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Narrow band imaging versus white light cystoscopy alone for transurethral resection of non-muscle invasive bladder cancer (Review)

Lai LY, Tafuri SM, Ginier EC, Herrel LA, Dahm P, Maisch P, Lane GI

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[Intervention Review]

Narrow band imaging versus white light cystoscopy alone for transurethral resection of non-muscle invasive bladder cancer

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ABSTRACT

Background

Disease recurrence and progression remain major challenges for the treatment of non-muscle invasive bladder cancer. Narrow band imaging (NBI) is an optical enhancement technique that may improve resection of non-muscle invasive bladder cancer and thereby lead to better outcomes for people undergoing the procedure.

Objectives

To assess the effects of NBI- and white light cystoscopy (WLC)-guided transurethral resection of bladder tumor (TURBT) compared to WLC-guided TURBT in the treatment of non-muscle invasive bladder cancer.

Search methods

We performed a comprehensive literature search of 10 databases, including the Cochrane Library, the Cochrane Database of Systematic Reviews, MEDLINE, Embase, several clinical trial registries, and grey literature for published and unpublished studies, irrespective of language. The search was performed per an a priori protocol on 3 December 2021.

Selection criteria

We included randomized controlled trials of participants with suspected or confirmed non-muscle invasive bladder cancer. Participants in the control group must have received WLC-guided TURBT alone (hereinafter simply referred to as 'WLC TURBT'). Participants in the intervention group had to have received NBI- and WLC-guided TURBT (hereinafter simply referred to as 'NBI + WLC TURBT').

Data collection and analysis

Two review authors independently selected studies for inclusion/exclusion, performed data extraction, and assessed risk of bias. We conducted meta-analysis on time-to-event and dichotomous data using a random-effects model in RevMan, according to Cochrane methods. We rated the certainty of evidence for each outcome according to the GRADE approach.

Primary outcomes were time to recurrence, time to progression, and the occurrence of a major adverse event, defined as a Clavien-Dindo III, IV, or V complication. Secondary outcomes included time to death from bladder cancer and the occurrence of a minor adverse event, defined as a Clavien-Dindo I or II complication.

Main results

We included eight studies with a total of 2152 participants randomized to the standard WLC TURBT or to NBI + WLC TURBT. A total of 1847 participants were included for analysis.

Based on limited confidence in the time-to-event data, we found that NBI + WLC TURBT may lower the risk of disease recurrence over time compared to WLC TURBT (hazard ratio 0.63, 95% CI 0.45 to 0.89; I^2 = 53%; 6 studies, 1244 participants; low certainty of evidence). No studies examined disease progression as a time-to-event outcome or a dichotomous outcome. There may be little to no difference in the risk of a major adverse event between participants who underwent NBI + WLC TURBT and those who underwent WLC TURBT (risk ratio 1.77, 95% CI 0.79 to 3.96; 4 studies, 1385 participants; low certainty of evidence).

No studies examined death from bladder cancer as a time-to-event outcome or a dichotomous outcome. There may be little to no difference in the risk of a minor adverse event between participants who underwent NBI + WLC TURBT and those who underwent WLC TURBT (risk ratio 0.88, 95% CI 0.49 to 1.56; I^2 = 61%; 4 studies, 1385 participants; low certainty of evidence).

Authors' conclusions

Compared to WLC TURBT alone, NBI + WLC TURBT may lower the risk of disease recurrence over time while having little or no effect on the risks of major or minor adverse events.

PLAIN LANGUAGE SUMMARY

Comparing narrow band imaging to regular cystoscopy for treatment of bladder cancer

Review question

How does a resection of bladder tissues guided by a special visualization method called narrow band imaging compare to a resection of bladder tissues guided by the standard visualization method (using white light) in people with tumors in their inner bladder wall?

Background

When people are suspected to have bladder cancer or have been diagnosed with bladder cancer, their doctors need to inspect the bladder closely and remove tissues for further examination. The removal of tumorous tissues also serves as treatment. The procedure to remove tumors in the bladder is called transurethral resection of bladder tumor, or TURBT. TURBT is done by passing a special instrument through the urethra and into the bladder. Sometimes, it is difficult to distinguish healthy normal bladder tissue from tumorous tissue. Some doctors use a special visualization method known as narrow band imaging to help visualize the tumorous tissues.

Study characteristics

We analyzed data from published studies called randomized controlled trials to understand if narrow band imaging reduces the risk of bladder cancer getting worse, and to see if there are any side effects. We only included randomized controlled trials because this study type is the most reliable.

Key results

We identified eight randomized controlled trials that addressed our review question. Participants included in these studies were suspected to have bladder cancer or were diagnosed with bladder cancer that was limited to the inner wall, meaning that the cancer did not invade the underlying muscle layers. Based on limited available data, the use of narrow band imaging may lower the risk of disease recurrence over time.

None of the randomized controlled trials examined whether the choice of visualization method made any difference to the risk of bladder cancer becoming worse or the risk of the person dying from bladder cancer, so we do not know if the use of narrow band imaging is effective in improving these two outcomes.

We found that the use of narrow band imaging may have little or no increased risk of complications, compared to the standard visualization method.

Quality of the evidence

Due to certain flaws in the design of these clinical trials and some contradictory findings between trials, our confidence in these findings was low. With more research in the future, more reliable data may likely change these findings. The evidence is up to date to December 2021.

Summary of findings 1. NBI + WLC TURBT compared to WLC TURBT for transurethral resection of bladder tumors in people with suspected or diagnosed non-muscle invasive bladder cancer

NBI + WLC TURBT compared to WLC TURBT for transurethral resection of bladder tumors in people with non-muscle invasive bladder cancer

Patient or population: transurethral resection of bladder tumors in people with suspected or diagnosed non-muscle invasive bladder cancer
Setting: outpatient or inpatient setting
Intervention: NBI + WLC TURBT
Comparison: WLC TURBT

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)		What happens
				Risk with WLC TURBT	Risk difference with NBI + WLC TURBT	
Time to disease recurrence Follow-up: range 12 months to 35 months Assumed MCID: 5% (absolute effect size estimate based on events at 12 months)	1244 (6 RCTs)	⊕⊕⊖⊖ LOW[a,b]	HR 0.63 (0.45 to 0.89)	Low[c]		In the low risk population, NBI + WLC TURBT may lower the risk of disease recurrence over time. We have limited confidence about this finding.
				150 per 1000	53 fewer per 1000 (79 fewer to 15 fewer)	
		⊕⊕⊖⊖ LOW[a,b]		High[c]		In the high risk population, NBI + WLC TURBT may lower the risk of disease recurrence over time. We have limited confidence about this finding.
				610 per 1000	163 fewer per 1000 (265 fewer to 43 fewer)	
Time to disease progression Follow-up: not applicable Assumed MCID: 2%	-	-	-	-	-	We found no data on time to disease progression.
Major adverse event (Clavien-Dindo grade III, IV, and V)	1385 (4 RCTs)	⊕⊕⊖⊖ LOW[a,b]	RR 1.77 (0.79 to 3.96)	Study population		

Follow-up: range 3 months to 24 months Assumed MCID: 2%				13 per 1000	10 more per 1000 (3 fewer to 39 more)	NBI + WLC TURBT may have little to no effect on major adverse events. We have limited confidence about this finding.
Time to death from bladder cancer Follow-up: not applicable Assumed MCID: 2%	-	-	-	-	-	We found no data on time to death from bladder cancer.
Minor adverse event (Clavien-Dindo grade I and II) Follow-up: range 3 months to 24 months Assumed MCID: 5%	1385 (4 RCTs)	⊕⊕⊖⊖ LOW [a,b]	RR 0.88 (0.49 to 1.56)	Study population 113 per 1000	14 fewer per 1000 (58 fewer to 63 more)	NBI + WLC TURBT may have little to no effect on the risk of a minor adverse event. We have limited confidence about this finding.

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

CI: confidence interval; **HR:** hazard ratio; **MCID:** minimal clinically important difference; **NBI:** narrow band imaging; **RCT:** randomized controlled trial; **RR:** risk ratio; **TURBT:** transurethral resection of bladder tumor; **WLC:** white light cystoscopy

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

[a]We rated down by one level for study limitations due to unclear or high risk of bias.

[b]We rated down by one level for imprecision given few events, wide confidence intervals, or both.

[c]The recurrence rate after TURBT for participants with non-muscle invasive bladder cancer is highly variable in the literature. Among the pooled cohort of 2596 participants from seven European Organization for Research and Treatment of Cancer clinical trials, the probabilities of recurrence at one year after TURBT ranged from 15% to 61% (Sylvester 2006). Therefore, we considered 15% as low risk and 61% as high risk.

BACKGROUND

Description of the condition

Bladder cancer is the tenth most common malignancy and the second most common urologic malignancy worldwide, with an estimated 550,000 new cases and 200,000 deaths per year (Bray 2018). Specifically, urothelial carcinoma accounts for 90% of all bladder cancers in the USA and Europe. Smoking contributes to 50% to 65% of all bladder cancer cases, increasing the risk of disease by up to four-fold (Freedman 2011). Additional risk factors include environmental and occupational exposure to chemical carcinogens such as aromatic amines, and treatment of leukemia and lymphoma with cyclophosphamide (Chang 2016).

People with bladder cancer most often present with blood in their urine, but tumors can also be found during the evaluation for other symptoms, such as irritative voiding symptoms. The prevalence of bladder cancer ranges between 13% and 35% in people presenting with macroscopic hematuria and between 5% and 10% in those with microscopic hematuria (Sun 2015). People with bladder tumors then proceed to undergo transurethral resection of bladder tumor (TURBT), where tumorous tissues are removed for staging and treatment.

Pathologists classify tumors based on cell histology and the depth of invasion into the layers of the bladder wall (in order of depth: mucosa, lamina propria, and muscle layers). The majority of bladder cancers present as superficial tumors that do not invade the underlying bladder muscle at diagnosis. These superficial tumors are referred to as non-muscle invasive bladder cancer, and have a 60% to 70% risk of recurrence (Aldousari 2010). Histologic characteristics can also predict the risk of progression. In general, papillary tumors on the mucosa of the bladder (Ta) are indolent, whereas the subset of superficial tumors called carcinoma in situ (CIS or Tis), and tumors that invade to the lamina propria layer (T1), are considered more aggressive and of concern for progression to muscle invasive disease (Humphrey 2016).

Once non-muscle invasive bladder cancer invades the muscle layers, the disease is referred to as muscle invasive bladder cancer. Muscle invasive bladder cancer is associated with high rates of morbidity and mortality, and its treatment approach is highly invasive (Sun 2015). As bladder cancer progresses, the survival rate drops significantly. Within the USA, the five-year survival rate for people with carcinoma in situ is 95.8%; for those with localized disease confined to primary site, it is 69.2%; for those with regional disease with spread of disease to regional lymph nodes, it is 36.5%; and for those with metastatic disease, it is 5.5% (SEER 2020).

Description of the intervention

Traditionally, TURBT is performed using white light cystoscopy (WLC). During this procedure, experienced urologists visually distinguish conspicuous lesions from normal mucosa. However, complete identification and removal of tumors during TURBT can be challenging, as the sensitivity of WLC ranges from 62% to 84% for identifying bladder tumors, and the specificity ranges from 43% to 98% (Sun 2015). The sensitivity of WLC is particularly low for small or flat lesions that are visually subtle or difficult to differentiate from areas of inflammation. Consequently, some recurrences can be attributable to, if not entirely consisting of, lesions left behind due to incomplete resection (Sylvester 2006). On second-look TURBT using WLC, the residual tumor rate was reported to be as high as 43% to 62% (Goh 2009). Given these limitations, additional technologies are needed to augment the visual detection of tumors in the lower urinary tract. One such technology is narrow band imaging (NBI).

The NBI setting on the cystoscope changes the optical filters used to visualize the bladder, resulting in an image that may potentially improve visualization of tumors. At the time of the TURBT, urologists can toggle between white light and NBI using camera setting buttons, to help identify tumors.

How the intervention might work

The working principle of NBI relies on two phenomena. First, hemoglobin characteristically absorbs blue light at 415 nm and green light at 540 nm (Srivastava 2019). NBI uses optical filters to narrow the bandwidth of white light, such that only blue and green light pass through. NBI light is then preferentially absorbed by vessels, and reflected by mucosa. Second, the depth of light penetration into tissues depends on wavelength; the shorter the wavelength, the more superficial the penetration. The shorter NBI light wavelength only penetrates the superficial layers of the mucosa. Together, the differential absorption and penetration enhance the visibility of surface capillaries and blood vessels in the submucosa.

Under NBI mode, tumors with richer vasculature appear dark green or black in a background of normal urothelium, which appears mostly white (Naselli 2009). In contrast, lesions appear red under white light mode against the normal urothelium, which appears pink. Because tumors have more blood vessels than normal mucosa, NBI can potentially improve visualization of lesions that are difficult to see, and delineation of tumor margins, which together can enable more thorough tumor excision.

The impact of NBI on time-to-disease recurrence outcomes may not only be in the primary detection and resection of tumors, but also due to the fact that increased detection and resection of tumors may impact the individual's risk stratification and lead to more aggressive observation and intervention schedules (Chang 2016). Therefore, the benefit (or harm) of NBI + WLC TURBT may be compounded due to the impact of the intervention on subsequent patient care.

In contrast to blue light cystoscopy, another form of optical enhancement technology (Maisch 2021), NBI does not require any chemical to function. Moreover, systems integrating WLC and NBI are readily available (Naselli 2009). The NBI mode on a cystoscope can be activated with a control button, without adding significant risks or interruptions to the flow of the procedure.

Adverse effects of the intervention

NBI highlights areas of increased blood vessels, which is a surrogate for a potential tumor. The technology does not specifically identify tumors. The increased sensitivity compounded by decreased specificity may increase false positive rates. This can lead to more extensive resection and over-treatment, increasing the risk of bleeding or complications, such as bladder perforation. Also, NBI cannot be used when there is active bleeding, since blood can absorb NBI light and obstruct visibility.

Why it is important to do this review

The impact of NBI during TURBT remains unclear. The detection and complete resection of non-muscle invasive bladder cancer lesions are central to the treatment of the disease. Optical advances, such as NBI, offer the potential to improve clinicians' ability to detect tumors. However, the effect of NBI on decreasing recurrence and progression is not well assessed.

