der Meijden 2001 ⁸
			Lamm 2000 ⁹
			Palou 2001 ¹⁰
			Ojea 2007 ¹¹
			Friedrich 2007 ¹²
			Di Stasi 2006 ¹³
			Di Stasi 2003 ¹⁴
Shang 2011 ¹⁵	Intravesical Bacillus Calmette-Guérin versus epirubicin for Ta and T1 bladder cancer	SR+MA	Cheng 2005 ¹⁶
			Sylvester 2010 ¹⁷
Jones 2012 ¹⁸	Intravesical gemcitabine for non-muscle invasive bladder cancer	SR	Porena 2010 ¹⁹
			Böhle 2009 ²⁰
Perlis 2013 ²¹	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	SR+MA	Rajala 2002 ²²
			Okamura 2002 ²³
			EL-Ghobashy 2007 ²⁴
			Berrum-Svennung 2008 ²⁵
			Gudjonsson 2009 ²⁶
			De Nunzio 2011 ²⁷
Li 2014 ²⁸	Long-term versus short-term introvesical chemotherapy in patients with non-muscle-invasive bladder cancer: a systematic review and meta-analysis of the published results of randomized clinical trials	SR+MA	Nomata 2002 ²⁹
			Koga 2004 ³⁰
			Kuroda 2004 ³¹
			Isbarn 2008 (part1 & 2) ³²
			Hendricksen 2008 ³³
			Serretta 2010 ³⁴
			Mitsumori 2004 ³⁵
Zeng 2015 ³⁶	Low-Dose Versus Standard Dose of Bacillus Calmette-Guerin in the Treatment of Nonmuscle Invasive Bladder Cancer: A Systematic Review and Meta-Analysis	SR+MA	Inamoto 2013 ³⁷
			Vijjan 2006 ³⁸
			Agrawal 2007 ³⁹
			Oddens 2013 ⁴⁰
Cui 2016 ⁴¹	Combination of Intravesical Chemotherapy and Bacillus Calmette-Guerin Versus Bacillus Calmette-Guerin Monotherapy in Intermediate- and High-risk Nonmuscle Invasive Bladder Cancer: A Systematic Review and Meta-analysis	SR+MA	Kaasinen 2003 ⁴²
			Cai 2008 ⁴³
			Gülpınar 2012 ⁴⁴
			Solsona 2015 ⁴⁵

Sylvester 2016 ⁴⁶	Systematic Review and Individual Patient Data Meta-analysis of Randomized Trials Comparing a Single Immediate Instillation of Chemotherapy After Transurethral Resection with Transurethral Resection Alone in Patients with Stage pTa-pT1 Urothelial Carcinoma of the Bladder: Which Patients Benefit from the Instillation?	SR+IPD-MA	Barghi 2006 ⁴⁷
Chou 2017 ⁴⁸	Intravesical Therapy for the Treatment of Nonmuscle Invasive Bladder Cancer: A Systematic Review and Meta-Analysis	SR+MA	Arends 2016 ⁴⁹
Shepherd 2017 ⁵⁰	Intravesical Bacillus Calmette-Guérin with interferon-alpha versus intravesical Bacillus Calmette-Guérin for treating non-muscle-invasive bladder cancer	SR+MA	Nepple 2010 ⁵¹
Jung 2017 ⁵²	Intravesical electromotive drug administration for non-muscle invasive bladder cancer	SR	Di Stasi 2011 ⁵³
Quan 2017 ⁵⁴	Dose, duration and strain of bacillus Calmette-Guerin in the treatment of nonmuscle invasive bladder cancer: Meta-analysis of randomized clinical trials	SR+MA	Martinez-Pinneiro 2002 ⁵⁵ Martinez-Pinneiro 2005 ⁵⁶ Sengiku 2013 Rentsch 2014 Hinotsu 2011 Martinez-Pineiro 2015 ⁵⁷ Nakai 2016 ⁵⁸
Boehm 2017 ⁵⁹	Efficacy of bacillus Calmette-Guérin Strains for Treatment of Nonmuscle Invasive Bladder Cancer: A Systematic Review and Network Meta-Analysis	SR+MA	Gårdmark 2007 ⁶⁰ Hemdan 2014 ⁶¹ Järvinen 2012 ⁶² Järvinen 2009 ⁶³ Koga 2010 ⁶⁴
Mahran 2018 ⁶⁵	Bladder irrigation after transurethral resection of superficial bladder cancer: a systematic review of the literature	SR+MA	Bijalwan 2017 ⁶⁶ Onishi 2017 ⁶⁷
Van Hemelrijck 2019 ⁶⁸	Patient-reported outcomes in randomised clinical trials of bladder cancer: an updated systematic review	SR	Huang 2015 ⁶⁹
Uhlig 2018 ⁷⁰	Gender-specific Differences in Recurrence of Non-muscle-invasive Bladder Cancer: A Systematic Review and Meta-analysis	SR+MA	RCTs ALREADY INCLUDED

Chen 2018 ⁷¹	Maintenance versus non-maintenance intravesical Bacillus Calmette-Guerin instillation for non-muscle invasive bladder cancer: A systematic review and meta-analysis of randomized clinical trials	SR+MA	RCTs ALREADY INCLUDED
Tabayoyong 2018 ⁷²	Systematic Review on the Utilization of Maintenance Intravesical Chemotherapy in the Management of Non-muscle-invasive Bladder Cancer	SR	RCTs ALREADY INCLUDED
Deng 2017 ⁷³	Systematic Review and Cumulative Analysis of the Combination of Mitomycin C plus Bacillus Calmette-Guérin (BCG) for Non-Muscle-Invasive Bladder Cancer	SR	RCTs ALREADY INCLUDED

SR- systematic review; MA- meta-analysis;

