





Review

Impact of enhanced optical techniques at time of transurethral resection of bladder tumour, with or without single immediate intravesical chemotherapy, on recurrence rate of non-muscle-invasive bladder cancer: a systematic review and network meta-analysis of randomized trials

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Objective

To assess whether single immediate intravesical chemotherapy (SIIC) adds value to bladder tumour management in combination with novel optical techniques: enhanced transurethral resection of bladder tumour (TURBT).

Methods

A systematic search was performed using the PubMed and Web of Science databases in September 2020 according to the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) extension statement for network meta-analyses. Studies that compared recurrence rates among intervention groups (TURBT with photodynamic diagnosis [PDD] ± SIIC, narrow-band imaging [NBI] ± SIIC, or white-light cystoscopy [WLC] + SIIC) and a control group (TURBT with WLC alone) were included. We used the Bayesian approach in the network meta-analysis.

Results

Twenty-two studies ($n = 4519$) met our eligibility criteria. Out of six different interventions including three different optical techniques, compared to WLC alone, blue-light cystoscopy (BLC) plus SIIC (odds ratio [OR] 0.349, 95% credible interval [CrI] 0.196–0.601) and BLC alone (OR 0.668, 95% CrI 0.459–0.931) were associated with a significantly lower likelihood of 12-month recurrence rate. In the sensitivity analysis, out of eight different interventions compared to WLC alone, PDD by 5-aminolevulinic acid plus SIIC (OR 0.327, 95% CrI 0.159–0.646) and by hexaminolevulinic acid plus SIIC (OR 0.376, 95%

CrI 0.172–0.783) were both associated with a significantly lower likelihood of 12-month recurrence rate. NBI with and without SIIC was not associated with a significantly lower likelihood of 12-month recurrence rate (OR 0.385, 95% CrI 0.105–1.29 and OR 0.653, 95% CrI 0.343–1.15).

Conclusion

Blue-light cystoscopy during TURBT with concomitant SIIC seems to yield superior recurrence outcomes in patients with non-muscle-invasive bladder cancer. The use of PDD was able to reduce the 12-month recurrence rate; moreover, concomitant SIIC increased this risk benefit by a 32% additional reduction in odds ratio. Although using PDD could reduce the recurrence rate, SIIC remains necessary. Moreover, ranking analysis showed that both PDD and NBI, plus SIIC, were better than these techniques alone.

Keywords

blue-light cystoscopy, hexaminolevulinic acid, narrow band imaging, non-muscle-invasive urothelial carcinoma, photodynamic diagnosis, single immediate intravesical chemotherapy, #blcsm, #BladderCancer, #uroonc

Introduction

The goal of transurethral resection of bladder tumour (TURBT) is to diagnose and, if possible, eradicate visible tumorous lesions, thereby lowering and delaying disease recurrence and progression [1]. Various strategies have been implemented to overcome the shortcomings of standard TURBT, such as image-enhanced TURBT and single immediate intravesical chemotherapy (SIIC). White-light cystoscopy (WLC) has indeed been shown to miss some tumours [2]. SIIC has been established as a standard, based on its ablative effects on the residual tumour cells at the resection site and/or small microscopic missed tumours, thereby lowering the recurrence rate. Enhanced optical techniques, such as narrow-band imaging (NBI) and fluorescence cystoscopy or photodynamic diagnosis (PDD), have been shown to improve the visibility of bladder tumours during TURBT, thereby also lowering the recurrence rate.

Currently, major guidelines therefore recommend using both fluorescence cystoscopy (i.e. blue-light cystoscopy [BLC]) with photoactive compounds (intravesical hexaminolevulinic acid [HAL]) during TURBT as well as SIIC [3–5]. The value of each of these strategies in different combinations is not clear, with the possibility that it may be unnecessary to perform both enhanced optical TURBT and SIIC. The primary aim of this systematic review and network meta-analysis was to determine the optimal initial bladder tumour management based on a combination of different optical techniques during TURBT and SIIC as compared to WLC alone.