Currently, the American Urological Association/Society of Urologic Oncology guideline suggests a conditional recommendation for the use of NBI + WLC TURBT (Chang 2016). While the European Association of Urology acknowledges that NBI may improve cancer detection, its guideline states that evidence for potential reductions in recurrence rate is limited (Babjuk 2019). Meanwhile, the National Institute for Health and Care Excellence guideline suggests that NBI may be offered to people with suspected bladder cancer in conjunction with WLC TURBT (NICE 2015). In this context, we conducted a stringent examination of current evidence to help inform clinicians and guideline developers on the use of NBI at time of TURBT.

OBJECTIVES

To assess the effects of NBI- and white light cystoscopy (WLC)-guided transurethral resection of bladder tumor (TURBT) compared to WLC-guided TURBT in the treatment of non-muscle invasive bladder cancer.

METHODS

Criteria for considering studies for this review

Types of studies

We included all relevant randomized controlled trials, in which individual participants were randomized.

We excluded quasi-experimental studies and cluster-randomized trials due to their lack of random assignment at the individual level (Puffer 2005). We excluded cross-over trials from our review, as both the comparator and the experimental interventions involve removal of bladder tumors. Inclusion of cross-over trials would present a serious carry-over effect (Higgins 2011).

Types of participants

We defined the eligible population as adults, aged 18 and over, with a suspected or established diagnosis of primary or recurrent urothelial carcinoma of the bladder, based on one of the following.

- Bladder mass or abnormal bladder mucosa findings per clinic-based WLC
- Bladder mass on cross-sectional imaging, such as bladder filling defects and hydronephrosis
- Positive or atypical urinary cytology
- Positive fluorescence in situ hybridization test

We excluded participants undergoing NBI-guided surveillance, as we were only considering the use of NBI in the treatment setting. We also excluded participants with distant metastatic disease.

If studies included multiple participant groups or interventions, we only included the subset of participants of interest. If multiple articles were published by the same group with the same participant cohort, we merged and analyzed relevant data from each article as one study.

Types of interventions

Concomitant interventions had to be the same in the experimental and control groups to establish fair comparisons. Trials that described more than one use of NBI + WLC (for example: during subsequent cystoscopy or TURBT) were included, and this information was reported separately if available.

Experimental intervention

WLC- and NBI- guided TURBT (herein referred to as NBI + WLC TURBT)

Comparator intervention

WLC-guided TURBT (herein referred to as WLC TURBT)

Comparison

NBI + WLC TURBT versus WLC TURBT in the treatment of non-muscle invasive bladder cancer.

Types of outcome measures

We included studies assessing the impact of NBI + WLC TURBT on the recurrence or progression of non-muscle invasive bladder cancer and excluded studies that reported data on NBI + WLC TURBT solely for the detection of bladder cancer.

Primary outcomes

- Time to disease recurrence (time-to-event outcome)
- Time to disease progression (time-to-event outcome)
- Major adverse event: Clavien-Dindo grade III, IV, or V (dichotomous outcome)

Secondary outcomes

- Time to death from bladder cancer (time-to-event outcome)
- Minor adverse event: Clavien-Dindo grade I or II (dichotomous outcome)

Method and timing of outcome measurement

Primary outcomes

1. **Time to disease recurrence**: measured from the time of random sequence generation to time of any recurrence of bladder cancer, based on TURBT, regardless of tumor stage or grade.
2. **Time to disease progression**: measured from the time of random sequence generation to time of progression of bladder cancer as documented by histopathology. Consistent with the International Bladder Cancer Group (Lamm 2014), we defined progression as follows.
   a. Increase in T stage from CIS or Ta to T1
   b. Development of T2 or greater or lymph node disease or distant metastasis
   c. Increase in grade from low to high, including CIS
3. **Major adverse event**: Clavien-Dindo grade III, IV, or V (Clavien 2009), within 90 days of TURBT

Secondary outcomes

1. **Time to death from bladder cancer**: measured from the time of random sequence generation to the time of death from bladder cancer.
2. **Minor adverse event**: Clavien-Dindo grade I or II (Clavien 2009), within 90 days of TURBT

When data on the time to disease recurrence, time to disease progression, or time to death from bladder cancer were incomplete and could not be analyzed as time-to-event outcomes, we had planned to analyze these outcomes as dichotomous outcomes (up to 12 months, or 13 to 24 months after randomization) in efforts to increase the comprehensiveness of our analysis. This was not necessary.

Thresholds for clinical relevance of outcomes

Primary outcomes

1. Time to disease recurrence: considered clinically relevant if the observed absolute difference is 5% or more at 12-month follow-up
2. Time to disease progression: considered clinically relevant if the observed absolute difference is 2% or more at 12-month follow-up
3. Major adverse event: considered clinically relevant if the observed absolute difference is 2% or more at initial TURBT or re-resection

Secondary outcomes

1. Time to death from bladder cancer: considered clinically relevant if the observed absolute difference is 2% or more at 12-month follow-up
2. Minor adverse event: considered clinically relevant if the observed absolute difference is 5% or more at initial TURBT or re-resection

We established these thresholds based on the expert opinions of the review authors, taking into consideration the relative importance of the given outcome, and the expected control event rate.

Search methods for identification of studies

We conducted a comprehensive search, inclusive of all languages and publication statuses. We reran the search within three months prior to anticipated publication of the review.

Electronic searches

We searched for relevant studies in the following ten databases from their respective dates of inception to 14 September 2020 and 3 December 2021, using the search strategies outlined in the Appendices.

1. Cochrane Library (via Wiley); Appendix 1
2. International Pharmaceutical Abstracts (via Ovid); Appendix 2
3. MEDLINE (via Ovid); Appendix 3
4. Embase (via embase.com); Appendix 4
5. Web of Science Core Collection (via Clarivate); Appendix 5
6. Scopus (via Scous.com); Appendix 6
7. Latin American and Caribbean Health Science Information database (LILACS; lilacs.bvsalud.org/en/)
8. Open Grey (www.opengrey.eu/); Appendix 7
9. ClinicalTrials.gov (www.clinicaltrials.gov/); Appendix 8
10. World Health Organization (WHO) International Clinical Trials Registry Platform (apps.who.int/trialssearch/); Appendix 9

We incorporated additional relevant key words found during these searches into our search strategies, and documented changes accordingly.

Searching other resources

We attempted to identify other potentially eligible studies by searching the reference lists of included publications.

Data collection and analysis

Selection of studies

After removing duplicate records, two review authors (LL, ST) independently scanned the titles and abstracts of studies identified by the electronic search for eligibility. The two review authors (LL, ST) screened the full-text reports for all potentially eligible studies, according to predefined criteria. They resolved any discrepancies through consensus or arbitration of a third review author (GL). For studies identified in trial registries, we contacted the authors or institutions recorded in the registry for trial reports. We translated papers that were published in languages other than English to assess eligibility. We presented a PRISMA flowchart, showing study selection, including reasons for exclusion of studies (Liberati 2009).

Data extraction and management

Two review authors (LL, ST or GL) conducted data extraction using an extraction form developed for this review, based on the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions* (Li 2020). We resolved any disagreements by consensus, or by arbitration of a third review author (GL or LH) if needed.

We extracted the following data.

- Study information: author, title, source, publication date, publication type, language, duplicate publications, source of funding, authors' conflict of interest
- Study characteristics: study design, randomization method, number of study center(s), country of study center(s), inclusion and exclusion criteria, subgroup analysis, statistical methods, period of enrollment, follow-up period
- Participants characteristics: number of participants, number of participants per study arm, age, gender, ethnicity, clinical stage of disease (presentation, focality, tumor size)
- Intervention and comparator information: name, frequency, duration of treatment, adjuvant therapy, re-intervention, follow-up
- Outcomes: according to the review's predefined primary and secondary outcomes (including tumor stage and grade), events of intervention and comparator groups, timing of outcome measurement, number of re-resections

We extracted the relevant outcome data needed to calculate summary statistics and measures of variance. For dichotomous outcomes, we obtained numbers of events and totals to populate a 2 x 2 table, and calculated summary statistics with corresponding measures of variance. For continuous outcomes, we obtained

means and standard deviations or data necessary to calculate this information. For time-to-event outcomes, we extracted hazard ratios with corresponding measures of variance or data necessary to calculate this information.

Dealing with duplicate and companion publications

In the event of duplicate publications, companion documents, or multiple reports associated with one primary study, we maximized the yield of information by mapping all publications to a unique study ID. In case of doubt, we gave priority to the publication reporting the longest follow-up associated with our primary or secondary outcomes.

Assessment of risk of bias in included studies

Two review authors (LL, ST) independently assessed the risk of bias of each included study, using the Cochrane risk of bias assessment tool (Higgins 2011). They resolved disagreements by consensus, or through arbitration by a third review author (GL). We determined if risk of bias was low, high, or unclear, and presented our findings in a risk of bias summary figure. We assessed the trials for the following biases.

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

We evaluated the risk of performance bias and detection bias separately for each outcome. We grouped outcomes according to whether they were measured subjectively or objectively in the risk of bias tables.

Performance bias - susceptible

- We considered that all outcomes were similarly susceptible to performance bias.

Detection bias - susceptible

- Time to disease recurrence (time-to-event outcome)
- Time to disease progression (time-to-event outcome)
- Time to death from bladder cancer (time-to-event outcome)
- Minor adverse event: (Clavien-Dindo grade I or II; dichotomous outcome)

Detection bias - not susceptible

- Major adverse event: (Clavien-Dindo grade III, IV, or V; dichotomous outcome)

We assessed Incomplete outcome data, or attrition bias, on an outcome-specific basis. We considered the rate of attrition as low (less than 10%), unclear (between 10% and 20%), and high (20% or more).

We assessed selective reporting bias on a study-specific basis. We only considered the risk of selective reporting bias as low if we could identify an a priori protocol, and if the analyses and outcomes matched what the investigators preplanned.

We summarized the risk of bias within and across outcomes and studies in graphs. We used study-specific risk of bias assessments to inform the preplanned sensitivity analyses.

Measures of treatment effect

We expressed outcomes with dichotomous data using risk ratios (RR), with 95% confidence intervals (CIs). We expressed outcomes with time-to-event data using hazard ratios (HR) with 95% CIs.

Unit of analysis issues

The unit of analysis was the individual participant. For studies with repeated outcome measures, we performed time-to-event analysis. If this was not possible, we defined outcome measures as short term (< 12 months) versus long term (13 to 24 months) (Higgins 2020).

Dealing with missing data

We contacted study investigators for missing data. We only analyzed available data; we did not impute missing data. We investigated attrition rates (e.g. dropouts, losses to follow-up, and withdrawals), and critically appraised issues of missing data and imputation methods (e.g. last observation carried forward, if used by the study authors). We addressed the impact of missing data on the findings of the review in the Discussion section (Deeks 2020).

We conducted intention-to-treat analysis whenever possible. If intention-to-treat analysis was not possible, we conducted as-treated and per-protocol population analyses. We considered this a potential source of bias.

Assessment of heterogeneity

In the event of substantial clinical, methodological, or statistical heterogeneity, unexplained by subgroup analyses, we planned to exclude such results from the pooled effect estimate in the meta-analysis and provide a narrative description of the results of each study instead.

We identified heterogeneity by assessing overlaps in CIs in forest plots. We also assessed the impact of heterogeneity on the meta-analysis using the I^2 statistic (Higgins 2002; Higgins 2003). We interpreted the I^2 statistic as follows (Deeks 2020).

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

The importance of the observed value of the I^2 statistic depended on the magnitude and direction of effects, and the strength of evidence for heterogeneity. When we identified heterogeneity, we attempted to determine possible reasons for it by examining individual study and subgroup characteristics.

Assessment of reporting biases

We attempted to obtain study protocols to assess for selective outcome reporting. Since there were not at least 10 studies available for meta-analysis, we could not assess for publication bias by creating and visually inspecting funnel plots.

Data synthesis

We conducted a meta-analysis with a random-effects model for pooling data (Wood 2008). We conducted statistical analyses according to the statistical guidelines contained in the *Cochrane Handbook for Systematic Reviews of Interventions* (Li 2020). We analyzed dichotomous outcomes with the Mantel-Haenszel method and continuous outcomes with the inverse variance method. We analyzed time-to-event outcomes using the generic inverse variance method. We used Review Manager 5 software to conduct all analyses (Review Manager 2020).

Subgroup analysis and investigation of heterogeneity

Certain tumor characteristics may impact outcomes. There was not sufficient data to conduct any of our preplanned subgroup analyses, listed as follows.

- Setting: primary versus recurrent bladder cancer
- Multifocality: solitary versus multiple lesions of bladder cancer
- Tumor size: 3 cm or less versus larger than 3 cm
- Stage: positive cytology, or history of carcinoma in situ (CIS; in the case of recurrent disease), or both, versus negative cytology, or the absence of history of CIS, or both

The rationale underlying these subgroup analyses was as follows.

- Setting: per the European Organization for Research and Treatment of Cancer (EORTC) criteria, the setting of primary versus recurrent bladder cancer (primary with or without a recurrence, versus > 1 recurrence) can affect the risk of recurrence and progression (Sylvester 2006).
- Multifocality: per the EORTC criteria, the number of tumors (1, 2 to 7, versus ≥ 8) can affect the risk of recurrence and progression (Sylvester 2006).
- Tumor size: per the EORTC criteria, the size of tumors (< 3 cm versus ≥ 3 cm) can affect the risk of recurrence and progression (Sylvester 2006).
- Stage: compared to other histological types, the detection of CIS is particularly difficult due to its flat growth within the cell level (Sylvester 2006).

Sensitivity analysis

There was an insufficient number of studies to conduct sensitivity analyses to evaluate differences in methodology that could impact the results of meta-analyses. Therefore, we could not conduct preplanned sensitivity analyses by 1) excluding studies with high risk of bias (Deeks 2020), and 2) by excluding studies in which all participants underwent re-resection on a routine basis, since routine re-resection may mitigate potential benefits of NBI.