REFERENCES

- Shelley MD, Mason MD, Kynaston H. Intravesical therapy for superficial bladder cancer: A systematic review of randomised trials and meta-analyses. *Cancer Treatment Reviews*. 2010;36(3):195-205. doi:10.1016/j.ctrv.2009.12.005
- Kaasinen E, Rintala E, Pere A-K, et al. WEEKLY MITOMYCIN C FOLLOWED BY MONTHLY BACILLUS CALMETTE-GUERIN OR ALTERNATING MONTHLY INTERFERON- α 2B AND BACILLUS CALMETTE-GUERIN FOR PROPHYLAXIS OF RECURRENT PAPILLARY SUPERFICIAL BLADDER CARCINOMA. *Journal of Urology*. 2000;164(1):47-52. doi:10.1016/S0022-5347(05)67446-0
- Bilen CYu, Ozen H, Aki. FAZI I T, AygUn C, Ekici S, Kendi S. Clinical experience with BCG alone versus BCG plus epirubicin. *Int J Urol*. 2000;7(6):206-209. doi:10.1046/j.1442-2042.2000.00176.x
- Sekine H, Ohya K, Kojima S, Igarashi K, Fukui I. Equivalent efficacy of mitomycin C plus doxorubicin instillation to bacillus Calmette-Guerin therapy for carcinoma in situ of the bladder. *Int J Urol*. 2001;8(9):483-486. doi:10.1046/j.1442-2042.2001.00355.x
- Au JL, Badalament RA, Wientjes MG, et al. Methods to improve efficacy of intravesical mitomycin C: results of a randomized phase III trial. *J Natl Cancer Inst*. 2001;93(8):597-604. doi:10.1093/jnci/93.8.597
- de REIJE TM, Kurth KH, Sylvester RJ, et al. BACILLUS CALMETTE-GUERIN VERSUS EPIRUBICIN FOR PRIMARY, SECONDARY OR CONCURRENT CARCINOMA IN SITU OF THE BLADDER: RESULTS OF A EUROPEAN ORGANIZATION FOR THE RESEARCH AND TREATMENT OF CANCER—GENITO-URINARY GROUP PHASE III TRIAL (30906). *Journal of Urology*. 2005;173(2):405-409. doi:10.1097/01.ju.0000150425.09317.67
- Hinotsu S, Akaza H, Isaka S, et al. Sustained prophylactic effect of intravesical bacille Calmette-Guérin for superficial bladder cancer: A smoothed hazard analysis in a randomized prospective study. *Urology*. 2006;67(3):545-549. doi:10.1016/j.urology.2005.09.045
- van der Meijden AP, Brausi M, Zambon V, et al. Intravesical instillation of epirubicin, bacillus Calmette-Guerin and bacillus Calmette-Guerin plus isoniazid for intermediate and high risk Ta, T1 papillary carcinoma of the bladder: a European Organization for Research and Treatment of Cancer genito-urinary group randomized phase III trial. *J Urol*. 2001;166(2):476-481. doi:10.1097/00005392-200108000-00016

9. Lamm DL, Blumenstein BA, Crissman JD, et al. MAINTENANCE BACILLUS CALMETTE-GUERIN IMMUNOTHERAPY FOR RECURRENT TA, T1 AND CARCINOMA IN SITU TRANSITIONAL CELL CARCINOMA OF THE BLADDER: A RANDOMIZED SOUTHWEST ONCOLOGY GROUP STUDY. *Journal of Urology*. 2000;163(4):1124-1129. doi:10.1016/S0022-5347(05)67707-5
10. Palou J, Laguna P, Millán-Rodríguez F, Hall RR, Salvador-Bayarri J, Vicente-Rodríguez J. Control group and maintenance treatment with bacillus Calmette-Guerin for carcinoma in situ and/or high grade bladder tumors. *J Urol*. 2001;165(5):1488-1491.
11. Ojea A, Nogueira JL, Solsona E, et al. A Multicentre, Randomised Prospective Trial Comparing Three Intravesical Adjuvant Therapies for Intermediate-Risk Superficial Bladder Cancer: Low-Dose Bacillus Calmette-Guerin (27 mg) versus Very Low-Dose Bacillus Calmette-Guerin (13.5 mg) versus Mitomycin C. *European Urology*. 2007;52(5):1398-1406. doi:10.1016/j.eururo.2007.04.062
12. Friedrich MG, Pichlmeier U, Schwaibold H, Conrad S, Huland H. Long-Term Intravesical Adjuvant Chemotherapy Further Reduces Recurrence Rate Compared with Short-Term Intravesical Chemotherapy and Short-Term Therapy with Bacillus Calmette-Guérin (BCG) in Patients with Non-Muscle-Invasive Bladder Carcinoma. *European Urology*. 2007;52(4):1123-1130. doi:10.1016/j.eururo.2007.02.063
13. Di Stasi SM, Giannantoni A, Giurioli A, et al. Sequential BCG and electromotive mitomycin versus BCG alone for high-risk superficial bladder cancer: a randomised controlled trial. *Lancet Oncol*. 2006;7(1):43-51. doi:10.1016/S1470-2045(05)70472-1
14. Di Stasi SM, Giannantoni A, Stephen RL, et al. Intravesical Electromotive Mitomycin C Versus Passive Transport Mitomycin C for High Risk Superficial Bladder Cancer: A Prospective Randomized Study. *Journal of Urology*. 2003;170(3):777-782. doi:10.1097/01.ju.0000080568.91703.18
15. Shang PF, Kwong J, Wang ZP, et al. Intravesical Bacillus Calmette-Guérin versus epirubicin for Ta and T1 bladder cancer. *Cochrane Database Syst Rev*. 2011;(5):CD006885. doi:10.1002/14651858.CD006885.pub2
16. Cheng CW, Chan SFP, Chan LW, et al. Twelve-year follow up of a randomized prospective trial comparing bacillus Calmette-Guerin and epirubicin as adjuvant therapy in superficial bladder cancer. *Int J Urol*. 2005;12(5):449-455. doi:10.1111/j.1442-2042.2005.01064.x
17. Sylvester RJ, Brausi MA, Kirkels WJ, et al. Long-Term Efficacy Results of EORTC Genito-Urinary Group Randomized Phase 3 Study 30911 Comparing Intravesical Instillations of Epirubicin, Bacillus Calmette-Guérin, and Bacillus Calmette-Guérin plus Isoniazid in Patients with Intermediate- and High-Risk Stage Ta T1 Urothelial Carcinoma of the Bladder. *European Urology*. 2010;57(5):766-773. doi:10.1016/j.eururo.2009.12.024
18. Jones G, Cleves A, Wilt TJ, Mason M, Kynaston HG, Shelley M. Intravesical gemcitabine for non-muscle invasive bladder cancer. Cochrane Urology Group, ed. *Cochrane Database of Systematic Reviews*. Published online January 18, 2012. doi:10.1002/14651858.CD009294.pub2
19. Porena M, Del Zingaro M, Lazzeri M, et al. Bacillus Calmette-Guérin versus Gemcitabine for Intravesical Therapy in High-Risk Superficial Bladder Cancer: A Randomised Prospective Study. *Urol Int*. 2010;84(1):23-27. doi:10.1159/000273461
20. Böhle A, Leyh H, Frei C, 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. doi:10.1016/j.eururo.2009.06.010
21. 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. *Eur Urol*. 2013;64(3):421-430. doi:10.1016/j.eururo.2013.06.009

