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Blue versus white light for transurethral resection of non-muscle invasive bladder cancer (Review)

Maisch P, Koziarz A, Vajgrt J, Narayan V, Kim MH, Dahm P

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[Intervention Review]

Blue versus white light for transurethral resection of non-muscle invasive bladder cancer

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ABSTRACT

Background

Disease recurrence and progression remain major challenges in the treatment of non-muscle invasive bladder cancer (NMIBC). Blue light-enhanced transurethral resection of bladder cancer (TURBT) is an approach to improve staging and achieve a complete resection of NMIBC.

Objectives

To assess the effects of blue light-enhanced TURBT compared to white light-based TURBT in the treatment of NMIBC.

Search methods

We searched several medical literature databases, including the Cochrane Library, MEDLINE, and Embase, as well as trial registers, including ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform. We performed a comprehensive search with no restrictions on language of publication or publication status until March 2021.

Selection criteria

We included randomized controlled trials using blue light versus white light TURBT. Included participants had a high level of suspicion based on imaging or 'visible diagnosis' for primary urothelial carcinoma of the bladder or recurrent urothelial carcinoma of the bladder upon cytoscopy. We excluded studies in which blue light was used in a surveillance setting.

Data collection and analysis

Two review authors independently performed data extraction and risk of bias assessment. Our primary outcomes were time to disease recurrence, time to disease progression, and serious surgical complications. Secondary outcomes were time to death from bladder cancer, any adverse events, and non-serious complications. We rated the certainty of evidence using the GRADE approach.

Main results

We included 16 randomized controlled trials involving a total of 4325 participants in the review. The studies compared blue light versus white light TURBT for treatment of NMIBC.

Primary outcomes

Blue light TURBT may reduce the risk of disease recurrence over time (hazard ratio (HR) 0.66, 95% confidence interval (CI) 0.54 to 0.81; low-certainty evidence) depending on baseline risk. For participants with low-, intermediate-, and high-risk NMIBC, this corresponded to 48 (66 fewer to 27 fewer), 109 (152 fewer to 59 fewer), and 147 (211 fewer to 76 fewer) fewer recurrences per 1000 participants when compared to white light TURBT, respectively.

Blue light TURBT may also reduce the risk of disease progression over time (HR 0.65, 95% CI 0.50 to 0.84; low-certainty evidence) depending on baseline risk. For participants with low-, intermediate-, and high-risk NMIBC, this corresponded to 1 (1 fewer to 0 fewer), 17 (25 fewer to 8 fewer), and 56 (81 fewer to 25 fewer) fewer progressions per 1000 participants when compared to white light TURBT, respectively.

Blue light TURBT may have little or no effect on serious surgical complications (risk ratio (RR) 0.54, 95% CI 0.14 to 2.14; low-certainty evidence). This corresponded to 10 fewer (19 fewer to 25 more) surgical complications per 1000 participants with blue light TURBT.

Secondary outcomes

Blue light TURBT may have little or no effect on the risk of death from bladder cancer over time (HR 0.55, 95% CI 0.19 to 1.61; low-certainty evidence). This corresponded to 22 deaths per 1000 participants with white light TURBT and 10 fewer (17 fewer to 13 more) deaths per 1000 participants with blue light TURBT.

We are very uncertain how blue light TURBT affects the outcome adverse events of any grade (RR 1.09, 95% CI 0.88 to 1.33; low-certainty evidence).

No analysis was possible for the outcome non-serious surgical complications, as it was not reported by any of the included studies.

Authors' conclusions

Blue light-enhanced TURBT for the treatment of non-muscle invasive bladder cancer compared to white light-based TURBT may reduce the risk of disease recurrence and disease progression over time depending on baseline risk. There may be little or no effect on serious surgical complications. The certainty of evidence for our findings was low, meaning that future studies are likely change to the reported estimates of effect. Frequent issues that led to downgrading of the certainty of the evidence were study limitations, inconsistency, and imprecision.