Summary of findings and assessment of the certainty of the evidence

We presented the overall certainty of the evidence for each outcome according to the GRADE approach, which takes into account criteria related to internal validity (risk of bias, inconsistency, imprecision, publication bias), and external validity (directness of results) (Guyatt 2008). Two review authors (LL or GL) independently reviewed the quality of evidence for each outcome as high, moderate, low, or very low using GRADEpro GDT (GRADEpro GDT). We resolved any discrepancies by consensus, or if needed, by arbitration with a third review author (PD). We presented a summary of the evidence in a summary of findings table, which provides key information about the best estimate of the magnitude of the effect in relative terms and absolute differences; numbers of participants and studies addressing each important outcome; and the rating of the overall confidence in effect estimates for each outcome (Guyatt 2011; Schünemann 2019). If meta-analysis was not possible, we planned to present data in a narrative summary of findings table.

We presented a summary of findings table reporting the following outcomes, listed according to a priority rating established by the clinicians on our team with the input of external experts.

1. Time to disease recurrence
2. Time to disease progression
3. Major adverse event
4. Time to death from bladder cancer
5. Minor adverse event

RESULTS

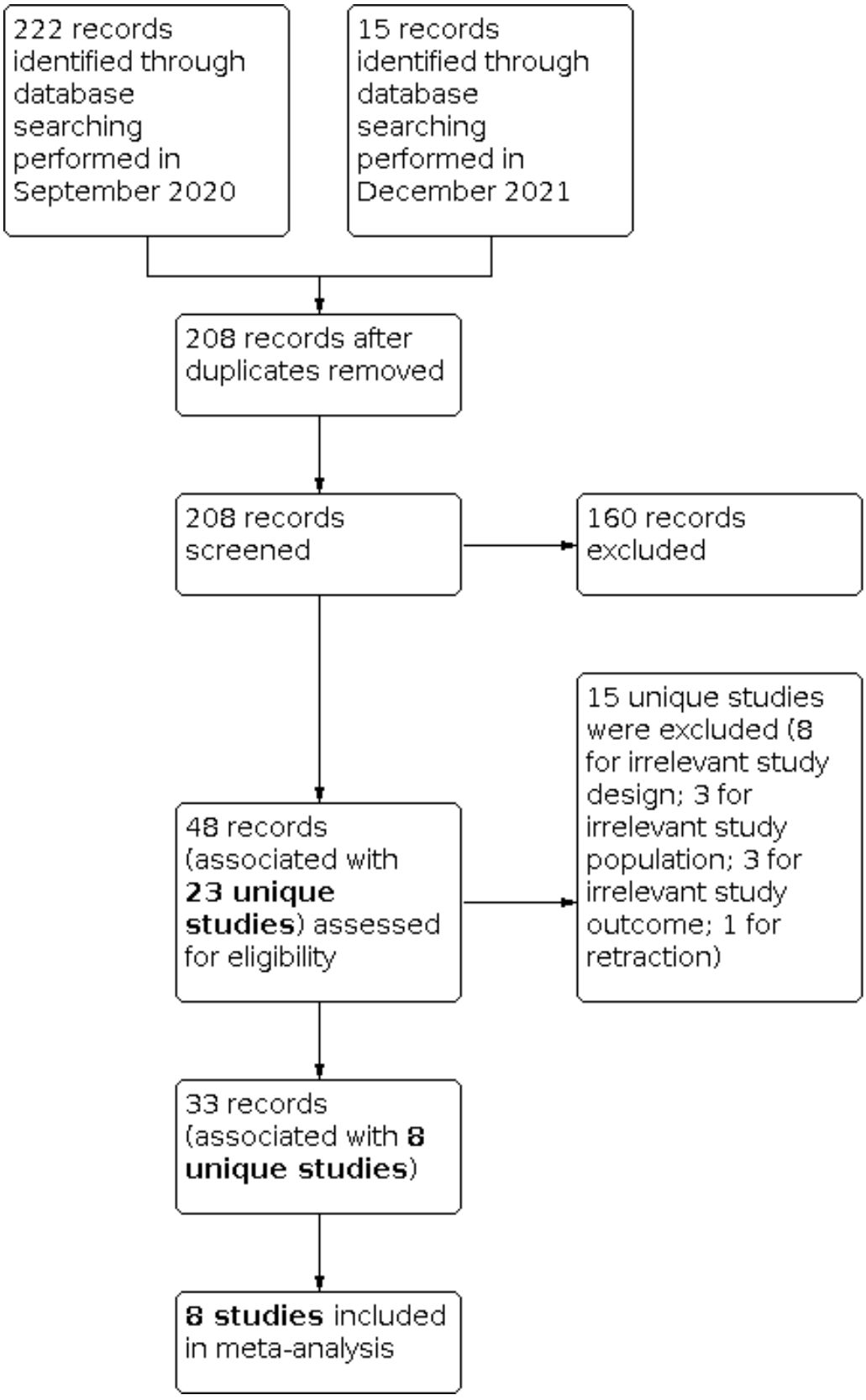
Description of studies

Results of the search

We identified 222 records during the first search in September 2020. We identified an additional 15 records during the repeated search in December 2021. After the exclusion of duplicates, we screened the title and abstract of 208 records. Of these, we deemed 160 to be irrelevant. We assessed 48 records (associated with 23 unique studies) for eligibility. Ultimately, eight randomized controlled trials, associated with 33 reports, met our inclusion criteria for the study question.

There were no ongoing studies nor studies awaiting classification. The details of study selection are presented as a PRISMA flow diagram in Figure 1.

Figure 1. PRISMA flow diagram summarizing the study screening process



Included studies

We identified eight randomized controlled trials eligible for inclusion (Buaban 2018; Kim 2018; Lee 2014; Longo 2013; Ma 2015; Naito 2016; Naselli 2012; Stănescu 2014). For descriptions of the included studies, see Table 1 'Overview of included studies' and Characteristics of included studies.

Participants

In total, 2152 participants were randomized. Inclusion criteria varied widely between studies. All but the study by Longo 2013 specified their participant selection process, including participants with suspected or diagnosed non-muscle invasive bladder cancer and excluding participants with muscle-invasive bladder cancer. Methods used for the initial discovery of suspected bladder tumors varied from bladder lavage fluids and voided urine cytology to cystoscopies and other imaging studies. One study specified that only participants with primary bladder cancer were included (Naito 2016).

Interventions

Transurethral resection began in the white light mode with the introduction of the resectoscope. For the control arm, participants underwent cystoscopy, tumor resection, and coagulation in the white light mode only. For the intervention arm, the instruments were originally introduced into the bladder under the white light mode, then switched to the NBI mode for cystoscopy, tumor resection, and coagulation. One study specified that the intervention was carried out entirely in the white light or NBI mode, in which switching from white light to NBI mode during the procedure was prohibited (Naselli 2012). One trial used holmium laser for resection (Ma 2015), and another used NBI-guided bipolar plasma vaporization (Stănescu 2014).

Outcomes

Outcomes were measured in ranges of 3 to 35 months. The studies reporting the primary outcomes for this review were as follows.

- Time to disease recurrence, reported by six studies (Kim 2018; Lee 2014; Ma 2015; Naito 2016; Naselli 2012; Stănescu 2014)
- Time to disease progression, reported by none
  - No studies reported the number of participants with disease progression at 12 months or 13 to 24 months, precluding the analysis of disease progression as a dichotomous outcome.
- Major adverse events, reported by four studies (Buaban 2018; Longo 2013; Naito 2016; Stănescu 2014)

The studies reporting the secondary outcomes for this review were as follows.

- Time to death from bladder cancer, reported by none.
  - No studies reported the number of participants with bladder cancer death at 12 months or 13 to 24 months, precluding the analysis of cancer death at 12 months as a dichotomous outcome.
- Minor adverse events, reported by four studies (Buaban 2018; Longo 2013; Naito 2016; Stănescu 2014)

Excluded studies

We excluded 15 reports of 15 studies. Eight were excluded for irrelevant study design (Doehn 2014; Geavlete 2012; Herr 2019; Mukherjee 2019; Naya 2015; Shen 2010; Shen 2012; Ye 2015). Three were excluded for irrelevant study population (Hirner 2016; Mita 2018; Tschirdewahn 2020). Three were excluded for irrelevant study outcomes (Dogra 2016; Hah 2018; Lee 2017). One was excluded because the report was retracted (Herr 2015). The process of study exclusion is summarized in the PRISMA diagram. (Figure 1)

Risk of bias in included studies

Visual representations of the risk of bias of the included studies are presented in Figure 2 and Figure 3. Details are shown in Characteristics of included studies. Since there were less than 10 included studies available for meta-analysis, we did not create a funnel plot to assess for publication bias.

Figure 2. Risk of bias summary

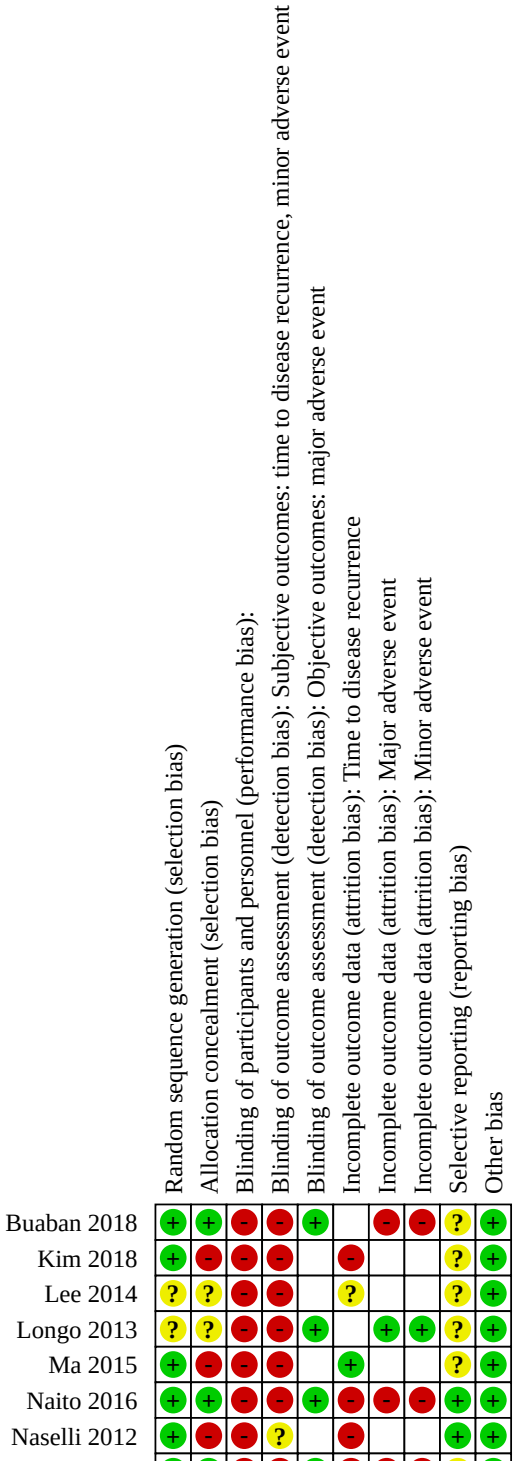


Figure 2. (Continued)

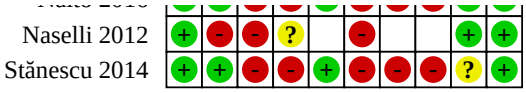
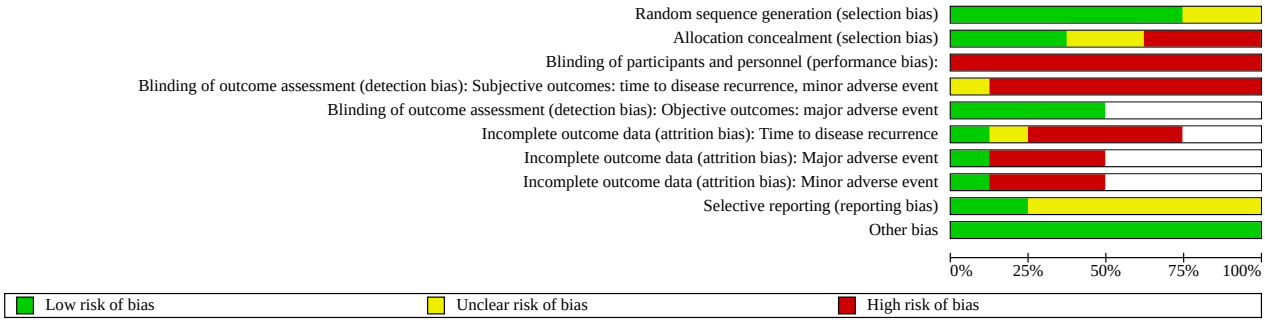


Figure 3. Risk of bias graph



Allocation

Six studies reported adequate efforts for random sequence generation (Buaban 2018; Kim 2018; Ma 2015; Naito 2016; Naselli 2012; Stănescu 2014). Two studies had no discussion of sequence generation; however, only the abstracts were available, so we deemed these to have an unclear risk of selection bias from random sequence generation (Lee 2014; Longo 2013).

Three out of eight studies reported adequate efforts to conceal allocation (Buaban 2018; Naito 2016; Stănescu 2014). Three full-text studies did not describe methods used for allocation concealment, so we assessed these as having a high risk of selection bias (Kim 2018; Ma 2015; Naselli 2012). The remaining two studies, which only provided abstracts, did not describe allocation concealment (Lee 2014; Longo 2013); we rated these as having an unclear risk of selection bias.

Blinding

WLC mode and NBI mode were visually distinct. Given the nature of the intervention, no trial was able to blind the personnel involved. We considered all outcomes to be susceptible to performance bias. The risk of performance bias was high for all eight studies (Buaban 2018; Kim 2018; Lee 2014; Longo 2013; Ma 2015; Naito 2016; Naselli 2012; Stănescu 2014).

In judging the risk of detection bias, we categorized outcomes as subjective outcomes or objective outcomes. We considered time to disease recurrence and minor adverse events to be subjective outcomes, susceptible to detection bias, and grouped them together.

The detection of time to disease recurrence and minor adverse events involved clinical outcomes, so we considered studies that did not specify how, if any, blinding was conducted to be at high risk of detection bias for these outcomes (Buaban 2018; Kim 2018; Lee 2014; Longo 2013; Ma 2015; Naito 2016; Stănescu 2014). One study discussed the blinding of the pathologist, which reduced the risk of detection bias for time to disease recurrence (Naselli 2012); however, it did not state how, if any, blinding of outcome assessment for minor adverse events was conducted. As such, we judged the overall risk of detection bias to be unclear for that study.