Methods

Literature Search

The protocol for this study was registered *a priori* in the International Prospective Register of Systematic Reviews (CRD42021228601). Our search was performed using the

electronic databases PubMed and Web of Science in September 2020. The systematic review and network meta-analysis of randomized controlled trials (RCTs) for different optical techniques at the time of TURBT (PDD, NBI and WLC) \pm SIIC (with WLC alone as the control arm) were conducted according to the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) extension statement for network meta-analyses [6]. The following search terms were used: ‘hexaminolevulinic’ AND ‘blue light’ AND ‘5-aminolevulinic’ AND ‘single immediate intravesical chemotherapy’ AND ‘transurethral resection of bladder tumour’ OR ‘TURBT’ AND ‘(randomizedcontrolledtrial [Filter])’. Manual searches of the reference lists of relevant articles were also performed to identify additional studies. The primary outcome of interest was recurrence rate during the first year after TURBT.

Inclusion and Exclusion Criteria

Studies were included if they investigated patients with bladder tumour (Patients) who had received TURBT using PDD \pm SIIC, NBI \pm SIIC, or WLC + SIIC (Intervention) compared with those treated with a TURBT by WLC alone (Comparison) to assess the first-year recurrence rate (Outcomes) in a randomized controlled study only. We excluded observational studies, reviews, letters, editorials, meeting abstracts, replies from authors, case reports, and articles not published in English. The references of all papers included were scanned for additional studies of interest. Studies were included only if they involved patients who received a TURBT by WLC as the control arm.

Study Selection

We selected RCTs that used fluorescence cystoscopy with a photoactive compound (HAL or 5-ALA), NBI or WLC to detect bladder tumour during TURBT. Moreover, use or no use of SIIC after TURBT was identified in the RCTs.

Although most of the RCTs that used WLC plus SIIC as an intervention arm and WLC alone as a control arm included only low-risk group patients, we selected only studies that included all risk groups of non-muscle-invasive bladder cancer (i.e. low-, intermediate- and high- risk patients), we made comparable network meta-analysis arms in the study population. Initial screening was performed independently by two investigators based on the titles and abstracts of the article to identify eligible and ineligible reports. Reasons for exclusion were noted. Potentially relevant reports were subjected to a full-text review, and the relevance of the reports was confirmed after the data extraction process. Disagreements were resolved via consensus among the co-authors and consultation with the senior author.

Data Extraction

Two investigators independently extracted the following information from the included articles: first author's name; publication year; period of patient recruitment; number of patients; optical technique and use of SIIC; age; study design; study funding and/or support; and the recurrence rate during the first year after TURBT according to the follow-up cystoscopy. Subsequently, the number of patients with recurrence was retrieved. All discrepancies regarding data extraction were resolved by consensus with the co-authors or by discussion with the senior author.

Methodological Quality

The 'risk-of-bias' evaluation, RoB 2, of each study was assessed according to the Cochrane Collaboration tool for assessing risk of bias [7]. This tool assesses selection bias (random sequence generation and allocation concealment), performance bias, detection bias, attrition bias, reporting bias, and other sources of bias. RoB 2 of each study was assessed independently by the two authors. Disagreements were resolved by consultation with the co-authors or discussion with the senior author. The robvis tool was used to create risk-of-bias plots [8].

Statistical Analysis

We conducted a network meta-analysis using random- and fixed-effect models with a Bayesian approach for direct and indirect treatment comparisons, with WLC as the common comparator arm [9,10]. Sensitivity analysis was conducted after categorizing PDD according to the different photoactive compounds (HAL and 5-ALA). Odds ratio (OR) was used to denote the results with a 95% credible interval (CrI), indicating the strength of association between treatments and outcomes. In Bayesian statistics, CrI is the interval within which an unobserved value falls with a particular probability. Pooled ORs and their 95% CrIs were also calculated. Statistical significance was established with a two sided P

value < 0.05 or a 95% CrI that did not include a value of 1. All treatments were ranked according to surface under the cumulative ranking curve (SUCRA) probability. Network plots were used to illustrate the connectivity of the treatment networks in terms of the proportion of patients. All Bayesian statistical calculations were performed using MetaInsight software [10] from the R package gemtc, gemtc: Network Meta-Analysis Using Bayesian Methods R package version 0.8-2. and R package BUGSNET, BUGSnet: Bayesian inference Using Gibbs Sampling to conduct NETWORK meta-analysis version 1.0.3 [11]. Statistical significance was set at $P < 0.05$.