PLAIN LANGUAGE SUMMARY

Blue light-enhanced versus white light resection in the treatment of non-muscle invasive bladder cancer

Review question

How does a resection (surgical removal) of bladder cancer supported with a special visualization method (blue light) compare to a standard resection with white light in people in whom a tumor of the inner bladder wall is suspected?

Background

In people suspected of having bladder cancer, suspicious tissue is cut from the inner bladder wall using a special instrument inserted through the urethra into the bladder. However, it is sometimes difficult to tell what is normal bladder versus what is cancer. In order to see the tumor better and remove it completely, a substance, or 'contrast agent,' is put into the bladder through a catheter. During surgery, a special light is used that is meant to make the cancerous area light up blue.

Study characteristics

We only included randomized controlled trials (a type of study where participants are randomly assigned to one of two or more treatment groups) for inclusion in the review, as this type of clinical study is considered to be of the highest quality producing the most reliable results. We included people who were very likely to have had bladder cancer because if had been seen on an imaging study (like a computed tomography (CT) scan) or when looking into the bladder. We included studies of people with newly suspected tumors and those who had been treated for bladder cancer before and there was concern it had come back.

Key results

We included 16 studies addressing our review question. Overall, blue light-enhanced resection of bladder cancer may reduce the risk of disease recurrence over time compared to white light resection (low-certainty evidence) and may reduce the risk of disease progression over time (low-certainty evidence). However, whether this effect is big enough to be meaningful to people with bladder cancer depends on whether they belong to the low, intermediate and high risk group for disease recurrence or progression.

We also found that blue light may have little or no effect on the occurrence of serious surgical complications (low-certainty evidence) or the risk of death from bladder cancer over time (low-certainty evidence). We are very uncertain as to whether blue light TURBT reduces the incidence of unwanted side effects, as the certainty of the evidence was assessed as low. We do not know how non-serious surgical complications are affected as no data were reported for this outcome.

Quality of the evidence

The certainty of the evidence was low, meaning that future research would likely change our results.

Summary of findings 1. Blue light compared to white light for transurethral resection of NMIBC

Blue versus white light for transurethral resection of non-muscle invasive bladder cancer

Population: people with non-muscle invasive bladder cancer

Setting: inpatient or outpatient

Intervention: blue light transurethral resection

Comparison of interest: white light transurethral resection

Outcome	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		What happens
				Assumed risk[1]		
				White light	Risk difference with blue light	
Time to disease recurrence (absolute event rates based on 12 months follow-up; MCID 5%)	2994 (15 RCTs)	⊕⊕◯◯ LOW [a,b]	**HR 0.66** (0.54 to 0.81)	**Low[2]**		Blue light TURBT may have little or no effect on the risk of recurrence in people at low risk, but may reduce the risk of recurrence in those at intermediate and high risk.
				150 per 1000	**48 fewer per 1000** (66 fewer to 27 fewer)	
				Intermediate[2]		
				380 per 1000	**109 fewer per 1000** (152 fewer to 59 fewer)	
				High[2]		
				610 per 1000	**147 fewer per 1000** (211 fewer to 76 fewer)	
Time to disease progression (absolute event rates based on 12 months follow-up; MCID 2%)	2200 (9 RCTs)	⊕⊕◯◯ LOW [a,c]	**HR 0.65** (0.50 to 0.84)	**Low[2]**		Blue light TURBT may have little or no effect on the risk of progression in people at low and intermediate risk, but may reduce the risk of progression in those at high risk.
				2 per 1000	**1 fewer per 1000** (1 fewer to 0 fewer)	