22. Rajala P, Kaasinen E, Raitanen M, Liukkonen T, Rintala E, the FINNBLADDER GROUP. Perioperative Single Dose Instillation of Epirubicin or Interferon- α After Transurethral Resection for The Prophylaxis of Primary Superficial Bladder Cancer Recurrence: A Prospective Randomized Multicenter Study—Finnbladder III Long-Term Results. *Journal of Urology*. 2002;168(3):981-985. doi:10.1016/S0022-5347(05)64556-9
23. Okamura K, Ono Y, Kinukawa T, et al. Randomized study of single early instillation of (2?R)-4?-O-tetrahydropyranyl-doxorubicin for a single superficial bladder carcinoma. *Cancer*. 2002;94(9):2363-2368. doi:10.1002/cncr.10496
24. El-Ghobashy S, El-Leithy TR, Roshdy MM, El-Ganzoury HM. Effectiveness of a single immediate mitomycin C instillation in patients with low risk superficial bladder cancer: short and long-term follow-up. *J Egypt Natl Canc Inst*. 2007;19(2):121-126.
25. Berrum-Svennung I, Granfors T, Jahnson S, Boman H, Holmäng S. A Single Instillation of Epirubicin After Transurethral Resection of Bladder Tumors Prevents Only Small Recurrences. *Journal of Urology*. 2008;179(1):101-106. doi:10.1016/j.juro.2007.08.166
26. Gudjónsson S, Adell L, Merdasa F, et al. Should All Patients with Non–Muscle-Invasive Bladder Cancer Receive Early Intravesical Chemotherapy after Transurethral Resection? The Results of a Prospective Randomised Multicentre Study. *European Urology*. 2009;55(4):773-780. doi:10.1016/j.eururo.2009.01.006
27. De Nunzio C, Carbone A, Albisinni S, et al. Long-term experience with early single Mitomycin C instillations in patients with low-risk non-muscle-invasive bladder cancer: prospective, single-centre randomised trial. *World J Urol*. 2011;29(4):517-521. doi:10.1007/s00345-011-0691-2
28. Li T, Xing Y, Liu S, Han X, Li W, Chen M. Long-term versus short-term introvesical chemotherapy in patients with non-muscle-invasive bladder cancer: A systematic review and meta-analysis of the published results of randomized clinical trials. *J Huazhong Univ Sci Technol [Med Sci]*. 2014;34(5):706-715. doi:10.1007/s11596-014-1340-y
29. Nomata K, Noguchi M, Kanetake H, et al. Intravesical adjuvant chemotherapy for superficial transitional cell bladder carcinoma: results of a randomized trial with epirubicin comparing short-term versus long-term maintenance treatment. *Cancer Chemotherapy and Pharmacology*. 2002;50(4):266-270. doi:10.1007/s00280-002-0487-6
30. Koga H, Kuroiwa K, Yamaguchi A, Osada Y, Tsuneyoshi M, Naito S. A Randomized Controlled Trial of Short-Term Versus Long-Term Prophylactic Intravesical Instillation Chemotherapy for Recurrence After Transurethral Resection of Ta/T1 Transitional Cell Carcinoma of the Bladder. *Journal of Urology*. 2004;171(1):153-157. doi:10.1097/01.ju.0000100386.07370.0a
31. Kuroda M, Niijima T, Kotake T, Akaza H, Hinotsu S, 6th Trial of the Japanese Urological Cancer Research Group. Effect of prophylactic treatment with intravesical epirubicin on recurrence of superficial bladder cancer--The 6th Trial of the Japanese Urological Cancer Research Group (JUCRG): a randomized trial of intravesical epirubicin at dose of 20mg/40ml, 30mg/40ml, 40mg/40ml. *Eur Urol*. 2004;45(5):600-605. doi:10.1016/j.eururo.2003.12.010
32. Isbarn H, Budäus L, Pichlmeier U, Conrad S, Huland H, Friedrich MG. Vergleich der Effektivität der Langzeitinstillation mit Mitomycin C gegen Kurzzeitprophylaxen mit MMC oder Bacillus Calmette-Guerin: Untersuchung bei Patienten mit nicht muskelinvasivem Urothelkarzinom der Harnblase. *Urologe*. 2008;47(5):608-615. doi:10.1007/s00120-008-1671-z
33. Hendricksen K, Witjes WPJ, Idema JG, et al. Comparison of Three Schedules of Intravesical Epirubicin in Patients with Non–Muscle-Invasive Bladder Cancer. *European Urology*. 2008;53(5):984-991. doi:10.1016/j.eururo.2007.12.033
34. Serretta V, Morgia G, Altieri V, et al. A 1-year maintenance after early adjuvant intravesical chemotherapy has a limited efficacy in preventing recurrence of intermediate risk non-muscle-invasive bladder cancer: MAINTENANCE

OF EARLY INTRAVESICAL CHEMOTHERAPY FOR NMI-BC. *BJU International*. 2010;106(2):212-217.
doi:10.1111/j.1464-410X.2009.09153.x