Results

Search Results

Our initial search identified 361 publications, and after the elimination of duplicates, 157 publications were available. A total of 118 articles were excluded after screening the titles and abstracts, and a full-text review was performed for 39 articles. Figure 1 shows the flowchart for the selection process.

Characteristics of the Studies Included

Based on the selection criteria, we identified 22 articles comprising 4519 patients for this systematic review and network meta-analysis [12–34]. Extracted data from the 22 studies are outlined in the online supplementary materials. All studies included patients with suspected bladder tumour and/or confirmed non-muscle-invasive bladder cancer including all risk group patients (i.e. low-, intermediate- and high-risk patients) who underwent TURBT using one optical technique (BLC, including HAL or 5-ALA as the photoactive compounds, NBI and WLC) with and/or without a concomitant SIIC. All studies were published between 2001 and 2018; they included a total of 21 two-arm studies and one multi-arm study, with six different interventions (Fig. 2).

Network Meta-Analysis

The network of eligible comparisons is graphically represented in network plots in terms of the recurrence rate (during at least 12 months of follow-up; Fig. 2).

A network meta-analysis of six different interventions including three different optical techniques (BLC, WLC and NBI) with or without concomitant SIIC was conducted for the primary outcome of 12-month recurrence rate. Compared with WLC at the time of TURBT, BLC plus SIIC (OR 0.349, 95% CrI 0.196–0.601), and BLC alone (OR 0.668, 95% CrI 0.459–0.931) were associated with a significantly lower

Fig. 1 Study selection process. RCT, randomized controlled trial.

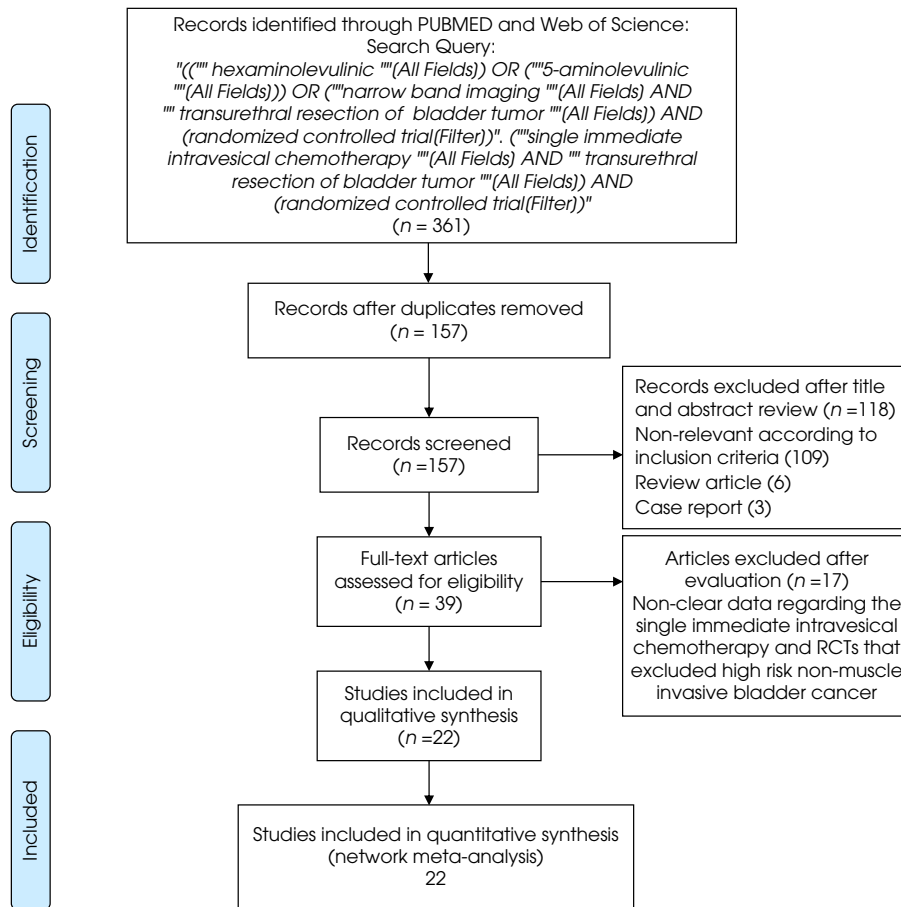
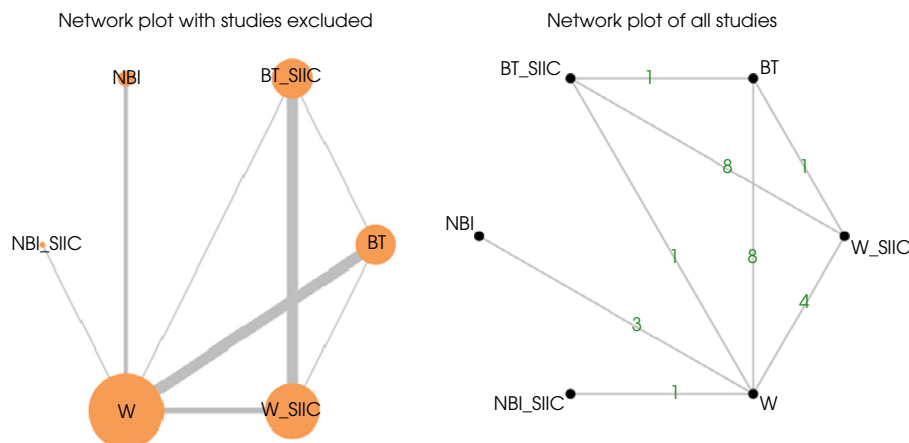