				Intermediate[2]		
				50 per 1000	**17 fewer per 1000** (25 fewer to 8 fewer)	
				High[2]		
				170 per 1000	**56 fewer per 1000** (81 fewer to 25 fewer)	
Surgical complications, serious (up to 90 days; MCID 2%)	525 (1 RCT)	⊕⊕◯◯ LOW [a,c]	**RR 0.54** (0.14 to 2.14)	22 per 1000	**10 fewer per 1000** (19 fewer to 25 more)	Blue light TURBT may have little to no effect on serious surgical complications.
Time to death from bladder cancer (absolute event rates based on 60 months follow-up; MCID 2%)	407 (1 RCT)	⊕⊕◯◯ LOW [a,c]	**HR 0.55** (0.19 to 1.61)	22 per 1000	**10 fewer per 1000** (17 fewer to 13 more)	Blue light TURBT may have little to no effect on the time to death from bladder cancer.
Any adverse events (up to 90 days; MCID 5%)	1375 (3 RCTs)	⊕⊕◯◯ LOW [d,e]	**RR 1.09** (0.88 to 1.33)	397 per 1000	**36 more per 1000** (48 fewer to 131 more)	We are very uncertain how blue light may affect adverse events.
Surgical complications, non-serious (up to 90 days; MCID 5%)	-	-	Not estimable	-	-	We do not know how non-serious surgical complications are affected as no data were reported for this outcome.

[1]We provide absolute effect size estimates for time to recurrence and time to progression to reflect risk stratification in clinical practice. Corresponding data were not found for time to death from bladder cancer. Baseline risk for other outcomes is assumed to be similar.
[2]Baseline risk at 12 months taken from Sylvester 2006.
[a]Downgraded by one level for study limitations due to concerns about performance, attrition, and reporting bias.
[b]Downgraded by one level for clinically relevant inconsistency ($I^2 > 60\%$).
[c]Downgraded by one level for imprecision given that 95% CI is consistent with both no effect and clinically important reduction.
[d]Downgraded by one level for study limitations due to concerns about performance and reporting bias.
[e]Downgraded by one level for imprecision given wide 95% CI consistent with both large increase and large reduction of adverse events.
MCID: minimal clinically important difference
NMIBC: non-muscle invasive bladder cancer

BACKGROUND

Description of the condition

Bladder cancer is the second most common malignancy in urologic cancer patients (Bray 2018), with a rising incidence in recent decades. In 2018, 549,393 new cases of bladder cancer were reported globally, leading to an estimated 200,000 cancer-related deaths per year, making bladder cancer the 10th most common malignancy worldwide (Bray 2018).

The most common presenting symptom is hematuria, either macroscopic or microscopic. Other, even less specific, symptoms include recurrent urinary tract infections or irritative voiding symptoms. Some bladder tumors are found incidentally on cross-sectional imaging either in the form of a bladder mass or secondary ureteral obstruction with hydronephrosis, or both.

The diagnostic workup for suspected bladder cancer typically includes a urine analysis and urine culture (to rule out infection), an upper tract study such as a computed tomogram with intravenous pyelogram, urine cytology, and a white light office cystoscopy. For both diagnostic and therapeutic purposes, patients then undergo transurethral bladder tumor resection (TURBT), as well as additional bladder biopsies of suspicious-appearing areas as indicated.

At initial diagnosis, about 70% to 75% of patients present with non-muscle invasive tumors (Burger 2013; Schned 2012). Non-muscle invasive bladder cancer (NMIBC) is defined as tumors that are limited to the mucosa (pTa, carcinoma in situ) or submucosa (pT1) and do not infiltrate the underlying deeper muscle layers (Humphrey 2016). Based on their appearance, NMIBC can either present as papillary or non-papillary tumor. Involvement of the deep muscle layer of muscularis propria constitutes muscle invasive (pT2) disease or muscle invasive bladder cancer and mandates different, more aggressive management, ideally in the form of radical cystectomy.