35. Mitsumori K, Tsuchiya N, Habuchi T, et al. Early and large-dose intravesical instillation of epirubicin to prevent superficial bladder carcinoma recurrence after transurethral resection. *BJU Int*. 2004;94(3):317-321.
doi:10.1111/j.1464-410X.2004.04884.x
36. Zeng S, Yu X, Ma C, et al. Low-Dose Versus Standard Dose of Bacillus Calmette-Guerin in the Treatment of Nonmuscle Invasive Bladder Cancer: A Systematic Review and Meta-Analysis. *Medicine*. 2015;94(49):e2176.
doi:10.1097/MD.0000000000002176
37. Inamoto T, Ubai T, Nishida T, Fujisue Y, Katsuoka Y, Azuma H. Comparable effect with minimal morbidity of low-dose Tokyo 172 strain compared with regular dose Connaught strain as an intravesical bacillus Calmette-Guérin prophylaxis in nonmuscle invasive bladder cancer: Results of a randomized prospective comparison. *Urol Ann*. 2013;5(1):7. doi:10.4103/0974-7796.106873
38. Kapoor R, Dubey D, Srivastava A, et al. A randomized trial comparing low dose (40 or 80 mg) with standard dose (120 mg) of bacillus Calmette-Guerin for superficial bladder cancer. *Indian J Urol*. 2006;22(4):317.
doi:10.4103/0970-1591.29117
39. Agrawal MS, Agrawal M, Bansal S, Agarwal M, Lavania P, Goyal J. The Safety and Efficacy of Different Doses of Bacillus Calmette Guérin in Superficial Bladder Transitional Cell Carcinoma. *Urology*. 2007;70(6):1075-1078.
doi:10.1016/j.urology.2007.07.017
40. Oddens J, Brausi M, Sylvester R, et al. Final Results of an EORTC-GU Cancers Group Randomized Study of Maintenance Bacillus Calmette-Guérin in Intermediate- and High-risk Ta, T1 Papillary Carcinoma of the Urinary Bladder: One-third Dose Versus Full Dose and 1 Year Versus 3 Years of Maintenance. *European Urology*. 2013;63(3):462-472. doi:10.1016/j.eururo.2012.10.039
41. Cui J, Wang W, Chen S, et al. Combination of Intravesical Chemotherapy and Bacillus Calmette-Guerin Versus Bacillus Calmette-Guerin Monotherapy in Intermediate- and High-risk Nonmuscle Invasive Bladder Cancer: A Systematic Review and Meta-analysis. *Medicine*. 2016;95(3):e2572. doi:10.1097/MD.0000000000002572
42. Kaasinen E, Wijkström H, Malmström P-U, et al. Alternating Mitomycin C and BCG Instillations versus BCG Alone in Treatment of Carcinoma in Situ of the Urinary Bladder: A Nordic Study. *European Urology*. 2003;43(6):637-645.
doi:10.1016/S0302-2838(03)00140-4
43. Cai T, Nesi G, Tinacci G, et al. Can Early Single Dose Instillation of Epirubicin Improve Bacillus Calmette-Guerin Efficacy in Patients With Nonmuscle Invasive High Risk Bladder Cancer? Results From a Prospective, Randomized, Double-Blind Controlled Study. *Journal of Urology*. 2008;180(1):110-115. doi:10.1016/j.juro.2008.03.038
44. Gülpinar Ö, Halilioğlu AH, Gökçe Mİ, Gögüş Ç, Baltacı S. The value of perioperative mitomycin C instillation in improving subsequent bacillus calmette-guerin instillation efficacy in intermediate and high-risk patients with non-muscle invasive bladder cancer: a prospective randomized study. *Int braz j urol*. 2012;38(4):474-479.
doi:10.1590/S1677-55382012000400006
45. Solsona E, Madero R, Chantada V, et al. Sequential Combination of Mitomycin C Plus Bacillus Calmette-Guérin (BCG) Is More Effective but More Toxic Than BCG Alone in Patients with Non-Muscle-invasive Bladder Cancer in Intermediate- and High-risk Patients: Final Outcome of CUETO 93009, a Randomized Prospective Trial. *European Urology*. 2015;67(3):508-516. doi:10.1016/j.eururo.2014.09.026
46. Sylvester RJ, Oosterlinck W, Holmang S, et al. Systematic Review and Individual Patient Data Meta-analysis of Randomized Trials Comparing a Single Immediate Instillation of Chemotherapy After Transurethral Resection with Transurethral Resection Alone in Patients with Stage pTa-pT1 Urothelial Carcinoma of the Bladder: Which Patients Benefit from the Instillation? *Eur Urol*. 2016;69(2):231-244. doi:10.1016/j.eururo.2015.05.050

47. Barghi MR, Rahmani MR, Hosseini Moghaddam SMM, Jahanbin M. Immediate intravesical instillation of mitomycin C after transurethral resection of bladder tumor in patients with low-risk superficial transitional cell carcinoma of bladder. *Urol J*. 2006;3(4):220-224.
48. Chou R, Selph S, Buckley DI, et al. Intravesical Therapy for the Treatment of Nonmuscle Invasive Bladder Cancer: A Systematic Review and Meta-Analysis. *Journal of Urology*. 2017;197(5):1189-1199. doi:10.1016/j.juro.2016.12.090
49. Arends TJH, Nativ O, Maffezzini M, et al. Results of a Randomised Controlled Trial Comparing Intravesical Chemohyperthermia with Mitomycin C Versus Bacillus Calmette-Guérin for Adjuvant Treatment of Patients with Intermediate- and High-risk Non-Muscle-invasive Bladder Cancer. *European Urology*. 2016;69(6):1046-1052. doi:10.1016/j.eururo.2016.01.006
50. Shepherd AR, Shepherd E, Brook NR. Intravesical Bacillus Calmette-Guérin with interferon-alpha versus intravesical Bacillus Calmette-Guérin for treating non-muscle-invasive bladder cancer. Cochrane Urology Group, ed. *Cochrane Database of Systematic Reviews*. Published online March 8, 2017. doi:10.1002/14651858.CD012112.pub2
51. Nepple KG, Lightfoot AJ, Rosevear HM, O'Donnell MA, Lamm DL, Bladder Cancer Genitourinary Oncology Study Group. Bacillus Calmette-Guérin With or Without Interferon α -2b and Megadose Versus Recommended Daily Allowance Vitamins During Induction and Maintenance Intravesical Treatment of Nonmuscle Invasive Bladder Cancer. *Journal of Urology*. 2010;184(5):1915-1919. doi:10.1016/j.juro.2010.06.147
52. Jung JH, Gudeloglu A, Kiziloz H, et al. Intravesical electromotive drug administration for non-muscle invasive bladder cancer. Cochrane Urology Group, ed. *Cochrane Database of Systematic Reviews*. Published online September 12, 2017. doi:10.1002/14651858.CD011864.pub2
53. Di Stasi SM, Valenti M, Verri C, et al. Electromotive instillation of mitomycin immediately before transurethral resection for patients with primary urothelial non-muscle invasive bladder cancer: a randomised controlled trial. *The Lancet Oncology*. 2011;12(9):871-879. doi:10.1016/S1470-2045(11)70190-5
54. Quan Y, Jeong CW, Kwak C, Kim HH, Kim HS, Ku JH. Dose, duration and strain of bacillus Calmette-Guérin in the treatment of nonmuscle invasive bladder cancer: Meta-analysis of randomized clinical trials. *Medicine*. 2017;96(42):e8300. doi:10.1097/MD.0000000000008300
55. Martínez-Piñeiro JA, Flores N, Isorna S, et al. Long-term follow-up of a randomized prospective trial comparing a standard 81 mg dose of intravesical bacille Calmette-Guérin with a reduced dose of 27 mg in superficial bladder cancer: COMPARISON OF STANDARD BCG DOSE VS THREE-FOLD LOWER DOSE. *BJU International*. 2002;89(7):671-680. doi:10.1046/j.1464-410X.2002.02722.x
56. Martínez-Piñeiro JA, Martínez-Piñeiro L, Solsona E, et al. HAS A 3-FOLD DECREASED DOSE OF BACILLUS CALMETTE-GUERIN THE SAME EFFICACY AGAINST RECURRENCES AND PROGRESSION OF T1G3 AND TIS BLADDER TUMORS THAN THE STANDARD DOSE? RESULTS OF A PROSPECTIVE RANDOMIZED TRIAL. *Journal of Urology*. 2005;174(4 Part 1):1242-1247. doi:10.1097/01.ju.0000173919.28835.aa
57. Martínez-Piñeiro L, Portillo JA, Fernández JM, et al. Maintenance Therapy with 3-monthly Bacillus Calmette-Guérin for 3 Years is Not Superior to Standard Induction Therapy in High-risk Non-muscle-invasive Urothelial Bladder Carcinoma: Final Results of Randomised CUETO Study 98013. *European Urology*. 2015;68(2):256-262. doi:10.1016/j.eururo.2015.02.040
58. Nakai Y, Anai S, Tanaka N, et al. Insignificant role of bacillus Calmette-Guérin maintenance therapy after complete transurethral resection of bladder tumor for intermediate- and high-risk non-muscle-invasive bladder cancer: Results from a randomized trial. *Int J Urol*. 2016;23(10):854-860. doi:10.1111/iju.13167
59. Boehm BE, Cornell JE, Wang H, Mukherjee N, Oppenheimer JS, Svatek RS. Efficacy of bacillus Calmette-Guérin Strains for Treatment of Nonmuscle Invasive Bladder Cancer: A Systematic Review and Network Meta-Analysis. *Journal of Urology*. 2017;198(3):503-510. doi:10.1016/j.juro.2017.01.086