Fig. 2 Network plot of randomized controlled trials that assessed the recurrence rate of non-muscle-invasive bladder cancer after transurethral resection according to optical technique with and without single immediate intravesical chemotherapy (SIIC). Number of trials shown on the line. Number of people indicated by size of the node. ALA, 5-aminolevulinic acid; BT, bladder tumour; HAL, hexaminolevulinic acid; NBI, narrow-band imaging; SIIC, single immediate intravesical chemotherapy; W, white light.



Number of Interventions: 6, Number of Studies: 22, Total Number of Patients in Network: 4519, Total Possible Pairwise Comparisons: 15, Total Number of Pairwise Comparisons With Direct Data: 8, Number of Two-arm Studies: 21, Number of Multi-Arms Studies: 1, Total Number of Events in Network: 1663, Number of Studies With No Zero Events: 22.

likelihood of recurrence at 12 months. The main results of the network meta-analysis are shown in Fig. 3. Based on Bayesian analysis and analysis of the treatment ranking according to SUCRA, it was highly likely that BLC plus SIIC was the best treatment strategy at the time of TURBT

(Fig. 3). NBI, both with and without SIIC, was not associated with a significantly lower likelihood of 12-month recurrence rate (OR 0.385, 95% CrI 0.105–1.29 and OR 0.653, 95% CrI 0.343–1.15), However, according to SUCRA, both were better than WLC alone (Figs 3 and 4).

Fig. 3 Summary of the Bayesian network meta-analysis. **A**, Forest plot of Bayesian random-effect consistency model for all studies compared to the white light cystoscopy (W). **B**, Ranking with all studies: network meta-analysis median rank chart. BL, blue light; NBI, narrow-band imaging; SIIC, single immediate intravesical chemotherapy.