NMIBC, especially carcinoma in situ (CIS), is known to have a high risk of tumor recurrence and progression after TURBT. Tumor recurrence at 3 and 12 months after TURBT as detected by cystoscopy is reported in up to 30% and 50% of patients, respectively (Palou 2015). The five-year recurrence rate is as high as 80%. Progression to muscle invasive bladder cancer may occur in up to 45% of patients within five years (Sylvester 2006). Additional interventions that have been demonstrated to improve the risk of recurrence and potentially progression are various forms of adjuvant intravesical therapy (Jones 2012; Schmidt 2020).

Description of the intervention

Effective treatment of NMIBC relies on both accurate staging, including the identification of CIS when present, as well as the complete resection of all visible tumor. White light cystoscopy of the bladder is the current gold standard procedure for the detection of bladder cancer. However, its sensitivity (6% to 84%) and specificity (43% to 98%) is limited, so not all tumors are always visualized (Jocham 2008). The diagnosis of small papillary tumors as well as CIS can be especially difficult, which may result in missed tumors, failure to provide adequate treatment, and cancer progression (Jocham 2008).

Different optical imaging techniques in combination with white light cystoscopy have been investigated to improve the visualization of tumors. Photodynamic diagnosis (PDD), or blue light (synonymous terms), is performed using fluorescent light after intravesical instillation of 5-aminolevulinic acid (5-ALA) or hexaminolevulinic acid (HAL, Hexvix), both for detection only at the time of diagnostic cystoscopy and therapeutically at the time of TURBT. HAL, an ester derivative of 5-ALA with improved pharmacokinetic characteristics, is the only approved drug for blue light in the United States (FDA 2010); however, both agents appear comparable in terms of sensitivity and specificity (Mowatt 2011).

Blue light is applied by intravesical instillation of the photoactive agents approximately one hour prior to cystoscopy either in the clinic or the operating room. Visualization and TURBT is then performed after drainage of the instilled fluid and activation of a fluorescent light.

How the intervention might work

Blue light uses photoactive compounds, and their interaction with fluorescent light is used to increase the optical difference between normal and malignant tissue (Krieg 2002; Witjes 2018). In malignant tissue, a dysregulation in the activity of transport proteins leads to the accumulation of protoporphyrin IX (PPIX) up to 20-fold. PPIX is a precursor of hemoglobin produced during the biosynthesis of 5-ALA, a natural amino acid. Since PPIX is photoactive, a red fluorescence is emitted by excitation at certain wavelengths of light, in particular visible blue light (375 to 445 nm) (Inoue 2017; Witjes 2018). A limiting factor in the use of 5-ALA is its low depth of penetration into the tissue due to its lipophilic characteristics (Krieg 2002). In contrast, with HAL, a synthesized ester derivative of 5-ALA, the uptake in cells is increased by passive diffusion of the cell membrane (Zaak 2007). HAL undergoes local conversion to porphyrins that preferentially accumulate in malignant cells, and the use of blue light with selective filters can highlight these areas within the bladder mucosa (typically with a red appearance before a dark-blue background).

Consequently, with the contrast enhancement of blue light from healthy to malignant tissue, more tumors can be made visible, which can then be resected more completely.

Adverse effects of the intervention

The accumulation of HAL in inflammatory tissue reduces its specificity and may lead to the resection of non-cancerous areas of the bladder, thereby resulting in unnecessary overtreatment of patients (Ray 2010). This may potentially result in a higher risk of bleeding, clot retention, and the need for secondary procedures. Other grave complications of more extensive resection include bladder perforation with the need for open surgical repair or tumor spillage into the abdomen, which may result in incurable spread.

In addition, the use of blue light cystoscopy requires changes in workflow, specialized training of staff, and oftentimes capital investment for suitable equipment, which all represent additional costs. Due to this operative time may be longer.