60. Gårdmark T, Jahnson S, Wahlquist R, Wijkström H, Malmström P-U. Analysis of progression and survival after 10 years of a randomized prospective study comparing mitomycin-C and bacillus Calmette-Guérin in patients with high-risk bladder cancer. *BJU Int.* 2007;99(4):817-820. doi:10.1111/j.1464-410X.2006.06706.x
61. Hemdan T, Johansson R, Jahnson S, et al. 5-Year outcome of a randomized prospective study comparing bacillus Calmette-Guérin with epirubicin and interferon- α 2b in patients with T1 bladder cancer. *J Urol.* 2014;191(5):1244-1249. doi:10.1016/j.juro.2013.11.005
62. Järvinen R, Kaasinen E, Rintala E, Group TF. Long-term results of maintenance treatment of mitomycin C or alternating mitomycin C and bacillus Calmette-Guérin instillation therapy of patients with carcinoma in situ of the bladder: a subgroup analysis of the prospective FinnBladder 2 study with a 17-year follow-up. *Scand J Urol Nephrol.* 2012;46(6):411-417. doi:10.3109/00365599.2012.694906
63. Järvinen R, Kaasinen E, Sankila A, Rintala E, FinnBladder Group. Long-term efficacy of maintenance bacillus Calmette-Guérin versus maintenance mitomycin C instillation therapy in frequently recurrent TaT1 tumours without carcinoma in situ: a subgroup analysis of the prospective, randomised FinnBladder I study with a 20-year follow-up. *Eur Urol.* 2009;56(2):260-265. doi:10.1016/j.eururo.2009.04.009
64. Koga H, Ozono S, Tsushima T, et al. Maintenance intravesical bacillus Calmette-Guérin instillation for Ta, T1 cancer and carcinoma in situ of the bladder: Randomized controlled trial by the BCG Tokyo Strain Study Group: Maintenance intravesical BCG. *International Journal of Urology.* 2010;17(9):759-766. doi:10.1111/j.1442-2042.2010.02584.x
65. Mahran A, Bukavina L, Mishra K, et al. Bladder irrigation after transurethral resection of superficial bladder cancer: a systematic review of the literature. *Can J Urol.* 2018;25(6):9579-9584.
66. Bijalwan P, Pooleri GK, Thomas A. Comparison of sterile water irrigation versus intravesical mitomycin C in preventing recurrence of nonmuscle invasive bladder cancer after transurethral resection. *Indian J Urol.* 2017;33(2):144-148. doi:10.4103/iju.IJU_371_16
67. Onishi T, Sasaki T, Hoshina A, Yabana T. Continuous saline bladder irrigation after transurethral resection is a prophylactic treatment choice for non-muscle invasive bladder tumor. *Anticancer Res.* 2011;31(4):1471-1474.
68. Van Hemelrijck M, Sparano F, Josephs D, Sprangers M, Cottone F, Efficace F. Patient-reported outcomes in randomised clinical trials of bladder cancer: an updated systematic review. *BMC Urol.* 2019;19(1):86. doi:10.1186/s12894-019-0518-9
69. Huang W, Wang F, Wu C, Hu W. Efficacy and safety of pirarubicin combined with hyaluronic acid for non-muscle invasive bladder cancer after transurethral resection: a prospective, randomized study. *Int Urol Nephrol.* 2015;47(4):631-636. doi:10.1007/s11255-015-0940-1
70. Uhlig A, Strauss A, Seif Amir Hosseini A, et al. Gender-specific Differences in Recurrence of Non-muscle-invasive Bladder Cancer: A Systematic Review and Meta-analysis. *Eur Urol Focus.* 2018;4(6):924-936. doi:10.1016/j.euf.2017.08.007
71. Chen S, Zhang N, Shao J, Wang X. Maintenance versus non-maintenance intravesical Bacillus Calmette-Guerin instillation for non-muscle invasive bladder cancer: A systematic review and meta-analysis of randomized clinical trials. *Int J Surg.* 2018;52:248-257. doi:10.1016/j.ijsu.2018.02.045
72. Tabayoyong WB, Kamat AM, O'Donnell MA, et al. Systematic Review on the Utilization of Maintenance Intravesical Chemotherapy in the Management of Non-muscle-invasive Bladder Cancer. *Eur Urol Focus.* 2018;4(4):512-521. doi:10.1016/j.euf.2018.08.019
73. Deng T, Liu B, Duan X, Zhang T, Cai C, Zeng G. Systematic Review and Cumulative Analysis of the Combination of Mitomycin C plus Bacillus Calmette-Guérin (BCG) for Non-Muscle-Invasive Bladder Cancer. *Sci Rep.* 2017;7(1):3172. doi:10.1038/s41598-017-03421-5

Supplemental Table 2. Verbatim outcomes used for

Outcome domain	Standardised outcome term
Adverse events/effects	Local toxicity
	Infection
	Cystitis
	Frequency
	Pain
	Haematuria

Bladder

Urethra

Residual urine

Other

Systemic toxicity

Musculoskeletal

Cardiovascular

Respiratory

Gastrointestinal

Infection

Non-specific/Other toxicity

Constitutional symptoms

Fever

Fatigue

**Allergic reactions
(Dermatological)**

Laboratory abnormaliies

Liver

Renal

Death due to toxicity



or reporting adverse events

Verbatim outcomes

Topical toxicity

Local symptoms

UTI

Pyuria

Cloudiness of urine

Cystitis

Chemical cystitis

Chemical toxicity

Bacterial cystitis

Drug induced cystitis

Drug induced cystitis (bacterial cystitis, chemical cystitis)

Cystitis-like symptoms

Stranguria with or without cystitis

Frequency

Frequency (more than once per hour)

Frequency (1 or greater/30 mins)

Urinary frequency

Urinary frequency/urgency

Urgency

Frequent diurnal micturition

Frequent nocturnal micturition.