We considered major adverse events to be objective outcomes, not susceptible to detection bias, because no clinical judgement was involved. The risk of detection bias for major adverse events was low for all five of the studies that assessed major adverse events (Buaban 2018; Longo 2013; Naito 2016; Naselli 2012; Stănescu 2014).

Incomplete outcome data

We rated the risk of attrition bias for each outcome based on the following predefined criteria: low (less than 10%), unclear (between 10% and 20%) and high (20% or higher).

Of the six studies that reported on time to disease recurrence or disease recurrence at 12 months or 13 to 24 months, one was at low risk of attrition bias (Ma 2015), one was at unclear risk of attrition bias (Lee 2014), and four were at high risk of attrition bias (Kim 2018; Naselli 2012; Naito 2016; Stănescu 2014).

Of the four studies that reported major and minor adverse events, one was at low risk of attrition bias (Longo 2013), and three were at high risk of attrition bias (Buaban 2018; Naito 2016; Stănescu 2014).

In total, 2152 participants were randomized but only 1847 participants were included in our analysis. This discrepancy was due to incomplete outcome data which precluded analysis.

Selective reporting

We assessed two studies to have a low risk of reporting bias as all outcomes were reported per trial registration (Naito 2016; Naselli 2012). None of the remaining studies had a trial registration or protocol available for comparison, so we assessed these to have an unclear risk of reporting bias.

Other potential sources of bias

We did not identify other potential sources of bias.

Effects of interventions

See: **Summary of findings 1** NBI + WLC TURBT compared to WLC TURBT for transurethral resection of bladder tumors in people with suspected or diagnosed non-muscle invasive bladder cancer

NBI versus white light cystoscopy alone for transurethral resection

See: Summary of findings 1

Primary outcomes

Time to disease recurrence (time-to-event)

Based on six studies involving 1244 participants that reported time to disease recurrence (Kim 2018; Lee 2014; Ma 2015; Naito 2016; Naselli 2012; Stănescu 2014), NBI + WLC TURBT may lower the risk of disease recurrence over time compared to WLC TURBT (hazard ratio 0.63 in favor of the NBI + WLC TURBT group, 95% CI 0.45 to 0.89; I^2 = 53%; low certainty of evidence; Analysis 1.1). The anticipated absolute effects varied depending on the baseline risk of recurrence. For the low-risk population, the use of NBI + WLC TURBT corresponded to 53 fewer (range: 79 fewer to 15 fewer) recurrences per 1000 participants at 12 months. For the high-risk population, the use of NBI + WLC TURBT corresponded to 163 fewer (range: 265 fewer to 43 fewer) recurrences per 1000 participants at 12 months. The point estimates and confidence intervals for absolute effects did not meet the previously established thresholds of clinically relevant difference decrease (5% or more). All data were extrapolated from Kaplan-Meier curves or outcomes data according to the Tierney method (Tierney 2007).

Disease progression (time-to-event or dichotomous)

No studies reported data on disease progression.

Major adverse event (Clavien-Dindo III, IV, V) (dichotomous)

Four studies involving 1385 participants reported on the occurrence of major adverse events. There were no major adverse events reported among either the NBI + WLC TURBT group or the WLC TURBT group in three of the four studies (Buaban 2018; Longo 2013; Stănescu 2014). One study found 16 major adverse events among 484 participants who underwent NBI + WLC TURBT and nine major adverse events among 481 participants who underwent WLC TURBT (Naito 2016) Considered together, there may be little to no difference in the risk of major adverse events between the two groups (risk ratio 1.77, 95% CI 0.79 to 3.96; calculated from 1 study (Naito 2016) with 965 participants; low certainty of evidence; Analysis 1.2). The anticipated absolute effect was 10 more (range: 3 fewer to 39 more) major adverse events per 1000 participants. The point estimates and confidence intervals did not meet the previously established thresholds of clinically relevant difference for major adverse events (2% or more).

Secondary outcomes

Death from bladder cancer (time-to-event or dichotomous)

No studies reported data on death from bladder cancer.

Minor adverse event (Clavien-Dindo I, II) (dichotomous)

Four studies involving 1385 participants reported on the occurrence of minor adverse events. All four studies had at least one minor adverse event in either the NBI + WLC TURBT group or the WLC TURBT group (Buaban 2018; Longo 2013; Naito 2016; Stănescu 2014). There were 78 minor adverse events among 704 participants who underwent NBI + WLC TURBT and 77 minor adverse events among 681 participants who underwent WLC TURBT. Considered together, there may be little to no difference in the risk of minor adverse events between the two groups (risk ratio 0.88, 95% CI 0.49 to 1.56; I^2 = 61%; 4 studies, 1385 participants; low certainty of evidence; Analysis 1.3). The anticipated absolute effect was 14 fewer (range: 58 fewer to 63 more) minor adverse events per 1000 participants. The point estimates and confidence intervals did not meet the previously established thresholds of clinically relevant difference for minor adverse events (5% or more).

Subgroup Analysis

There were insufficient data available to conduct our planned subgroup analysis.

Sensitivity Analysis

There were no full-text studies free of high risk of bias for all domains, precluding the ability to perform our prespecified sensitivity analyses.

DISCUSSION

Summary of main results

In total, we identified eight randomized controlled trials, involving 2152 participants with suspected or diagnosed non-muscle invasive bladder cancer, that compared NBI + WLC TURBT with WLC TURBT in the treatment of primary or recurrent non-muscle invasive bladder cancer. Of the 2152 participants randomized, we included 1847 participants in the analysis. The discrepancy between participants randomized and those analyzed was most commonly due to incomplete outcome data.

Based on limited time-to-event data, the addition of NBI + WLC TURBT may lower the risk of disease recurrence over time. We were not able to examine death from bladder cancer as a time-to-event outcome or a dichotomous outcome. Our analysis suggests that there is no difference in risk of major or minor adverse events between the two groups. However, the certainty of evidence was low.

Given the limited data available, subgroup analysis and sensitivity analysis were not possible.

Overall completeness and applicability of evidence

This Cochrane Review is based on eight randomized controlled trials published between 2009 and 2017. The studies included participants undergoing transurethral resection of bladder tumor for suspected or pathologically confirmed (primary or recurrent), non-muscle invasive bladder cancer (stage Ta, T1, and carcinoma in situ). This population is consistent with our inclusion criteria and represents a clinically relevant cohort for the use of NBI + WLC TURBT.

All but one study compared NBI + WLC TURBT to WLC TURBT alone. One study (Naselli 2012) compared NBI TURBT alone to WLC TURBT alone. We expect the results from this study to provide more conservative estimates for time to disease recurrence (favoring the null), since surgeons would be performing cystoscopy with only one light source (NBI) rather than with two light sources (NBI + WLC), which would theoretically lead to less opportunity for disease detection. We expect that the intervention of NBI TURBT alone vs WLC TURBT alone would underreport adverse events (favoring safety), since only one light source is used to examine the bladder. However, this particular study did not contribute data to adverse events, so our estimates are unchanged (Naselli 2012).

The majority of studies compared NBI + WLC TURBT with WLC TURBT alone using electrocautery to resect tumors, though one used laser resection of bladder tumor (Ma 2015), and another used bipolar plasma vaporization (Stănescu 2014). The influence on the type of resection of tumor performed on our outcomes is unknown and may introduce heterogeneity to our results. In addition to this, the type of WLC used (high definition versus standard definition) was not routinely described, and may influence the ability to detect tumors with WLC and the outcomes of the studies. The applicability of the intervention is improved by the fact that narrow band imaging is a standardized technology, though many differing manufacturers produce endoscopic cameras capable of NBI and not all studies described the NBI system they used.

Variation in the clinical management of people with non-muscle invasive bladder cancer introduced heterogeneity and decreased the applicability of our results. For example, the use of immediate (within 24 hours of TURBT) postoperative chemotherapy instillations and intravesical therapy was not consistent between studies, so we could not include this in the analysis. Studies varied in their administration of mitomycin-C, doxirubicin or epirubicin in the immediate (24-hour) postoperative period and in the intravesical therapy regimens people with non-muscle invasive bladder cancer may have received. In addition, the inclusion of people who underwent repeat transurethral resection and the timing of these resections were not well described and were likely to have been inconsistent between studies. These differences may impact the clinical applicability of our study results.

It is also important to discuss that the benefit of NBI + WLC TURBT on time to disease recurrence on clinical outcomes may be due to the fact that increased detection of tumors may lead to escalation of risk stratification, which then leads to more aggressive observation schedules and interventions. Therefore, the impact of NBI on disease recurrence may be indirect, through this cascade.

Quality of the evidence

We assessed the certainty of evidence using the GRADE approach, and considered it to be low for all outcomes. We consistently downgraded the certainty for risk of bias and imprecision.

- Risk of bias: due to the nature of TURBT, personnel could not be blinded to treatment assignment. We considered the risk of performance bias for all outcomes, and the risk of detection bias for susceptible outcomes (i.e. time to disease recurrence, minor adverse events) to be high. However, we would not expect the lack of blinding to bias the detection of major adverse events because no clinical judgement would be involved. We downgraded the certainty of evidence by one level for issues of performance bias, detection bias, incomplete outcome data, or selective reporting.
- Imprecision: we downgraded the certainty of evidence based on the confidence interval around the effect size, and whether it included both clinically relevant potential benefit and harm.

Potential biases in the review process

Few studies presented time to disease recurrence; among these, all data were presented in the form of Kaplan-Meier curves or dichotomous outcome data only. We contacted all study authors to request additional data via email, but did not receive any additional data. Therefore, we derived hazard ratios for the outcome of time to disease recurrence based on dichotomous outcome data and Kaplan-Meier curves, according to the Tierney method (Tierney 2007). This method can only reconstruct hazard ratios according to the information available and may have resulted in bias.

There were no data available on time to disease progression or time to death from bladder cancer, nor were dichotomous outcomes (disease progression, death from bladder cancer) reported.

Agreements and disagreements with other studies or reviews

Several systematic reviews have been performed on the topic of NBI + WLC TURBT for non-muscle invasive bladder cancer. They are listed chronologically with a brief discussion on the conclusions of each review.

- Lee 2015 performed a systematic review and network meta-analysis on the use of blue light-guided or NBI + WLC TURBT versus WLC TURBT alone. Of the 15 studies included, four were trials comparing NBI + WLC TURBT to WLC TURBT alone. Our review included three of the four trials included in their review (Geavlete 2012, which was an earlier publication for the Stănescu 2014 trial, Naselli 2012, Lee 2014). The remaining trial violated the randomization requirement (i.e. participants were consecutively enrolled) for eligibility of inclusion for our review. The authors used the Cochrane risk of bias assessment but did not grade certainty of evidence. Consistent with the directionality we found in our study, which favored NBI + WLC TURBT for decreasing disease recurrence at 12 months, the authors found that NBI + WLC TURBT was superior to that using WLC, with an odds ratio (OR) of 0.47 (95% CI 0.31 to 0.72; P < 0.001) for the outcome of recurrence rate, which was defined as the number of bladder cancer recurrences after initial TURBT.
- Kang 2017 performed a systematic review of six studies on the use of NBI in reducing recurrence risk (dichotomous outcome at three months, one year, and two years). Of these, one was retrospective, and one prospective study has subsequently been retracted; we included all four eligible randomized controlled trials in this Cochrane Review. The authors used the Cochrane risk of bias tool and found that all RCTs were at high risk of performance bias and low or unclear risk of other forms of bias. The certainty of evidence was not evaluated. Kang and colleagues found that NBI + WLC TURBT was associated with improvements in the three-month recurrence risk (relative risk [RR] 0.39, 95% CI 0.26 to 0.60; P < 0.0001), one-year recurrence risk (RR 0.52, 95% CI 0.40 to 0.67; P < 0.00001) and two-year recurrence risk (RR 0.60, 95% CI 0.42 to 0.85; P = 0.004) compared with WLC TURBT.

- Xiong 2017 performed a systematic review of 25 studies, including 17 full texts and eight abstracts, to compare NBI + WLC TURBT with WLC TURBT alone in detection and recurrence risk. The meta-analysis included both randomized and non-randomized studies. In the risk of recurrence assessment, six studies were included, three of which were not randomized controlled trials. The study used the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) to assess the quality and risk of bias of the studies included in their review. The QUADAS-2 only assesses four domains (participant selection, index test, reference standard, and flow and timing) versus the Cochrane risk of bias tool, which assesses six domains (selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias). Furthermore, Cochrane uses the GRADE approach to assess the quality of evidence. Consistent with our review, the authors found that NBI significantly reduced the recurrence rate of bladder cancer with a pooled risk ratio of 0.43 (95% CI 0.23 to 0.79) and 0.81 (95% CI 0.69 to 0.95) at three months and 12 months, respectively.
- Chen 2017 performed a systematic review inclusive of 22 trials with a total of 7767 participants to assess the use of NBI and/or blue light TURBT relative to WLC TURBT alone. We were only able to locate an abstract and found no corresponding manuscript, so we were not able to discern the number of studies that were relevant to our outcomes of interest and compare methodology. Their outcomes of interest were one-year, two-year, and five-year recurrence rates and progression rate, assessed with odds ratios. The authors found that the use of NBI + WLC TURBT was associated with lower odds of recurrence at one year (OR 0.56, 95% CI 0.31 to 0.91), compared to WLC TURBT. They reported that the use of NBI + WLC TURBT was associated with lower two-year and five-year recurrence rates, though odds ratios were not available. In addition, the authors concluded that NBI + WLC TURBT had "the higher probabilities to be the best intervention in lower 1-year, 2-year and 5- year recurrence rate" relative to WLC TURBT.
- Motlagh 2021 performed a systematic review and Bayesian sensitivity network meta-analysis of randomized trials, comparing the recurrence rates among the intervention group undergoing 1) blue light guided-TURBT with or without single immediate intravesical chemotherapy, 2) NBI + WLC TURBT with or without single immediate intravesical chemotherapy, or 3) WLC TURBT with single immediate intravesical chemotherapy and the control group undergoing WLC TURBT alone. The authors concluded that NBI, with or without single immediate intravesical chemotherapy, was not associated with a significantly lower likelihood of 12-month recurrence rate (OR 0.39, 95% CI 0.11 to 1.29; OR 0.65, 95% CI 0.343 to 1.15, respectively).
- Gravestock 2021 performed a systematic review inclusive of three trials with a total of 921 participants to assess the effect of NBI + WLC TURBT compared with white light on recurrence rates in NMIBC. Our review included three of the three trials included in their review (Kim 2018, Naito 2016, Naselli 2012). Their outcomes of interest were recurrence at 12 and 24 months and adverse events. The authors did not find a statistically significant result. However, the analysis showed a trend in favor of NBI + WLC TURBT with a risk ratio of 0.75 (95% CI 0.50 to 1.14; $P = 0.18$; $I^2 = 61\%$). The authors also reported that only one of the included studies (Naito 2016) reported on adverse events and no significant difference was observed between the two cohorts.