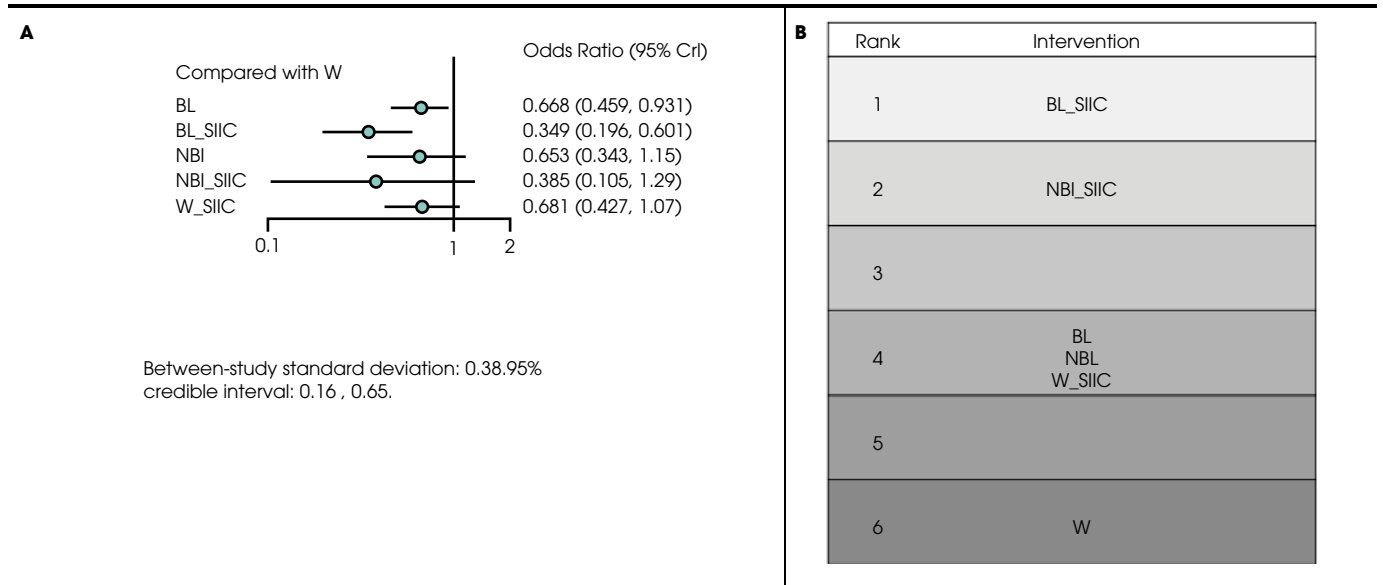
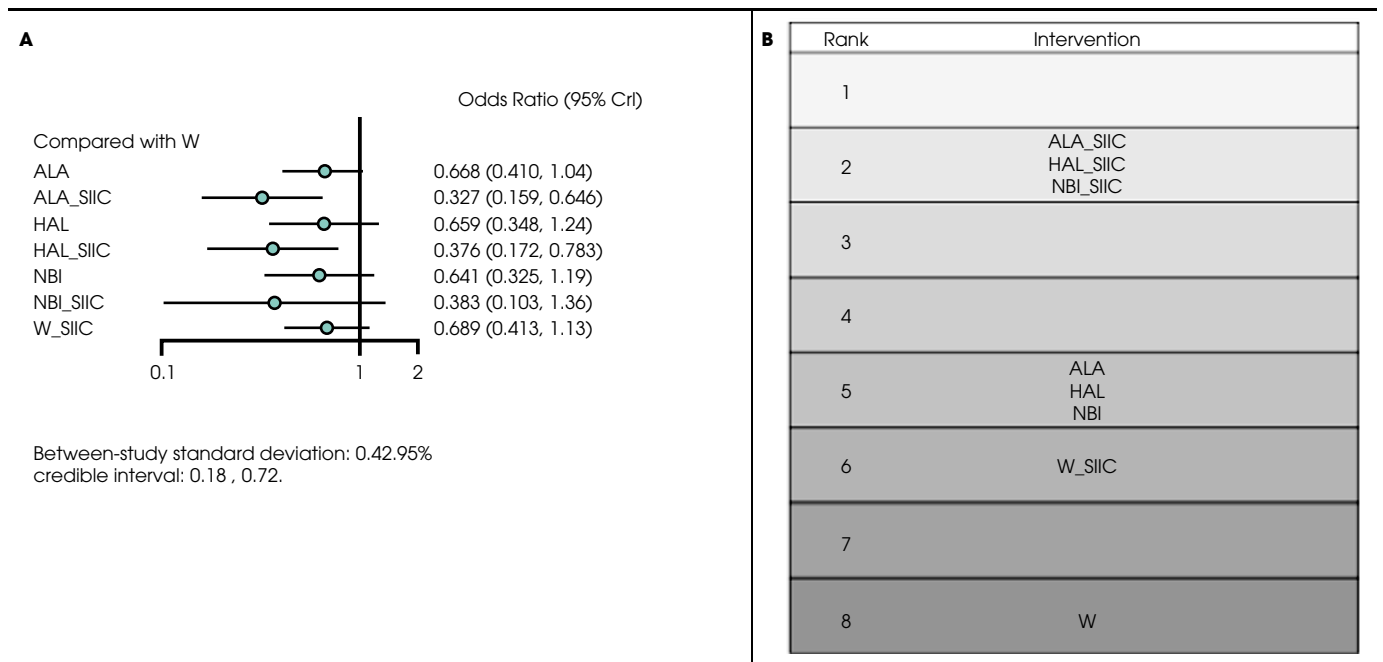