Nocturia

Pollakisuria

Pollakisuria during treatment sessions

Incontinence

Urinary incontinence

Pain on urination

Difficulty with urination

Difficulty in urination

Dysuria

Burning sensation during urination

Itching sensation

Intensive local pain

painful urination

pain with micturition

pain on urination

pain

micturition pain

Bladder pain

Lower abdominal pain

cramp/s

Mild storage symptoms (dysuria, urgency, frequency)

Gross haematuria

Haematuria
Visible haematuria
Persistent visible haematuria
Macroscopic hematuria
Macrohematuria
Clinically significant haematuria
Transient mild (pink) haematuria after instillation
Urethral bleeding
Bladder tamponade
Bladder retraction
Contracted bladder
Contracted bladders resulting in cystectomies
Bladder spasm/s
Bladder tissue reaction
Bladder perforation
Overt bladder perforation
Bladder perforation requiring bladder-wall repair
Bladder irritation
Irritative bladder symptoms
Irritative bladder symptoms (micturition pain and frequency of urination)
Symptoms of irritated bladder
Pain during sessions
Bladder pain between sessions
Bladder pain during sessions
Bladder pain
urethral strictures (most likely repeat TURBTs)
Repeat urethral injury by catheters
ureteral obstruction
urethral stricture/s
pain during sessions
irritative urinary symptoms.
stricture of urethra
Residual urine
urinary retention
urinary residual
retention
micturition
sense of retention
Sense of residual urine
Other local side effects
Epididymitis
necrotizing granulomatous epididymitis
prostatitis
granulomatous prostatitis
leakage of drug solution

difficult catheterisations

penile edema

systemic side effects

Arthritis

Arthralgia

Muscle pain

myalgia

arthritis

Hypertension

Chest pain, Abnormal ECG

pulmonary BCGitis.

influenza-like symptoms

BCG lung infection

transient dyspnea

Lung infection

nausea

transient nausea

vomiting

nausea and vomiting

abdominal pain

Systemic infection

Septicemia

Sepsis

Not specified, Other

Other systemic side effects

Anorexia

Alopecia

Headache

leg oedema

Pain

procedural pain

Reiter syndrome

polyneuropathy with axonal demyelination

dissemination of Mycobacterium bovis BCG with consecutive infiltration of a granuloma into the external carotid artery, which required immediate surgical intervention.

Accidental dose of MMC in TUBR and bladder perforation, may have resulted in bowel dysfunction, adhesive ileus

MMC extravasation

Constitutional symptoms

Fever

pyrexia

Fever ($\geq 38^\circ\text{C}$)

fever of $> 38^\circ\text{C}$

high fever ($> 39^\circ\text{C}$)

fever $\geq 39^{\circ}\text{C}$
high-grade fever, high fever
fever ($< 39^{\circ}\text{C}$ or $> 39^{\circ}\text{C}$)
temperature $> 37.5^{\circ}\text{C}$
recurrent fever of 39°C or higher
fever and chills
low grade fever
fatigue
general fatigue
General malaise
persistent general malaise
Malaise
severe malaise
tiredness
asthenia

allergic reactions

allergy
skin rash
allergic skin reaction
severe skin reaction
exanthema
dermatitis
rash and itching
rubor and itching
Allergic symptoms
Itch

Abnormal clinical laboratory tests

hematologic abnormality
Haematologic toxicity (Leucocytosis)
hematologic toxicity: Alteration of white blood cell count and CBC count/ mm^3
hematological changes
Abnormal Liver function
Abnormal LFT
Elevation in serum transamylase level
ALT elevation, AST elevatin, Gamma-GTP elevation.
Hepatitis
Elevated liver enzymes
Abnormal Renal function
Renal dysfunction
Renal morbidity
Urinalysis (Urinary protein positive, Microscopic haematuria, Urinary red blood cell increase, Urinary white blood cell increase)

Death due to toxicity

Treatment related death

Death due to serious adverse event
death

	Studies	POPULATION			
		pTa		pT1	
		low grade	high grade	low grade	high grade
C I S + / - P A P I L L A R Y	Lamm 2000	x	x	x	x
	Palou 2001		G3		G3
	Au 2001	x	x	x	x
	Sekine 2001	x	x	x	x
	Martinez-Pinneiro 2002		G2G3	G1	G2G3
	Di Stasi 2003			x	x
	Kaasinen 2003	x	x	x	x
	Martinez-Pinneiro 2005		G3		G3
	de Reijke 2005	x	x	x	x
	Di Stasi 2006				G2G3
	Gårdmark 2007	x	x	x	x
	Cai 2008		G2G3	G2	
	Neppe 2010	x	x	x	x
	Porena 2010		G3		G3
	Koga 2010		x	x	x
	Gülpınar 2012	x	x	x	x
	Järvinen 2012				
	Sengiku 2013	x	x	x	x
	Inamoto 2013	x	x	x	x
	Rentsch 2014	x	x	x	x
	Hemdan 2014				G2G3
	Martinez-Pineiro 2015	G1G2+cis	G3	G1G2+cis	G3
	Solsona 2015	G1+cis	G2G3	G1	G2G3
	Arends 2016	x	x	x	x
	Nakai 2016	x	x	x	x
	Kaasinen 2000	G1G2		G1G2	
	Bilen 2000				x
	Van der Meijden 2001	x	x	x	x
	Nomata 2002	G1G2		G1G2	
	Okamura 2002	x	x	x	x
	Rajala 2002	x	x	x	x
	Kuroda 2004	G1G2		G1G2	
Koga 2004	x	x	x	x	
Mitsumori 2004	x	x	x	x	
Cheng 2005	x	x	x	x	
Vijjan 2006	x	x	x	x	
Hinotsu 2006	x	x	x	x	
Barghi 2006	G1G2		G1		

Ojea 2007		G2	G1G2	
El-Ghobashy 2007	G1G2		G1G2	
Agrawal 2007	x	x	x	x
Friedrich 2007	x	x	x	x
Hendricksen 2008	x	x	x	x
Berrum-Svennung 2008	G1G2		G1G2	
Isbarn 2008	x	x	x	x
Böhle 2009	x	x	x	x
Gudjonsson 2009	G1G2		G1G2	
Järvinen 2009	x	x	x	x
Seretta 2010	G1G2		G1G2	
Sylvester 2010	x	x	x	x
De Nunzio 2011	G1G2			
Di Stasi 2011	x	x	x	x
Hinotsu 2011	x	x	x	x
Oddens 2013	x	x	x	x
Huang 2015	x	x	x	x
Onishi 2017	G1G2		G1G2	
Bijalwan 2017	x	x	x	x