In summary, several existing systematic reviews support a positive or neutral effect of NBI + WLC TURBT on reducing the risk of recurrence. Our rigorous inclusion of only randomized controlled trial data, extrapolation of time-to-event data, more recent systematic review, and assessment of the certainty of evidence rating on a per outcome basis distinguished our review from prior reviews.

AUTHORS' CONCLUSIONS

Implications for practice

White light cystoscopy (WLC)- and narrow band imaging (NBI)-guided transurethral resection of bladder tumor (TURBT) may lower the risk of disease recurrence over time compared to WLC TURBT in the treatment of non-muscle invasive bladder cancer. Overall, our confidence in the effect estimates is limited. The true effects on disease recurrence may be substantially different from the effect estimates.

Unfortunately, no studies analyzed the effect of NBI + WLC TURBT on the risk of disease progression or bladder cancer death. In terms of patient safety, NBI + WLC TURBT may have little to no effect on major or minor adverse effects, though we have low confidence in the effect estimates.

However, unlike blue light cystoscopy, NBI + WLC TURBT does not require instillation of photosensitizing agents into the bladder. Further, given that many cystoscopes can be switched from the white light mode to the NBI mode with no significant interruption to the procedural workflow, NBI + WLC TURBT may be considered as an additional intervention to improve outcomes.

Implications for research

The review identified only eight randomized controlled trials addressing certain aspects of the research question. The certainty of evidence was low. This underscores the importance of following higher methodological standards for designing trials, registering and peer reviewing trial protocols a priori, and using CONSORT guidelines when reporting trial results.

Further, few studies presented time-to-event data. While we were able to mitigate this limitation by using established methods to calculate time-to-event data, this additional calculation might have introduced bias in our results. When reporting time-to-event data, trialists may also consider including numbers at risk in their graphs or as supplementary data for improving data transparency. Standardizing data reporting and collection would facilitate additional systematic reviews and improve the quality of meta-analyses. Future studies may also consider examining the effectiveness of WLC TURBT alone versus NBI + WLC TURBT for surveillance of people with non-muscle invasive bladder cancer.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Buaban 2018

Study characteristics	
Methods	**Study design:** randomized controlled trial **Study grouping:** parallel group
Participants	**Inclusion criteria:** people with histopathology-visualized non-muscle invasive bladder cancer and complete resection of the visualized tumor **Exclusion criteria:** people with muscle-invasive bladder cancer, incomplete tumor resection, histopathology-visualized non-cancerous lesion, synchronous upper urinary tract cancer, and postoperative intravesical therapy before surveillance cystoscopy **Number randomized:** 79 participants to undergo WLC TURBT and 79 participants to undergo NBI + WLC TURBT

Buaban 2018 *(Continued)*

Number analyzed by authors: 25 participants who underwent a total of 31 WLC TURBTs and 37 participants who underwent a total of 44 NBI + WLC TURBTs

Baseline characteristics of participants analyzed. *NOTE: The authors reported the characteristics using the total number of TURBTs as the denominator rather than the number of unique participants undergoing TURBT, which invariably double-counted some participants.*

Comparator group: n = 25 participants who underwent a total of 31 WLC TURBTs.

- Age: mean 66 years old (IQR 59 to 74)
- Gender-male, n (%): 20 (64.5)
- Focality, n (%)
  - Unifocal: 14 (45.2)
  - Multifocal: 17 (54.8)
- Tumour size, n (%)
  - < 1 cm: 6 (19.4)
  - 1 cm: 13 (41.9)
  - > 1 cm: 12 (38.7)
- Pathological classification, n (%)
  - CIS: 2 (6.5)
  - pTa: 22 (71.0)
  - pT1: 7 (22.6)
  - > pT1: 0 (0.0)
- Tumor grade, n (%)
  - Low grade: 17 (54.8)
  - High grade: 14 (45.2)

Intervention group: n = 37 participants who underwent a total of 44 NBI + WLC TURBTs

- Age: mean 75 years old (IQR 67.5 to 81.5)
- Gender-male, n (%): 36 (82.8)
- Focality, n (%)
  - Unifocal: 19 (43.2)
  - Multifocal: 25 (56.8)
- Tumor size, n (%)
  - < 1 cm: 16 (36.3)
  - 1 cm: 12 (27.3)
  - > 1 cm: 16 (36.4)
- Pathological classification, n (%)
  - Cis: 0 (0.0)
  - pTa: 37 (84.1)
  - pT1: 7 (15.9)
  - > pT1: 0 (0.0)
- Pathological grade, n (%)
  - Low grade: 30 (68.2)
  - High grade: 14 (31.8)

Subsequent intravesical treatment among either group: no participant included had undergone subsequent intravesical treatment

Interventions	**Comparator arm:** WLC TURBT alone **Intervention arm:** NBI + WLC TURBT using an EVIS EXERA II CLV-180 (Olympus)
Outcomes	Disease recurrence at 3 months Complication rate

Buaban 2018 *(Continued)*

Funding sources	Not reported
Declarations of interest	The authors reported having no conflict of interest to declare.
Notes	**Contact with study author** Date of contact attempt: 13 January 2021 Contact status: no additional data

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "The prospective, randomized, single-blind control study...After enrollment, participants were randomly allocated with a computerized random permute block to TUR-BT with NBI or TUR-BT with WLI." **Comment**: The allocation sequence was random using computers.
Allocation concealment (selection bias)	Low risk	**Quote:** "After enrollment, participants were randomly allocated with a computerized random permute block to TUR-BT with NBI or TUR-BT with WLI. Both surgeons and participants were blinded from randomization before the procedure." **Comment:** There was central randomization and the allocation sequence was concealed to both participants and clinicians until the participant was registered.
Blinding of participants and personnel (performance bias)	High risk	**Quote:** "All TUR-BTs were done by experienced urology staff or by third-year urology residents under supervision." **Comment:** Personnel could not be blinded due to the nature of the intervention.
Blinding of outcome assessment (detection bias) Subjective outcomes: time to disease recurrence, minor adverse event	High risk	**Comment:** Authors did not specify how, if any, outcome assessment blinding was achieved. The detection of disease recurrence and minor adverse events would be affected by a lack of blinding of outcome assessors.
Blinding of outcome assessment (detection bias) Objective outcomes: major adverse event	Low risk	**Comment:** The authors did not specify how, if any, blinding of outcome assessment was conducted. However, we do not expect the lack of blinding to bias the detection or reporting of major adverse events as no clinical judgement was involved.
Incomplete outcome data (attrition bias) Major adverse event	High risk	**Comment:** Of the 158 participants randomized (79 to each arm), only 25 and 37 were included in the analysis (32% and 47%, respectively). The attrition rate was greater than 20% in both arms.
Incomplete outcome data (attrition bias) Minor adverse event	High risk	**Comment:** Of the 158 participants randomized (79 to each arm), only 25 and 37 were included in the analysis (32% and 47%, respectively). The attrition rate was greater than 20% in both arms.
Selective reporting (reporting bias)	Unclear risk	**Comment:** No associated trial registration was found.
Other bias	Low risk	**Comment:** No additional sources of potential bias were found.

Kim 2018

Study characteristics	
Methods	**Study design:** randomized controlled trial **Study grouping:** parallel group

Participants	**Inclusion criteria:** people who underwent TURBT for suspicion of a bladder tumor discovered by use of cystoscopy or another imaging study
	
	Exclusion criteria: people with muscle-invasive tumors, those undergoing radical cystectomy, those receiving chemotherapy or radiotherapy, those with nonurothelial carcinoma, those who were not histologically diagnosed with cancer, those lost to follow-up, and those who died for other reasons
	
	Number randomized: 198 (97 participants to undergo WLC TURBT and 101 participants to undergo NBI + WLC TURBT)
	
	Number analyzed by authors: 35 participants who underwent WLC TURBT and 39 participants who underwent NBI + WLC TURBT, and had follow-up at 12 months
	
	Baseline characteristics of randomized participants who were not found to have muscle-invasive tumor or nonurothelial carcinoma, those who did not undergo radical cystectomy during the study period, and those who did not receive chemotherapy (n = 67 comparison arm, n = 85 intervention arm)
	
	Comparator group, n = 67 participants
	
	• Age, mean (SD): 66.96 (11.51)
	• Gender-male, n (%): 54 (80.6)
	• Focality, n (%): not reported
	• Tumour size, n (%)
	  ○ < 1 cm: 40 (59.7)
	  ○ 1 to 3 cm: 19 (28.4)
	  ○ > 3 cm: 8 (11.9)
	• Pathological classification, n (%)
	  ○ pT0: 12 (17.9)
	  ○ CIS: 2 (3.0)
	  ○ pTa: 37 (55.2)
	  ○ pT1: 16 (23.9)
	• Pathological grade, n (%)
	  ○ No tumor or carcinoma in situ: 14 (20.9)
	  ○ Low: 24 (35.8)
	  ○ High: 29 (43.3)
	
	Intervention group, n = 85 participants
	
	• Age, mean (SD): 65.54 (12.01)
	• Gender-male, n (%): 62 (72.9)
	• Focality, n (%): not reported
	• Tumour size, n (%)
	  ○ < 1 cm: 42 (49.4)
	  ○ 1 to 3 cm: 35 (41.4)
	  ○ > 3 cm: 8 (9.4)
	• Pathological classification, n (%)
	  ○ pT0: 13 (15.3)
	  ○ CIS: 3 (3.5)
	  ○ pTa: 52 (61.2)
	  ○ pT1: 17 (20.0)

Kim 2018 *(Continued)*

- Pathological grade, n (%)
  - No tumor or carcinoma in situ: 17 (20.0)
  - Low: 33 (38.8)
  - High: 35 (41.2)

Subsequent intravesical treatment among either group: no documentation of subsequent intravesical treatment

Interventions	**Comparator group:** WLC TURBT **Intervention group:** NBI + WLC TURBT
Outcomes	Number of tumors identified Disease recurrence at 12 months
Funding sources	Not reported
Declarations of interest	The authors reported having no conflict of interest to declare.
Notes	**Contact with study author** Date of contact attempt: 13 January 2021 Contact status: no reply to-date

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "The participants were randomly divided into the NBI (experimental) and WLC (control) groups. Randomization was conducted by means of a computer-generated random sequence of numbers" **Comment:** Randomization was performed by a computer-generated random sequence.
Allocation concealment (selection bias)	High risk	**Quote**: "Before procedures, participants eligible for the study were contacted by medical staff and provided with verbal and written information." **Comment**: There was no mention of allocation concealment methods.
Blinding of participants and personnel (performance bias)	High risk	**Comment**: Personnel could not be blinded due to the nature of the intervention.
Blinding of outcome assessment (detection bias) Subjective outcomes: time to disease recurrence, minor adverse event	High risk	**Comment**: Authors did not specify how, if any, outcome assessment blinding was achieved. The detection of disease recurrence would be affected by a lack of blinding of outcome assessors.
Incomplete outcome data (attrition bias) Time to disease recurrence	High risk	**Comment**: Of the 198 participants enrolled, 97 and 101 were randomized to the WLC TURBT arm and the NBI + WLC TURBT arm, respectively. Only 35 participants of the WLC TURBT arm and 39 participants of the NBI + WLC TURBT arm were included for analysis of disease recurrence at 12 months (36% and 39%, respectively). The attrition rate was greater than 20% in both arms.

Kim 2018 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	**Comment**: This study was registered in the Korea University Anam Hospital clinical trial center (approval number: MD13008). However, the registration protocol was not available for comparison.
Other bias	Low risk	**Comment**: No additional sources of potential bias were identified.

Lee 2014

Study characteristics	
Methods	**Study design:** randomized controlled trial **Study grouping:** parallel group

Participants	**Inclusion criteria:** people with overt or suspected non-muscle invasive bladder cancer
	
	Exclusion criteria: people with muscle-invasive bladder cancer, negative pathologic examination, or without follow-up
	
	Number randomized: 68 (35 participants to undergo WLC TURBT alone and 33 participants to undergo NBI + WLC TURBT)
	
	Number analyzed by authors: 35 participants who underwent WLC TURBT alone and 33 participants who underwent NBI + WLC TURBT
	
	Baseline characteristics of participants analyzed
	
	Comparator group, n = 35
	
	• Age: unclear; mean age of entire study cohort was 63
	• Gender-male, n (%): not reported
	• Focality, n (%)
	  ○ Unifocal: 12 (34.3)
	  ○ Multifocal: 23 (65.7)
	• Tumor size: not reported
	• Pathological classification, n (%)
	  ○ CIS: 8 (22.9)
	• Pathological grade, n (%)
	  ○ High grade: 16 (45.7)
	
	Intervention group, n = 33
	
	• Age: unclear; mean age of entire study cohort was 63
	• Gender-male, n (%): not reported
	• Focality, n (%)
	  ○ Unifocal: 13 (39.4)
	  ○ Multifocal: 20 (60.6)
	• Tumor size: not reported
	• Pathological classification, n (%)
	  ○ CIS: 4 (12.1)
	• Pathological grade, n (%)
	  ○ High grade: 17 (51.5)
	
	Subsequent intravesical treatment among either group: no documentation of subsequent intravesical treatment

Interventions	**Comparator arm:** WLC TURBT alone

Lee 2014 *(Continued)*

	Intervention arm: NBI + WLC TURBT
Outcomes	Kaplan Meier curves of freedom from recurrence up to 35 months following treatment
Funding sources	Not reported
Declarations of interest	Not reported
Notes	**Contact with study author** Date of contact attempt: 19 January 2021 Contact status: no reply to-date

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment**: There were no discussions of sequence generation; however, only the abstract was available.
Allocation concealment (selection bias)	Unclear risk	**Comment**: The authors did not describe how, if any, concealment of allocation prior to assignment was conducted; however, only the abstract was available.
Blinding of participants and personnel (performance bias)	High risk	**Comment**: Personnel could not be blinded due to the nature of the intervention.
Blinding of outcome assessment (detection bias) Subjective outcomes: time to disease recurrence, minor adverse event	High risk	**Comment**: Authors did not specify how, if any, outcome assessment blinding was achieved. The detection of disease recurrence would be affected by a lack of blinding of outcome assessors.
Incomplete outcome data (attrition bias) Time to disease recurrence	Unclear risk	**Comment**: While survival curves were available, it was unclear whether participants had an event occurrence or were censored. Only the abstract was available.
Selective reporting (reporting bias)	Unclear risk	**Comment:** No discussion of trial registration or associated registration was identified.
Other bias	Low risk	**Comment**: No additional sources of potential bias were identified.