Fig. 4 Summary of the Bayesian sensitivity network meta-analysis. **A**, Forest plot of Bayesian random effect consistency model for all studies compared to the white light cystoscopy. **B**, Ranking with all studies: network meta-analysis median rank chart. ALA, 5-aminolevulinic; BL, blue-light; HAL, hexaminolevulinic; NBI, narrow-band imaging; SIIC, single immediate intravesical chemotherapy; W, white-light.



In the sensitivity analysis, BLC was categorized according to the photoactive compounds (HAL or 5-ALA). Thus, eight different interventions, as stated in the Materials and Methods section, were compared with WLC alone. We found that PDD using 5-ALA plus SIIC (OR 0.327, 95% CrI 0.159–0.646) and PDD using HAL plus SIIC (OR 0.376, 95% CrI 0.172–0.783) were both associated with a significantly lower possibility of recurrence at 12 months. The summary of the sensitivity analysis results is shown in Fig. 4. Based on SUCRA probability ranking analysis, it was highly likely that all new optical techniques plus SIIC were better than the new optical techniques alone and, furthermore, all new optical techniques with or without SIIC were better than WLC alone (Figs 3 and 4). We summarized our study design and main results as the recommendations for clinicians shown in Fig. 5.

Bias Assessment

The assesment of risk of bias in the RCTs was performed according to the Cochrane recommendations; the results are

presented in Table 1. Generally, studies included in this systematic review and network meta-analysis had a low risk of bias, unlike the randomization process (Domain 1).

Discussion

We confirmed that recurrence rate at 12 months in patients with non-muscle-invasive bladder cancer was significantly reduced when BLC was performed (PPD with HAL and/or 5-ALA) at the time of TURBT compared to WLC, regardless of SIIC. This reduction in the recurrence rate afforded by BLC was significantly heightened by adding SIIC (BLC plus SIIC), with approximately 32% improvement in OR for recurrence rate at 12 months. The use of NBI at the time of TURBT, with or without SIIC, resulted in ORs (0.653 and 0.385, respectively) that were not statistically different from those associated with WLC alone (Figs 3 and 4). However, according to the SUCRA ranking probability analysis, NBI, both with and without SIIC, was better than WLC alone in terms of 12-month recurrence risk.

Fig. 5 Recommendations for using the enhanced optical techniques according to the present network meta-analysis including 22 randomized clinical trials. *Blue light or photodynamic diagnosis is same in this systematic review. SIIC, single immediate intravesical chemotherapy; SUCRA, the surface under the cumulative ranking curve; TURBT, transurethral resection of bladder tumour.