CIS as authors have reported			INSTILLATION TREATMENT (S-single; I- induction; M- maintainance)	Number of outcomes domains (n/10)
primary cis	secondary cis	concomitant cis		
x		x	M	7
x		x	M	6
x		x	I	2
x	x	x	I	5
x		x	I	7
x		x	M	7
x	x	x	M	5
x		x	I	4
x	x	x	M	5
		x	M	6
x		x	M	4
		x	M	4
x		x	M	2
x		x	M	3
		x	M	5
x		x	I	4
x	x	x	M	5
x	x	x	I	3
x	x	x	I	4
		x	I	5
		x	M	4
		x	I vs M	5
x		x	I	5
x	x	x	M	4
x		x	I vs M	5
			M	2
			I	4
			M	4
			M	2
			S	3
			S	1
			M	4
			I vs M	2
			I	2
			M	5
			I	5
			I vs M	3
			S	3

			M	4
			S	4
			M	2
			M	2
			M	3
			S	3
			I vs M	2
			S	4
			S	1
			M	5
			I vs M	3
			M	6
			S	4
			S	5
			I vs M	4
			M	6
			M	4
			S	3
			S	3

TABLE 2

Studies	CLINICAL			DEATH		ADVERSE EVENTS	LIFE IMPACT			RESOURCE USE
	TUMOR RELATED OUTCOMES			SURVIVAL			DELIVERY OF CARE		GLOBAL QUALITY OF LIFE	ECONOMIC
	Recurrence	Progression	Treatment response (for cis)	Overall survival	Cancer-specific survival	Adverse events	Completion/adherence	Treatment failure/change of treatment reported (RC,RT)	Quality of life	Health Economics
C I S + / - P A P I L L A R Y	Lamm 2000	x	x	x	x	x	x	x		
	Palou 2001	x	x		x	x		x	x	
	Au 2001	x					x			
	Sekine 2001	x	x	x		x			x	
	Martinez-Pinneiro 2002	x	x		x	x	x	x	x	
	Di Stasi 2003	x	x	x	x	x	x		x	
	Kaasinen 2003	x	x	x			x		x	
	Martinez-Pinneiro 2005	x	x				x		x	
	de Reijke 2005	x	x	x	x				x	
	di Stasi 2006	x	x	x	x	x	x			
	Gårdmark 2007		x		x	x			x	
	Cai 2008	x	x	x					x	
	Neple 2010	x					x			
	Porena 2010	x					x		x	
	Koga2010	x	x	x			x			x
	Gülpinar 2012	x	x				x		x	
	Järvinen 2012	x	x		x	x			x	
	Sengiku 2013	x		x			x			
	Inamoto 2013	x					x	x	x	
	Rentsch 2014	x	x		x	x	x			
Hemdan 2014	x	x			x			x		
Martinez-Pineiro 2015	x	x		x	x	x				
Solsona 2015	x	x		x	x	x				
Arends 2016	x	x	x			x				
Nakai 2016	x	x			x	x	x			
P A P I L L A R Y	Kaasinen 2000	x	x	NA			x			
	Bilen 2000	x	x	NA			x		x	
	Van der Meijden 2001	x	x	NA	x		x			
	Nomata 2002	x		NA			x			
	Okamura 2002	x	x	NA			x			
	Rajala 2002	x		NA						
	Kuroda 2004	x		NA	x	x	x			
	Koga 2004	x		NA			x			
	Mitsumori 2004	x		NA			x			
	Cheng 2005	x	x	NA	x	x			x	
	Vijjan 2006	x	x	NA	x		x		x	
	Hinotsu 2006	x	x	NA			x			
	Barghi 2006	x	x	NA			x			
	Ojea 2007	x	x	NA		x	x			
	El-Ghobashy 2007	x	x	NA			x			
	Agrawal 2007	x		NA			x			
	Friedrich 2007	x		NA				x		
	Hendricksen 2008	x	x	NA			x			
	Berrum-Svennung 2008	x	x	NA						x
	Isbarn 2008	x		NA			x			
	Böhle 2009	x	x	NA			x		x	
	Gudjonsson 2009	x		NA						
	Järvinen 2009	x	x	NA	x	x		x		
	Seretta 2010	x	x	NA			x			
	Sylvester 2010	x	x	NA	x	x	x		x	
	De Nunzio 2011	x	x	NA			x		x	
	Di Stasi 2011	x	x	NA	x	x	x			
	Hinotsu 2011	x	x	NA			x	x		
	Oddens 2013	x	x	NA	x	x	x	x		
Huang 2015	x		NA			x	x		x	
Onishi 2017	x	x	NA			x				
Bijalwan 2017	x	x	NA			x				
TOTAL (n%)	56/57 (98%)	42/57 (74%)	10/25(40%)	19/57 (33%)	19/57 (33%)	44/57 (77%)	10/57(17%)	21/57(37%)	2/57 (3 %)	1/57 (2 %)
Number of individual verbatim outcomes	35	20	14	10	11	36	14	6	2	2

study ID					
	Time to recurrence	RFS	Recurrence rate (%)	2 yr recurrence-free rates (%)	3 yr recurrence-free rates (%)
Kaasinen 2000	x		x		
Bilen 2000	x		x		
Van der Meijden 2001	x	x			x
Nomata 2002					x
Okamura 2002		x			
Rajala 2002	x	x			
Kuroda 2004			x	x	
Koga 2004	x		x		x
Mitsumori 2004		x	x		
Cheng 2005	x	x			
Vijjan 2006	x		x		
Hinotsu 2006		x		x	x
Barghi 2006		x			
Ojea 2007	x	x	x		
El-Ghobashy 2007		x	x		
Agrawal 2007			x		
Friedrich 2007		x	x	x	x
Hendricksen 2008	x	x	x		
Berrum-Svennung 2008	x		x		
Isbarn 2008			x	x	x
Böhle 2009		x	x		
Gudjonsson 2009	x	x	x		
Järvinen 2009	x		x		
Seretta 2010	x	x	x	x	x
Sylvester 2010	x				
De Nunzio 2011		x			
Di Stasi 2011		x	x		
Hinotsu 2011		x	x	x	
Oddens 2013	x		x		5yr DFR
Huang 2015	x	x	x		
Onishi 2017	x	x			x
Bijalwan 2017	x		x		

PROGRESSION						
DEFINITION				Progression rate	Progression rate at the time of first recurrence	Time to progression to MIBC
T-stage	Grade	MIBC	Metastases			
				x		
≥pT2				x		
		x	x			x
		x	x			
		x	x			x
Ta->T1, T1->MIBC		x				
≥pT2		x	x			
		x		x		
		x	x	x		
≥pT2		x	x			
≥pT2, cis		x	x	x		x
		x				
		x				
≥pT2		x	x	x		
≥pT2		x		x		
≥pT2		x	x			x
≥pT2		x				
≥pT2		x		x		x
≥pT2	x	x	x		x	
≥pT2, cis			x	x		x
not specified	x			x		
Ta->T1	LG->HG			x		