Longo 2013

Study characteristics

Methods	**Study design:** randomized controlled trial **Study grouping**: parallel group
Participants	**Inclusion criteria:** people who underwent a TURBT for suspicious bladder cancer diagnosed by WLC **Exclusion criteria:** not reported

Longo 2013 *(Continued)*

	Number randomized: 66 participants to undergo WLC TURBT alone and 71 participants to undergo NBI + WLC TURBT **Number analyzed by authors:** 66 participants who underwent WLC TURBT alone and 71 participants who underwent NBI + WLC TURBT Baseline characteristics of participants analyzed Comparator group, n = 66 • Age: not reported • Gender-male, n (%): not reported • Focality, n (%): not reported • Tumour size, n (%): not reported • Pathological classification, n (%): not reported • Pathological grade, n (%): not reported Intervention group, n = 71 • Age: not reported • Gender-male, n (%): not reported • Focality, n (%): not reported • Tumor size, n (%): not reported • Pathological classification, n (%): not reported • Pathological grade, n (%): not reported **Subsequent intravesical treatment among either group**: no documentation of subsequent intravesical treatment
Interventions	**Comparator arm:** WLC TURBT alone **Intervention arm:** NBI + WLC TURBT (Olympus)
Outcomes	Surgical complication (Clavien-Dindo) Mean time to catheter removal Absence of muscle tissue in the specimen False-positive rate
Funding sources	Not reported
Declarations of interest	Not reported
Notes	**Contact with study author** Date of contact attempt: 5 October 2020 Contact status: no reply to-date

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment**: Authors did not specify how random assignments were generated; however, only the abstract was available.

Longo 2013 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	**Comment**: The authors did not describe how, if any, concealment of allocations prior to assignment was conducted; however, only the abstract was available.
Blinding of participants and personnel (performance bias)	High risk	**Comment:** Personnel could not be blinded due to the nature of the intervention.
Blinding of outcome assessment (detection bias) Subjective outcomes: time to disease recurrence, minor adverse event	High risk	**Comment:** Authors did not specify how, if any, outcome assessment blinding was achieved. The detection of minor adverse events would be affected by a lack of blinding of outcome assessors.
Blinding of outcome assessment (detection bias) Objective outcomes: major adverse event	Low risk	**Comment:** The authors did not specify how, if any, blinding of outcome assessment was conducted. However, we do not expect the lack of blinding to bias the detection or reporting of major adverse events as no clinical judgement was involved.
Incomplete outcome data (attrition bias) Major adverse event	Low risk	**Comment:** Of the 137 participants randomized, 66 and 71 were randomized to the WLC TURBT arm and to the NBI + WLC TURBT arm, respectively. All participants were included in the analysis of adverse events. The attrition rate was less than 10% in both arms.
Incomplete outcome data (attrition bias) Minor adverse event	Low risk	**Comment:** Of the 137 participants randomized, 66 and 71 were randomized to the WLC TURBT arm and to the NBI + WLC TURBT arm, respectively. All participants were included in the analysis of adverse events. The attrition rate was less than 10% in both arms.
Selective reporting (reporting bias)	Unclear risk	**Comment**: No associated trial registration was found.
Other bias	Low risk	**Comment**: No additional potential sources of bias were identified.

Ma 2015

Study characteristics	
Methods	**Study design:** randomized controlled trial **Study grouping:** parallel group
Participants	**Inclusion criteria:** between February 2013 and February 2014, 209 participants were initially diagnosed with original or recurrent bladder cancer. They were randomized into WLC TURBT alone and NBI + WLC guided Holmium laser resection of bladder tumor groups **Exclusion criteria:** presence of invasive bladder cancer; no immediate postoperative intravesical bladder instillation of therapeutic agent; underwent other treatment for cancer; presence of lymph node or distant metastasis **Number randomized:** 209 participants **Number analyzed by authors:** 92 participants who underwent WLC TURBT alone and 86 participants who underwent NBI-guided holmium laser resection of bladder tumors Baseline characteristics of participants analyzed Comparator group, n = 92

Ma 2015 *(Continued)*

- Age, mean (SD): 62 (8)
- Gender-male, n (%): 79 (85.9)
- Focality, n (%)
  - Unifocal: 54 (58.7)
  - Multifocal: 38 (41.3)
- Tumour size, n (%)
  - < 3 cm: 63 (68.5)
  - ≥ 3 cm: 29 (31.5)
- Pathological classification, n (%): not reported
- Pathological grade, n (%): not reported

Intervention group, n = 86

- Age, mean (SD): 63 (9)
- Gender-male, n (%): 69 (80.3)
- Focality, n (%)
  - Unifocal: 50 (58.1)
  - Multifocal: 36 (41.9)
- Tumour size, n (%)
  - < 3 cm: 65 (75.6)
  - ≥ 3 cm: 21 (24.4)
- Pathological classification, n (%): not reported
- Pathological grade, n (%): not reported

Subsequent intravesical treatment among either group: All participants underwent postoperative instillation. Intermediate- and high-risk participants continued instillation for one year.

Interventions	**Comparator arm:** WLC TURBT alone **Intervention arm:** NBI + WLC guided holmium laser resection of bladder tumor
Outcomes	Disease recurrence at 3 months Disease recurrence at 12 months In-situ recurrence Ex-situ recurrence (recurrence at other locations)
Funding sources	Two government sources
Declarations of interest	Not reported
Notes	**Contact with study author** Date of contact attempt: 19 January 2021 Contact status: no reply to-date

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Comment:** Authors generated two comparison groups using simple randomization.
Allocation concealment (selection bias)	High risk	**Comment:** The authors did not discuss the method used, if any, to conceal the allocation sequence.

Ma 2015 *(Continued)*

Blinding of participants and personnel (performance bias)	High risk	**Comment**: Personnel could not be blinded due to the nature of the intervention.
Blinding of outcome assessment (detection bias) Subjective outcomes: time to disease recurrence, minor adverse event	High risk	**Comment**: Authors did not specify how, if any, outcome assessment blinding was achieved. The detection of disease recurrence would be affected by a lack of blinding of outcome assessors.
Incomplete outcome data (attrition bias) Time to disease recurrence	Low risk	**Comment**: Of the 209 participants enrolled and 178 randomized (92 of the WLC TURBT arm and 86 participants of the NBI + WLC TURBT arm), all participants were available for follow-up at 12 months.
Selective reporting (reporting bias)	Unclear risk	**Comment**: No associated trial registration was identified.
Other bias	Low risk	**Comment**: No additional sources of potential bias were found.

Naito 2016

Study characteristics	
Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group

Participants	**Inclusion criteria:** people scheduled for TURBT with papillary bladder tumor(s) detected by imaging or cystoscopy or those scheduled for random biopsies and/or TURBT because of bladder lavage fluid or voided urine cytology with malignant (grade 3) cells
	
	Exclusion criteria: people with presence of tumors in the upper urinary tract, muscle-invasive bladder tumour, previous irradiation of the pelvis, gross hematuria that might interfere with cystoscopy at the time of TURBT, participation in other clinical studies with investigational drugs either concurrently or within the previous 30 days, pregnancy, any condition associated with a risk of poor protocol compliance
	
	Number randomized: 481 participants to undergo WLC TURBT alone and 484 participants to undergo NBI + WLC TURBT
	
	Number analyzed by authors: 481 participants to undergo WLC TURBT alone and 484 participants to undergo NBI + WLC TURBT; of which 294 participants who underwent WLC TURBT alone and 303 participants who underwent NBI + WLC TURBT completed the 12-month follow-up.
	
	Baseline characteristics of intention-to-treat cohort
	
	Comparator group, n = 481
	
	• Age, mean (SD): 65.8 years old (12.5)
	• Gender-male, n (%): 383 (79.6)
	• Focality, n (%)
	  ◦ Unifocal: 279 participants (59.9)
	  ◦ Multifocal: 187 participants (40.1)
	• Tumor size, mm; mean (SD) (range)
	  ◦ 21.5 (13.6) (2.0 to 100.0)
	• Pathological classification, n (%)

Naito 2016 *(Continued)*

- Tx: 27 (5.7)
- T0: 40 (8.4)
- Ta: 214 (45.1)
- TIS: 7 (1.5)
- T1 or higher: 186 (39.3)

- Pathological grade, n (%)
  - Grade 1: 144 (33.8)
  - Grade 2: 145 (34.0)
  - Grade 3: 127 (32.3)

Intervention group, n = 484

- Age, mean (SD): 66.7(12.3)
- Gender-male, n (%): 390 (80.6)
- Focality, n (%)
  - Unifocal: 266 participants (55.0)
  - Multifocal: 212 participants (45.0)
- Tumour size, mm; mean (SD) (range)
  - 20.4 (12.6) (2.0 to 60.0)
- Pathological classification, n (%)
  - pTx: 24 (5.0)
  - pT0: 38 (8.0)
  - pTa: 218 (45.8)
  - pTIS: 12 (2.5)
  - pT1 or higher: 184 (38.7)
- Pathological grade, n (%)
  - Grade 1: 155 (35.5)
  - Grade 2: 149 (34.1)
  - Grade 3: 133 (30.4)

Subsequent intravesical treatment among either group: no documentation of subsequent intravesical treatment

Interventions	**Comparator group:** WLC TURBT **Intervention group:** NBI + WLC TURBT
Outcomes	Surgical complication (Clavien-Dindo) Disease recurrence during re-TURBT Disease recurrence at 3 months Disease recurrence at 12 months
Funding sources	Funded by Olympus through an unrestricted educational grant
Declarations of interest	The authors reported having no conflict on interest to declare.
Notes	**Contact with study author** Date of contact attempt: 13 January 2021 Contact status: no reply to-date

Risk of bias

Bias	Authors' judgement	Support for judgement

Naito 2016 *(Continued)*

Random sequence generation (selection bias)	Low risk	**Quote:** "After enrollment, participants were randomly allocated in a 1:1 ratio to parallel control (WL) and intervention (NBI) arms. Randomization was conducted by means of a concealed computer-generated random sequence of numbers using permuted blocks..." **Comment:** Participants were randomized by means of a concealed computer-generated random sequence of numbers.
Allocation concealment (selection bias)	Low risk	**Quote:** "The process was implemented through the online data management system. Participants were blinded for the treatment arm to which they were randomized." **Comment:** There was central randomization and participants were blinded, suggesting that adequate allocation sequence concealment.
Blinding of participants and personnel (performance bias)	High risk	**Comment:** Personnel could not be blinded due to the nature of the intervention.
Blinding of outcome assessment (detection bias) Subjective outcomes: time to disease recurrence, minor adverse event	High risk	**Comment**: Authors did not specify how, if any, outcome assessment blinding was achieved. The detection of disease recurrence and minor adverse events would be affected by a lack of blinding of outcome assessors.
Blinding of outcome assessment (detection bias) Objective outcomes: major adverse event	Low risk	**Comment:** The authors did not specify how, if any, blinding of outcome assessment was conducted. However, we do not expect the lack of blinding to bias the detection or reporting of major adverse events as no clinical judgement was involved.
Incomplete outcome data (attrition bias) Time to disease recurrence	High risk	**Comment**: Of the 481 and 484 participants randomized to the WLC TURBT arm and the NBI + WLC TURBT arm, respectively, 294 (61%) and 303 (63%) completed the study. The attrition rate was greater than 20% in both arms.
Incomplete outcome data (attrition bias) Major adverse event	High risk	**Comment**: Of the 481 and 484 participants randomized to the WLC TURBT arm and the NBI + WLC TURBT arm, respectively, 294 (61%) and 303 (63%) completed the study. The attrition rate was greater than 20% in both arms.
Incomplete outcome data (attrition bias) Minor adverse event	High risk	**Comment**: Of the 481 and 484 participants randomized to the WLC TURBT arm and the NBI + WLC TURBT arm, respectively, 294 (61%) and 303 (63%) completed the study. The attrition rate was greater than 20% in both arms.
Selective reporting (reporting bias)	Low risk	**Comment**: Trial was registered (nl3513) in the Netherlands Trial Register, and no discrepancies were identified between registration and the reported outcomes.
Other bias	Low risk	**Comment**: No additional sources of potential bias were identified.

Naselli 2012

Study characteristics	
Methods	**Study design:** randomized controlled trial **Study grouping:** parallel group

Naselli 2012 *(Continued)*

Participants	**Inclusion criteria:** people from two centers with overt or suspected bladder cancer.
	
	Exclusion criteria: invasive bladder cancer, absence of urothelial cancer after pathologic examination, or without follow-up
	
	Number randomized: 188 (95 participants to undergo WLC TURBT alone and 93 participants to undergo NBI + WLC TURBT)
	
	Number analyzed by authors: 72 participants who underwent WLC TURBT and 76 participants who underwent NBI + WLC TURBT and had completed follow-up at 12-months.
	