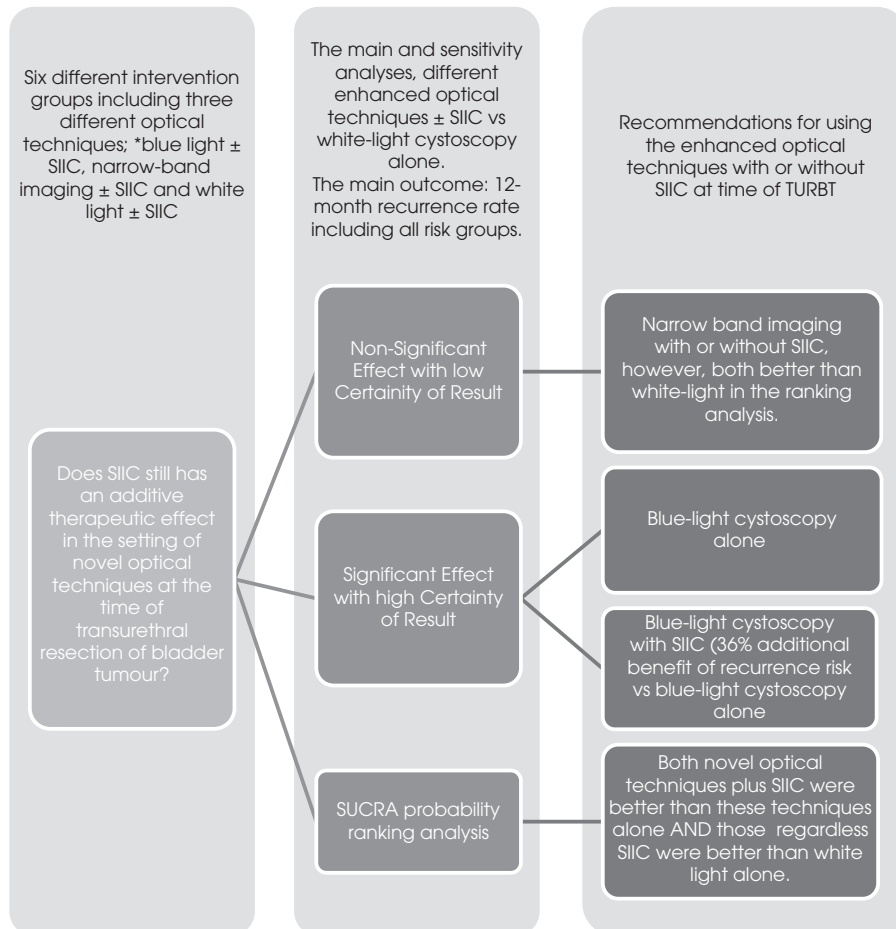





Table 1 Risk of bias assessment for all studies that included in the systematic review and network meta-analysis.

| | Risk of bias domains | | | | | |
|---|----------------------|----|----|----|----|---------|
| | D1 | D2 | D3 | D4 | D5 | Overall |
| Drăgoescu et al. 2017 [12] | - | + | + | - | + | + |
| Gkritisios et al. 2014 [14] | + | + | + | + | + | + |
| O'Brien et al. 2013 [15] | - | - | + | + | + | + |
| Karaolides et al. 2012 [16] | X | + | + | + | - | - |
| Geavlete et al. 2011 [17] | + | + | - | + | - | + |
| Drăgoescu et al. 2011 [34] | - | + | + | - | + | + |
| Stenzl et al. 2010 [2] (Grossman et al 2012 [18]) | + | + | + | + | + | + |
| Hermann et al. 2010 [19] | - | + | - | + | + | + |
| Rolevich et al. 2016 [20] | + | + | + | + | + | + |
| Stenzl et al. 2011 [21] | - | + | + | + | + | + |
| Schumacher et al. 2010 [22] | + | + | + | + | + | + |
| Denzinger et al. 2007 [23] | + | + | + | + | + | + |
| Bobjuk et al. 2005 [33] | X | + | + | - | + | - |
| Daniltschenko et al. 2005 [24] | + | + | + | + | + | + |
| Filbeck et al. 2002 [25] | + | + | + | + | + | + |
| Elsawy et al. 2018 [26] | + | - | + | + | + | + |
| Böhle et al. 2009 [27] | + | + | + | + | + | + |
| Rajla et al. 2002 [28] | + | + | + | + | - | + |
| Kim et al. 2018 [29] | + | - | + | + | - | + |
| Naito et al. 2016 [30] | + | - | + | + | + | + |
| Naselli et al. 2012 [31] | + | + | + | + | + | + |
| Geavlete et al. 2012 [32] | X | - | + | + | + | - |

Domains:
 D1: Bias arising from the randomization process.
 D2: Bias due to deviations from intended intervention.
 D3: Bias due to missing outcome data.
 D4: Bias in measurement of the outcome.
 D5: Bias in selection of the reported result.