Time to progression to distant metastasis	5-yr PFR	Progression as the first event included as recurrence?	Progression-free survival
		x	
x			
		NA	
		NA	
		NA	
		NA	
		NA	
x			x
		NA	
		NA	
x	x		
		x	
		x	
x		x	
x			
x		x	
		NA	
			x

Carcinoma in Situ Response					
Complete response					
	No Cis, no Ta/T1	at 9 mo no progression; at 12 mo no recurrence	Complete response in cis patients	Time to recurrence in complete responders	Recurrence after complete response (%)
Lamm 2000			x	x	
Palou 2001					
Au 2001					
Sekine 2001			x		x
Martinez-Pinneiro 2002					
Di Stasi 2003	x				
Kaasinen 2003		x			
Martinez-Pinneiro 2005					
de Reijke 2005	x			x	
di Stasi 2006	x				
Gårdmark 2007					
Cai 2008	x				
Neple 2010					
Porena 2010					
Koga2010	x				
Gülpınar 2012					
Järvinen 2012					
Sengiku 2013			x		
Inamoto 2013					
Rentsch 2014					
Hemdan 2014					
Martinez-Pineiro 2015					
Solsona 2015					
Arends 2016			x		
Nakai 2016					

	Partial response	No change				
First recurrence type after complete response (papillary, cis, papillary+cis)	no Cis, but Ta/T1 persists	Cis or Ta/T1 persists	Recurrence rate (%)	Disease-free interval	Recurrence-free survival	Time to recurrence
					x	x
					x	
						x
				x		x
			x	x		x
				x		
						x
x	x	x				
				x (for cis pts)		x
			x	x	x	x
			x	x		
					x	
					x	
			x		x	x
			x			x
					x	
					x	
			x		x	
				x		x
				x		
					x	
					x	

RECURRENCE

5-year Recurrence-free survival (%)	1-year Recurrence-free survival (%)	Interval before recurrence (mo)	Recurrence rate at 5 years	Regression of grade/stage (%)	Worsening-free survival (mo, %)
x					x
x					
x		x			
x					
				x	
x					
	x				
x					
			x		

Low-grade relapse (n)	High-grade superficial relapse (n)	DEFINITION			
		T-stage	Grade	MIBC	Metastases
		≥pT2			
x	x			x	x
				x	x
		≥pT2		x	x
				x	
		≥pT1			
		≥pT2		x	x
		≥pT2			
				x	x
		Ta->T1; T1->T2			
		x	x		
				x	x
				x	x
		≥pT2		x	x
		x	x		
				x	x
				x	x
				x	
				x	x

PROGRESSION						
Progression rate	Time to progression	Progression-free time	Progression-free survival	5 year progression-free survival	Other?	Not defined
			x			
x						
	x			x	for cis -> extravesical extension	
	x					
	x					
	x					
	x	x				
x	x (stage)					
						x
			x			
x						
				x		
x					Free of progression (%)	
	x					
		x				
			x			
			x			

Progression as the first event included as recurrence?
NA
x
NA
x
NA
x
NA
x
x
x
x

RECURRENCE	
Time to recurrence	
	median time to first recurrence
	time to initial recurrence
	early recurrence (0-2 years)
	late recurrence (>2 years)
	recurrence-free survival
	relapse-free survival
	recurrence-free period
	disease-free time
	disease-free survival
	first bladder recurrence
	first TCC recurrence
	Recurrence-free interval
	disease-free interval
Recurrence rate (%)	
	recurrence rate and recurrence free rate at different timepoints: 1,2,3,5, 10yrs
	incidence of recurrence
	probability of recurrence at 5,10 and 15 yrs
	Recurrence risk (at 3 year and 5 year)
	NMIBC recurrence (pTa,pT1)
	Type of recurrence (cis, papillary Ta/T1 or grater than T1)
Recurrence per year	
	recurrence rate per year
	tumor per year rate
Recurrence index/ 100 patients per month	
Number of recurrences	
50 % recurrence time (days)	
Recurrence-rate reduction	
	absolute recurrence risk reduction
Recurrence-free rate	
	non-recurrence rate
	relapse-free patients
	1-year recurrence-free survival
	5-year recurrence-free survival
Tumor size of first recurrence	

Time to pr
Progressio
Progressio

PROGRESSION
ogression
Time to first progression
Time to progression in stage
Time to progression to MIBC
Time to progression in grade
Time to progression to distant metastasis
Time to distant metastasis
n-free survival
5-year progression-free survival
Progression-free at 5 years
Worsening free survival
Progression-free time
Duration of progression-free interval
n rate
Disease progression rate
Free of progression
Progression-free survival rate
Rate of progression to T2 or grater
Progression rate at the first recurrence

OVERALL SURVIVAL
Survival rate
Overall survival
Overall mortality
Survival
Cancer deaths
Death
Survival time
5-year overall survival
Time to death by any cause
Duration of survival
Causes of deaths

CANCER-SPECIFIC SURVIVAL
Cancer-specific survival rate
Cancer deaths
Cancer-specific death rate
Disease-specific mortality
Death from bladder cancer
Cancer-specific survival time
Time to death due to bladder cancer
Cancer-specific survival
Cause-specific survival
Disease-specific survival
Disease-free survival
Cancer-specific survival time

ADVERSE EVENTS
Standardised outcome term
Local toxicity
Systemic toxicity
Allergic reactions (dermatological)
Constitutional symptoms
Laboratory abnormality
Treatment interruption
Death due to toxicity
Definition/Instruments used
CTCAE v3.0 (Common Terminology Criteria of
NCI-CTC v2.0 (National Cancer Institute-Common
WHO toxicity grading scale
WHO-ART (1979 WHO Adverse Reaction Terminology into 4 classes (I to IV); (class I—related symptoms,

TREATMENT RESPONSE (for cis)
complete response rate
complete response at 3 months and 1 year
response to treatment
efficacy of induction therapy
number of instillations need to achieve a complete response
complete response rate in patients with CIS or concomitant carcinoma in situ (pTa or pT1)
treatment efficacy in patients with CIS
overall complete response rate

DEFINITIONS FOR INSTILLATION TREATMENT COMPLETION

completion rate (all planned instillations in the cycle were administered)
performance rate (at least one of the three planned instillations in the cycle was administered)
completion and performance rate at 3, 6, 12 and 18 months
% of patients that received all 8 scheduled courses during 3 years
% of patients completed the planned 2-year programmed treatment
% of patients that received maintenance therapy for 6 months and 18 months
the mean number of instillations
number of patients receiving 6-11 instillations
number of patients receiving < 6 instillations
number of patients received induction treatment
maintenance (long-term arm): number of patients complete six instillations and also 1 yr, 2 and 3 yr
median number of instillations
probability of non-cessation of instillations (%) at 6, 12 and 15 months
number of patients received at least 4 instillations as induction course
number of patients that received fewer than the planned 28 instillations of the protocol

of maintenance therapy