	Baseline characteristics of participants analyzed
	
	Comparator group, n = 72
	
	• Age, mean (SD): 71.6 (12.4)
	• Gender-male, n (%): 17 (23.6)
	• Tumor focality, n (%)
	  ○ Unifocal: 39 (54.2)
	  ○ Multifocal: 33 (45.8)
	• Tumor size, n (%)
	  ○ ≤ 3 cm: 53 (73.6)
	  ○ > 3 cm: 19 (26.4)
	• Pathological classification, n (%)
	  ○ pTa/CIS: 52 (72.2)
	  ○ pT1: 20 (27.8)
	• Pathological grade, n (%)
	  ○ Low: 41 (56.9)
	  ○ High: 31 (43.0)
	
	Intervention group, n = 76
	
	• Age, mean (SD): 70.8 (10.3)
	• Gender-male, n (%): 12 (15.8)
	• Tumor focality, n (%)
	  ○ Unifocal: 37 (48.7)
	  ○ Multifocal: 39 (51.3)
	• Tumor size, n (%)
	  ○ ≤ 3 cm: 55 (72.4)
	  ○ > 3 cm: 21 (27.6)
	• Pathological classification, n (%)
	  ○ pTa/CIS: 58 (76.3)
	  ○ pT1: 18 (23.7)
	• Pathological grade, n (%)
	  ○ Low: 39 (51.3)
	  ○ High: 37 (48.7)
	
	Subsequent intravesical treatment among either group: no participant included had undergone subsequent intravesical treatment

Interventions	**Comparator group:** WLC TURBT **Intervention group:** NBI + WLC TURBT
Outcomes	Detection rate Recurrence free survival rate at 12 months Logistic regression of 12 months and 3 months recurrence risks

Naselli 2012 *(Continued)*

Funding sources	None
Declarations of interest	The authors reported having no conflicts of interest to declare
Notes	**Contact with study author** Date of contact attempt: 13 January 2021 Contact status: no reply to-date

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "Randomization was centralized and performed by means of a random table." **Comment:** Randomization was performed via a centralized random table.
Allocation concealment (selection bias)	High risk	**Comment:** The authors did not describe how, if any, concealment of allocation was conducted.
Blinding of participants and personnel (performance bias)	High risk	**Comment:** Personnel could not be blinded due to the nature of the intervention.
Blinding of outcome assessment (detection bias) Subjective outcomes: time to disease recurrence, minor adverse event	Unclear risk	**Support:** "The specimen of each lesion was analyzed individually by a pathologist blinded to the mode of identification of the single lesion (WL or NBI)." **Comment:** The pathologist was blinded. However, the authors did not specify if the personnel responsible for assessing minor adverse events were blinded. The detection of minor adverse events would be affected by a lack of blinding of outcome assessors.
Incomplete outcome data (attrition bias) Time to disease recurrence	High risk	**Comment:** Of the 93 participants who were randomized to the WLC TURBT arm, 72 (77%) had completed follow-up. Of the 95 participants were randomized to the NBI + WLC TURBT arm, 76 (80%) had completed follow-up. With attrition rates of 23% and 20%, the risk of attrition bias was deemed high.
Selective reporting (reporting bias)	Low risk	**Comment:** The trial was registered in the Netherlands Trial Register (NTR3645). Outcomes were reported as noted in registration. Primary and secondary outcomes reported as registered.
Other bias	Low risk	**Comment:** No additional sources of potential bias were identified.

Stănescu 2014

Study characteristics

Methods	**Study design:** randomized controlled trial **Study grouping:** parallel group
Participants	**Inclusion criteria:** people with one or more suspected non-muscle invasive bladder cancer of over 3 cm in diameter. **Exclusion criteria:** people with muscle invasive bladder cancer

Stănescu 2014 *(Continued)*

Number randomized: 260 (130 participants to undergo WLC TURBT and 130 participants to undergo NBC+WLC guided bipolar plasma vaporization)

Number analyzed by authors

- Adverse events: 109 participants to undergo WLC TURBT and 112 participants to undergo NBI-guided bipolar plasma vaporization
- 1- and 2-year recurrence: 93 participants who underwent WLC TURBT and 97 participants who underwent NBI + WLC guided bipolar plasma vaporization

Baseline characteristics (unclear if reported characteristics were of participants randomized or participants analyzed)

Comparator group, n = unclear

- Age, mean (range): 64.8 (33 to 86)
- Gender-male, n (%): not reported
- Tumor focality, n (%): not reported
- Tumor size: only included participants with tumors > 3 cm in diameter
- Pathological classification, n (%): not reported
- Pathological grade, n (%): not reported

Intervention group, n = unclear

- Age, mean (range): 65.2 (32 to 87)
- Gender-male, n (%): not reported
- Tumor focality, n (%): not reported
- Tumor size: only included participants with tumors > 3 cm in diameter
- Pathological classification, n (%): not reported
- Pathological grade, n (%): not reported

Subsequent intravesical treatment: In all cases without bladder wall perforations, a single postoperative mitomycin-C instillation was performed. In all participants with NMIBT, standard monopolar repeat TUR was performed 4 weeks after the initial procedure followed by a 1-year bacille Calmette-Guérin intravesical instillation.

Interventions	**Comparator arm:** WLC TURBT, followed by a single postoperative instillation with doxorubicin or epirubicin within 24 hours after surgery **Intervention arm:** NBI + WLC guided bipolar plasma vaporization (Visera video system), followed by a single postoperative instillation with doxorubicin or epirubicin within 24 hours after surgery
Outcomes	Adverse events Tumor detection rate by pathology Re-TURBT rate Recurrence rate at 12 months Recurrence rate at 24 months
Funding sources	Not reported
Declarations of interest	Not reported
Notes	**Contact with study author** Date of contact attempt: 13 January 2021 Contact status: no reply to-date

Stănescu 2014 *(Continued)*

Time to disease recurrence data found in Geavlete 2012 (Urology) companion paper.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "All participants signed an approved written informed consent form that properly explained the aims, methods, anticipated benefits, potential hazards, and any other aspect of the study relevant to the participant's decision to participate. They were subsequently randomized using sealed envelopes and were unaware of which diagnostic and treatment alternative was applied in each case." **Comment:** Sealed envelopes were used for sequence generation, which was deemed adequate.
Allocation concealment (selection bias)	Low risk	**Quote:** "All participants signed an approved written informed consent form that properly explained the aims, methods, anticipated benefits, potential hazards, and any other aspect of the study relevant to the participant's decision to participate. They were subsequently randomized using sealed envelopes and were unaware of which diagnostic and treatment alternative was applied in each case." **Comment:** There was central randomization with allocation sequence concealment.
Blinding of participants and personnel (performance bias)	High risk	**Comment:** Personnel could not be blinded due to the nature of the intervention.
Blinding of outcome assessment (detection bias) Subjective outcomes: time to disease recurrence, minor adverse event	High risk	**Comment:** Authors did not specify how, if any, outcome assessment blinding was achieved. The detection of disease recurrence and minor adverse events would be affected by a lack of blinding of outcome assessors.
Blinding of outcome assessment (detection bias) Objective outcomes: major adverse event	Low risk	**Comment:** The authors did not specify how, if any, blinding of outcome assessment was conducted. However, we do not expect the lack of blinding to bias the detection or reporting of major adverse events as no clinical judgement was involved.
Incomplete outcome data (attrition bias) Time to disease recurrence	High risk	**Comment:** Of the 260 participants randomized (130 to the WLC TURBT arm, and 130 to the NBI + WLC TURBT arm), 97 (75%) and 93 (72%) participants of the respective arms completed the follow-up. The attrition rate was greater than 20% in both arms.
Incomplete outcome data (attrition bias) Major adverse event	High risk	**Comment:** Of the 260 participants randomized (130 to the WLC TURBT arm, and 130 to the NBI + WLC TURBT arm), 97 (75%) and 93 (72%) participants of the respective arms completed the follow-up. The attrition rate was greater than 20% in both arms.
Incomplete outcome data (attrition bias) Minor adverse event	High risk	**Comment:** Of the 260 participants randomized (130 to the WLC TURBT arm, and 130 to the NBI + WLC TURBT arm), 97 (75%) and 93 (72%) participants of the respective arms completed the follow-up. The attrition rate was greater than 20% in both arms.
Selective reporting (reporting bias)	Unclear risk	**Comment:** No associated trial registration found.

Stănescu 2014 *(Continued)*

Other bias	Low risk	**Comment:** No additional sources of potential bias were identified.

Abbreviations and descriptions:
CIS/Tis: urothelial carcinoma in situ, "flat tumor"; IQR: interquartile range; NBI: narrow band imaging; SD: standard deviation; pT0: no evidence of primary tumor (pathologically staged); pT1: tumor invades lamina propria (pathologically staged); pTa: noninvasive papillary carcinoma (pathologically staged); TURBT: transurethral resection of bladder tumor; TX: primary tumor cannot be assessed; WLC: white light cystoscopy

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

Study	Reason for exclusion
Doehn 2014	Irrelevant study design: this was a sequential intervention study where participants received WLC TURBT, blue light-guided TURBT, and NBI + WLC TURBT in a randomized order.
Dogra 2016	Irrelevant outcome: this study compared the detection of bladder cancer, rather than our outcomes of interest (disease recurrence, progression, death, adverse events).
Geavlete 2012	Irrelevant study design: all participants underwent WLC TURBT, followed by NBI + WLC TURBT.
Hah 2018	Irrelevant outcome: this study compared the detection of bladder cancer, rather than our outcomes of interest (disease recurrence, progression, death, adverse events).
Herr 2015	Article was retracted.
Herr 2019	Irrelevant design: editorial.
Hirner 2016	Irrelevant study population: this study examined the use of NBI in participants on surveillance, a population which we have specified to exclude in our protocol since we are only considering the use of NBI in the treatment setting in this review.
Lee 2017	Irrelevant outcome: this study compared the detection of bladder cancer, rather than our outcomes of interest (disease recurrence, progression, death, adverse events).
Mita 2018	Irrelevant study population: this study examined the use of NBI in participants on surveillance, a population which we have specified to exclude in our protocol since we are only considering the use of NBI in the treatment setting in this review.
Mukherjee 2019	Irrelevant study design: this was a sequential intervention study where participants received WLC TURBT and NBI + WLC TURBT in a randomized order.
Naya 2015	Irrelevant study design: this was a sequential intervention study where participants received WLC TURBT and NBI + WLC TURBT in a randomized order.
Shen 2010	Irrelevant study design: this was a sequential intervention study where participants received WLC TURBT and NBI + WLC TURBT in a randomized order.
Shen 2012	Irrelevant study design: this was a sequential intervention study where participants received WLC TURBT and NBI + WLC TURBT in a randomized order.
Tschirdewahn 2020	Irrelevant study population: this study examined the use of NBI in participants on surveillance, a population which we have specified to exclude in our protocol since we are only considering the use of NBI in the treatment setting in this review.

Study	Reason for exclusion
Ye 2015	Irrelevant study design: this was a sequential intervention study where participants received WLC TURBT and NBI + WLC TURBT in a randomized order.

NBI: narrow band imaging; TURBT: transurethral resection of bladder tumor; WLC: white light cystoscopy

DATA AND ANALYSES

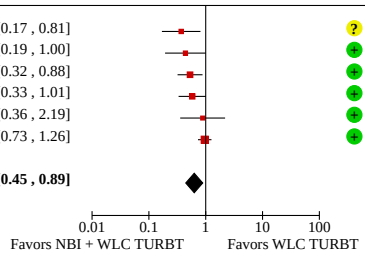
Comparison 1. NBI + WLC TURBT vs WLC TURBT alone

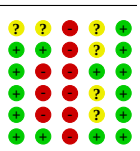
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Time to disease recurrence	6	1244	Hazard Ratio (IV, Random, 95% CI)	0.63 [0.45, 0.89]
1.2 Major adverse event (Clavien-Dindo III, IV, V)	4	1385	Risk Ratio (IV, Random, 95% CI)	1.77 [0.79, 3.96]
1.3 Minor adverse event (Clavien-Dindo grade I, II)	4	1385	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.49, 1.56]

Analysis 1.1. Comparison 1: NBI + WLC TURBT vs WLC TURBT alone, Outcome 1: Time to disease recurrence

Study or Subgroup	log[Hazard Ratio]	SE	NBI + WLC TURBT Total	WLC TURBT alone Total	Weight	Hazard Ratio IV, Random, 95% CI
Lee 2014	-0.994252	0.398282	33	35	12.4%	0.37 [0.17 , 0.81]
Stănescu 2014	-0.820981	0.4211	89	90	11.5%	0.44 [0.19 , 1.00]
Naselli 2012	-0.634878	0.258066	76	72	19.7%	0.53 [0.32 , 0.88]
Ma 2015	-0.544727	0.282827	86	92	18.1%	0.58 [0.33 , 1.01]
Kim 2018	-0.124	0.46408	39	35	10.1%	0.88 [0.36 , 2.19]
Naito 2016	-0.04	0.139243	303	294	28.2%	0.96 [0.73 , 1.26]
Total (95% CI)			**626**	**618**	**100.0%**	**0.63 [0.45 , 0.89]**

Heterogeneity: Tau² = 0.09; Chi² = 10.62, df = 5 (P = 0.06); I² = 53%
Test for overall effect: Z = 2.65 (P = 0.008)
Test for subgroup differences: Not applicable



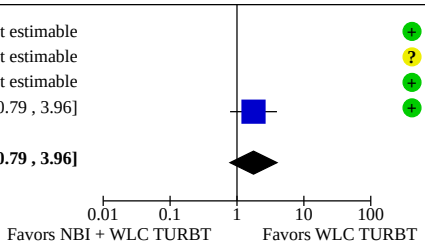


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias):
(D) Selective reporting (reporting bias)
(E) Other bias

Analysis 1.2. Comparison 1: NBI + WLC TURBT vs WLC TURBT alone, Outcome 2: Major adverse event (Clavien-Dindo III, IV, V)

Study or Subgroup	NBI + WLC TURBT Events	NBI + WLC TURBT Total	WLC TURBT alone Events	WLC TURBT alone Total	Weight	Risk Ratio IV, Random, 95% CI
Buaban 2018	0	37	0	25		Not estimable
Longo 2013	0	71	0	66		Not estimable
Stănescu 2014	0	112	0	109		Not estimable
Naito 2016	16	484	9	481	100.0%	1.77 [0.79 , 3.96]
Total (95% CI)		**704**		**681**	**100.0%**	**1.77 [0.79 , 3.96]**
Total events:	16		9			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.38 (P = 0.17)
Test for subgroup differences: Not applicable