Judgement
 High
 Some concerns
 Low

A sensitivity analysis confirmed the main analysis findings. We categorized PDD according to the type of photoactive compound (HAL and 5-ALA) and use of SIIC, as well as eight different interventions including four different optical techniques. We found that using PDD with 5-ALA and/or HAL (both with concomitant SIIC) at the time of TURBT significantly reduced the recurrence rate at 12 months. Although PDD using 5-ALA and/or HAL (both without concomitant SIIC) both demonstrated this, statistical significance was not reached (OR 0.668, 95% CrI 0.410–1.04 and OR 0.659, 95% CrI 0.348–1.24, respectively). The latter result could be explained by the decreasing power of analysis due to the decreasing number of RCTs after categorizing PDD in each new arm of the network. Pharmacological studies have suggested some favourable characteristics of HAL vs 5-ALA, such as greater bioavailability due to its lipophilic property, twofold increased fluorescence intensity, and pharmacological stability at room temperature. Moreover, 5-ALA is readily photobleached and therefore not feasible to use in daily clinical practice, and is no longer commercially available. However, according to our results and those of other cohort studies, its clinical benefits are comparable to HAL when used at the time of TURBT [35]. Cost-effectiveness, in addition to clinical effectiveness, is an important factor in the uptake of new technologies. The use of a single-instillation HAL for TURBT is cost-neutral or cost-saving in over 5 years, saving approximately €537 per patient in addition to its clinical benefits [36,37].

Our results showed that use of concomitant SIIC at the time of WLC TURBT did not significantly decrease the 12-month recurrence rate compared to use of WLC alone. As stated above, only RCTs that involved all risk groups of patients with non-muscle-invasive bladder cancer (i.e. low-, intermediate- and high-risk patients) were included in this review [26–28]. This finding is in accordance with the current recommended guidelines (European Urological Association and AUA), which do not recommend SIIC for patients with high-risk non-muscle-invasive bladder cancer because the greatest effect is in those with single, small, low-grade tumours [3,4].

The main limitation of the present network meta-analysis was the lack of RCTs that used PDD with HAL plus SIIC as an intervention arm and WLC alone as a control arm. RCTs that used PDD with 5-ALA plus SIIC compared to WLC alone were included instead. Although both PDD using 5-ALA and/or HAL seem to have the same clinical effect, there were more RCTs that used 5-ALA with or without a concomitant SIIC as an intervention arm. Additionally, owing to lack of the reported data, a sensitivity analysis according to the patient risk groups (low-, intermediate- and high-risk) was not feasible, consequently, our results could not mention the specified subgroup of patients. However, because the exact pathological stage and risk group are not clear to clinicians at

the first presentation of bladder tumours, the use of both PDD and SIIC could be recommended as the optimal management of bladder tumours at first presentation (Fig. 5). Another limitation was the small number of RCTs that investigated the effect of NBI on non-muscle-invasive bladder cancer recurrence risk, but with concerns regarding the assessment of bias. Our results on the use of NBI during TURBT should be considered with caution; future well-designed RCTs need to confirm the effect of NBI with or without SIIC on the recurrence rate of patients with non-muscle-invasive bladder cancer.

In conclusion, the findings of the present network meta-analysis support the combination of PDD at the time of TURBT and concomitant SIIC as the optimal initial treatment in patients with non-muscle-invasive bladder cancer. Usage of PDD at the time of TURBT can reduce the recurrence rate at 12 months and with concomitant SIIC enhancing this benefit by 32% additional reduction of odds ratio of the 12 months recurrence risk. Although PDD can increase the rate of tumour detection during TURBT and consequently reduce the recurrence rate, SIIC is still warranted. According to the SUCRA probability ranking analysis, PDD and NBI, both plus SIIC, were better than these techniques alone, and moreover, all novel optical techniques regardless SIIC were better than WLC alone.

Disclosure of Interests

None declared.

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Abbreviations: ALA, aminolevulinic acid; BLC, blue-light cystoscopy; CrI, credible interval; HAL, hexaminolevulinic acid; NBI, narrow-band imaging; OR, odds ratio; PDD, photodynamic diagnosis; RCT, randomized controlled trial; SIIC, single immediate intravesical chemotherapy; SUCRA, surface under the cumulative ranking curve; TURBT, transurethral resection of bladder tumour; WLC, white-light cystoscopy.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Fig. S1. Main analysis.

Fig. S2. Sensitivity analysis.

Fig. S3. Main analysis Gelman convergence assessment plot for all studies.

Fig. S4. Sensitivity analysis Gelman convergence assessment plot for all studies.

Table S1. Inconsistency test with notesplitting model.

Table S2. Characteristics of the randomized clinical trials was included to network meta-analysis.