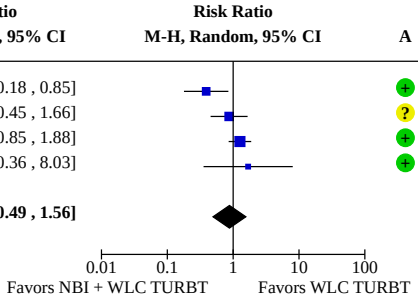


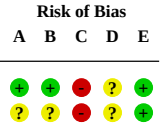
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias):
(D) Selective reporting (reporting bias)
(E) Other bias

Analysis 1.3. Comparison 1: NBI + WLC TURBT vs WLC TURBT alone, Outcome 3: Minor adverse event (Clavien-Dindo grade I, II)

Study or Subgroup	NBI + WLC TURBT Events	NBI + WLC TURBT Total	WLC TURBT alone Events	WLC TURBT alone Total	Weight	Risk Ratio M-H, Random, 95% CI
Stănescu 2014	8	112	20	109	24.5%	0.39 [0.18 , 0.85]
Longo 2013	14	71	15	66	28.4%	0.87 [0.45 , 1.66]
Naito 2016	51	484	40	481	36.7%	1.27 [0.85 , 1.88]
Buaban 2018	5	37	2	25	10.4%	1.69 [0.36 , 8.03]
Total (95% CI)		**704**		**681**	**100.0%**	**0.88 [0.49 , 1.56]**
Total events:	78		77			

Heterogeneity: Tau² = 0.19; Chi² = 7.67, df = 3 (P = 0.05); I² = 61%
Test for overall effect: Z = 0.44 (P = 0.66)
Test for subgroup differences: Not applicable





Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias):
(D) Selective reporting (reporting bias)
(E) Other bias

ADDITIONAL TABLES

Table 1. Overview of included studies

Reference identification	Publication type	Trial period	Country	Description of participants (number randomized)	Comparator vs intervention	Outcome assessed (time point)	Mean age	Male, n (%)
Buaban 2018	Full text	2015 to 2016	Thailand	Participants with histopathology-visualized non-muscle invasive bladder cancer and complete resection of the visualized tumor (n = 158)	WLC TURBT	Disease recurrence (3 months) Surgical complication	Unclear. Characteristics were reported on a per-procedure basis, and some participants had undergone more than one procedure.	Unclear. Characteristics were reported on a per-procedure basis, and some participants had undergone more than one procedure.
					NBI + WLC TURBT		See above	
Kim 2018	Full text	2013 to 2017	Korea	Participants who underwent TURBT for suspicion of a bladder tumor discovered by use of cystoscopy or another imaging study (n = 198)	WLC TURBT	Number of tumors identified Disease recurrence (12 months)	66.96 ± 11.51	54 (81)
					NBI + WLC TURBT		64.54 ± 12.01	62 (73)
Lee 2014	Abstract	2010 to 2013	Korea	Participants with overt or suspected non-muscle invasive bladder cancer (n = 68)	WLC TURBT	Disease recurrence (24 months)	63.03 ± 12.43	Not reported
					NBI + WLC TURBT		63.82 ± 12.31	
Longo 2013	Abstract	Not reported	Italy	Not reported (n = 137)	WLC TURBT	Surgical complication	Not reported	
					NBI + WLC TURBT			

Table 1. Overview of included studies *(Continued)*

						Mean time to catheter removal		
						Absence of muscle tissue in specimen		
						False positive rate		
Ma 2015	Full text	2013 to 2014	China	Participants initially diagnosed with primary or recurrent non-muscle invasive bladder cancer (n = 178)	WLC TURBT	Disease recurrence (3 months, 12 months)	62 ± 8	79 (85)
					NBI-guided holmium laser resection of bladder tumor		63 ± 9	69 (80)
Naito 2016	Full text	2010 to 2014	16 countries	Participants with primary non-muscle invasive bladder cancer (n = 965)	WLC TURBT	Surgical complication	65.8 ± 12.5	383 (80)
					NBI + WLC TURBT		66.7 ± 12.3	390 (81)
						Disease recurrence (during re-TURBT, 3 months, 12 months)		
Naselli 2012	Full text	2009 to 2010	Italy	Participants from two centers with overt or suspected bladder cancer (n = 188)	WLC TURBT: white light cystoscopy guided TURBT *exclusively*	Detection rate Disease recurrence (12 months)	71.6 ± 12.4	17 (24)
					NBI TURBT: NBI guided TURBT *exclusively*		70.8 ± 10.3	12 (16)
Stănescu 2014	Full text	Not reported	Romania	Participants with non-muscle invasive bladder cancer (n = 260)	WLC TURBT	Tumor detection rate	64.8 (33 to 86)	Not reported
					NBI-guided bipolar plasma vaporization		65.2 (32 to 87)	
						Surgical complication		

Table 1. Overview of included studies *(Continued)*

		Disease recurrence (12 months, 24 months)

NBI: narrow band imaging; TURBT: transurethral resection of bladder tumor; WLC: white light cystoscopy

APPENDICES

Appendix 1. Cochrane Library search strategy

#1 MeSH descriptor: [Urinary Bladder Neoplasms] explode all trees

#2 (bladder* near/3 (cancer* OR carcinoma* OR neoplas* OR tumor* OR tumour*)):ti,ab,kw (Word variations have been searched)

#3 (NMIBC):ti,ab,kw (Word variations have been searched)

#4 (TURBT):ti,ab,kw (Word variations have been searched)

#5 #1 or #2 or #3 or #4

#6 MeSH descriptor: [Narrow band imaging] explode all trees

#7 (("narrow band" or narrowband or narrow-band) near/3 imaging):ti,ab,kw

#8 nbi:ti,ab,kw

#9 #6 OR #7 OR #8

#10 #5 AND #9

Appendix 2. International Pharmaceutical Abstracts search strategy

1 (bladder$ adj3 (cancer$ or carcinoma$ or neoplas$ or tumo?r$)).tw.

2 NMIBC.tw.

3 TURBT.tw.

4 1 or 2 or 3

5 (("narrow band" or narrowband or narrow-band) adj3 imaging).tw.

6 NBI.tw.

7 5 or 6

8 4 and 7

Appendix 3. MEDLINE Ovid search strategy

1 exp urinary bladder neoplasms/

2 (bladder$ adj3 (cancer$ or carcinoma$ or neoplas$ or tumo?r$)).tw.

3 NMIBC.tw.

4 TURBT.tw.

5 1 or 2 or 3 or 4

6 exp narrow band imaging/

7 (("narrow band" or narrowband or narrow-band) adj3 imaging).tw.

8 NBI.tw.

9 6 or 7 or 8

10 5 and 9

11 randomized controlled trial.pt.

12 controlled clinical trial.pt.

13 randomized.ab.

14 placebo.ab.

15 drug therapy.fs.

16 randomly.ab.

17 trial.ab.

18 groups.ab.

19 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18

20 exp animals/ not humans.sh.

21 19 not 20

22 10 and 21

Appendix 4. Embase search strategy

#1 'bladder tumor'/exp

#2 (bladder* NEAR/3 (cancer* OR carcinoma* OR neoplas* OR tumor* OR tumour*)):ab,ti

#3 nmibc:ab,ti

#4 turbt:ab,ti

#5 #1 OR #2 OR #3 OR #4

#6 'narrow band imaging'/exp

#7 (("narrow band" or narrowband or narrow-band) NEAR/3 imaging):ab,ti

#8 nbi:ab,ti

#9 #6 OR #7 OR #8

#10 #5 AND #9

#11 'crossover procedure':de OR 'double-blind procedure':de OR 'randomized controlled trial':de OR 'single-blind procedure':de OR random*:de,ab,ti OR factorial*:de,ab,ti OR crossover*:de,ab,ti OR ((cross NEXT/1 over*):de,ab,ti) OR placebo*:de,ab,ti OR ((doubl* NEAR/1 blind*):de,ab,ti) OR ((singl* NEAR/1 blind*):de,ab,ti) OR assign*:de,ab,ti OR allocat*:de,ab,ti OR volunteer*:de,ab,ti

#12 'animals'/exp NOT ('humans'/exp AND 'animals'/exp)

#13 #11 NOT#12

#14 #10 AND #13

Appendix 5. Web of Science search strategy

#1 TS=((bladder* NEAR/3 (cancer* OR carcinoma* OR neoplas* OR tumor* OR tumour*)) OR NMIBC OR TURBT)

#2 TS=((("narrow band" or narrowband or narrow-band) NEAR/3 imaging) OR NBI)

#3 #1 AND #2

#4 TS=clinical trial* OR TS=research design OR TS=comparative stud* OR TS=evaluation stud* OR TS=controlled trial* OR TS=follow-up stud* OR TS=prospective stud* OR TS=random* OR TS=placebo* OR TS=(single blind*) OR TS=(double blind*)

#5 #3 AND #4

Appendix 6. Scopus search strategy

#1 TITLE-ABS-KEY((bladder* W/3 (cancer* OR carcinoma* OR neoplas* OR tumor* OR tumour*)) OR NMIBC OR TURBT)

#2 TITLE-ABS-KEY((("narrow band" or narrowband or narrow-band) W/3 imaging) OR NBI)

#3 #1 AND #2

#4 ("clinical trials" OR "clinical trials as a topic" OR "randomized controlled trial" OR "Randomized Controlled Trials as Topic" OR "controlled clinical trial" OR "Controlled Clinical Trials" OR "random allocation" OR "Double-Blind Method" OR "Single-Blind Method" OR "Cross-Over Studies" OR "Placebos" OR "multicenter study" OR "double blind procedure" OR "single blind procedure" OR "crossover procedure" OR "clinical trial" OR "controlled study" OR "randomization" OR "placebo") OR (TITLE-ABS-KEY (("clinical trials" OR "clinical trials as a topic" OR "randomized controlled trial" OR "Randomized Controlled Trials as Topic" OR "controlled clinical trial" OR "Controlled Clinical Trials as Topic" OR "random allocation" OR "randomly allocated" OR "allocated randomly" OR "Double-Blind Method" OR "Single-Blind Method" OR "Cross-Over Studies" OR "Placebos" OR "cross-over trial" OR "single blind" OR "double blind" OR "factorial design" OR "factorial trial"))) OR (TITLE-ABS (clinical trial* OR trial* OR rct* OR random* OR blind*))

#5 #3 AND #4

Appendix 7. Open Grey literature search strategy

"Bladder Cancer" AND ("narrow band imaging" OR "narrow-band imaging" OR "narrowband imaging" OR NBI)

Note: The Open Grey search was conducted during the initial search in September 2020. The service was discontinued in 2021, precluding its inclusion in the second search in December 2021.

Appendix 8. ClinicalTrials.gov search strategy

#1 Bladder Cancer

#2 Narrow band imaging OR narrow-band imaging OR narrowband imaging OR NBI

#3 1 AND 2

Appendix 9. WHO search strategy

#1 bladder cancer AND narrow band imaging

#2 bladder cancer AND NBI

#3 bladder cancer AND narrow-band imaging

#4 bladder cancer AND narrowband imaging

#5 1 OR 2 OR 3 OR 4

Appendix 10. LILACS search strategy

(mh:("Urinary Bladder Neoplasms") OR tw:(((bladder OR bexiga OR vejiga) AND (cancer$ OR carcinoma$ OR tumor$ OR tomour$ OR neoplasm$ OR neoplasia$ OR neoplasma$)) OR "NMIBC" OR "TURBT")) AND (mh:("Narrow band imaging") OR tw:("Narrow band imaging" OR "narrowband imaging" OR "narrow-band imaging" OR "imagem de banda estreita" OR imágenes de banda estrecha" OR NBI)) AND (PT:"randomized controlled trial" OR PT:"controlled clinical trial" OR PT:"multicenter study" OR MH:"randomized controlled trials as topic" OR MH:"controlled clinical trials as topic" OR MH:"multicenter studies as topic" OR MH:"random allocation" OR MH:"double-blind method" OR MH:"single-blind method" OR ((ensaio$ OR ensayo$ OR trial$) AND (azar OR acaso OR placebo OR control$ OR aleat$ OR random$ OR enmascarado$ OR simpleciego OR ((simple$ OR single OR duplo$ OR doble$ OR double$) AND (cego OR ciego OR blind OR mask))) AND clinic$)) AND NOT (MH:animals OR MH:rabbits OR MH:rats OR MH:primates OR MH:dogs OR MH:cats OR MH:swine OR PT:"in vitro")

WHAT'S NEW

Date	Event	Description
23 May 2022	Amended	Minor typographical error correction.

HISTORY

Protocol first published: Issue 3, 2021
Review first published: Issue 4, 2022

CONTRIBUTIONS OF AUTHORS

- Drafted the protocol: LL, ST, EG, LH, PD, PM, GL
- Study selection: LL, ST, GL
- Extracted data from studies: LL, ST, GL
- Entered data into RevMan: LL, ST, EG
- Carried out the analysis: LL, ST, PM, PD, GL
- Interpreted the analysis: LL, ST, EG, LH, PM, PD, GL
- Disagreement resolution: GL, PD

DECLARATIONS OF INTEREST

LL, ST, EG, LH, PD, PM, and GL report no conflicts of interest.

SOURCES OF SUPPORT

Internal sources

- Minneapolis VA Healthcare, USA

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External sources

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- National Institutes of Health, USA

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- Society for Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction and National Institutes of Health, USA

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We made the following changes between the protocol (Lai 2021) and the review.

- We have revised the definition of disease progression to follow the standardized criteria published by the International Bladder Cancer Group.
- The protocol stated that the detection of minor adverse events was not susceptible to bias. However, after further discussion, the author team recognized that significant clinical judgement was involved in assessing minor adverse events such that the detection of minor adverse was susceptible to bias.

INDEX TERMS

Medical Subject Headings (MeSH)

Cystoscopy; Narrow Band Imaging [methods]; Neoplasm Recurrence, Local; Randomized Controlled Trials as Topic; *Urinary Bladder Neoplasms [diagnostic imaging] [drug therapy] [surgery]

MeSH check words

Humans