Why it is important to do this review

Several systematic reviews have investigated the role of blue light in aiding TURBT, and their findings suggest improved cancer outcomes over white light TURBT. Based on these findings, several widely used evidence-based, AUA 2016; EAU 2021; NICE 2015, and consensus-based, NCCN 2020, guidelines support the use of blue light. However, the existing reviews have since become outdated (Chou 2017; Mowatt 2011), as additional trials have become available, and existing trials have provided longer follow-up. In addition, none of the existing systematic reviews has applied the same methodological rigor that is the current standard for a Cochrane Review, which includes the comprehensiveness of the search, completion of study screening and data abstraction in duplicate, risk of bias assessment on per-outcome basis, and the use of the GRADE approach to rate the certainty of the evidence. The results of this review may therefore provide important new insights to inform guideline recommendations that will add to the existing suite of Cochrane Reviews on non-muscle invasive bladder cancer (Han 2021; Hwang 2019; Jung 2017; Schmidt 2020; Shepherd 2017). A closely related review on narrow band imaging is currently ongoing (Lai 2021).

OBJECTIVES

To assess the effects of blue light-enhanced TURBT compared to white light-based TURBT in the treatment of non-muscle invasive bladder cancer.

METHODS

Criteria for considering studies for this review

Types of studies

We searched for randomized controlled trials (RCTs) to address the comparisons of interest. We planned to include pseudo-randomized studies given their greater risk of selection bias, but our search did not identify any. We did not consider cluster-randomized or cross-over trials, as they are not applicable to our review question.

Types of participants

We included participants older than 18 years with a high level of suspicion or 'visible diagnosis' for primary urothelial carcinoma of the bladder or recurrent urothelial carcinoma of the bladder. This high level of suspicion was based on one or more of the following:

- bladder mass or abnormal bladder mucosa findings based on white light office cystoscopy;
- findings suggestive of a bladder mass (bladder filling defect or hydronephrosis, or both) based on cross-sectional imaging;
- positive or atypical urinary cytology (and/or other markers such as positive fluorescence in situ hybridization (FISH) test).

We only considered studies of participants without any evidence of distant metastatic disease. We did not consider studies of participants in which blue light was used in a surveillance setting (cystoscopy in a diagnostic setting only).

Types of interventions

We planned to investigate the following comparisons of experimental intervention versus comparator intervention. Concomitant interventions had to be the same in the experimental and comparator groups to establish fair comparisons.

Experimental intervention

Blue light cystoscopy with 5-ALA or HAL in combination with TURBT.

Comparator intervention

White light cystoscopy in combination with TURBT.

Comparison

Blue light cystoscopy via 5-ALA or HAL versus white light cystoscopy.

Types of outcome measures

The measurement of outcomes assessed in this review was not a study eligibility criterion.

Primary outcomes

- Time to disease recurrence (time-to-event outcome).
- Time to disease progression (time-to-event outcome).
- Surgical complications, serious (grade III, IV, and V according to Clavien-Dindo) (dichotomous outcome) (Clavien 2009).

Secondary outcomes

- Time to death from bladder cancer (time-to-event outcome).
- Any adverse events (assessed using the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE)) (dichotomous outcome).
- Surgical complications, non-serious (grade I and II according to Clavien-Dindo) (dichotomous outcome).

Method and timing of outcome measurement

- Time to disease recurrence: measured from the time of random sequence generation to the time of any recurrence of bladder cancer (based on TURBT; irrespective of tumor stage or grade).
- Time to disease progression: measured from the time of random sequence generation to the time of progression of bladder cancer as documented by histopathology at the time of TURBT (prompted by abnormal cystoscopy). We defined progression as an increase in tumor stage (defined as lamina propria invasion, e.g. increase from Ta to T1, or CIS to T1; development of muscle invasive disease (stage ≥ T2) and development of new lymph node involvement or metastatic disease) or grade (increase in grade from low to high (including CIS) following the definition of the International Bladder Cancer Group) (Lamm 2014).
- Surgical complications, serious: measured within 90 days of initial TURBT according to the Clavien-Dindo classification.
- Time to death from bladder cancer: measured from the time of random sequence generation to the time of death from bladder cancer.
- Adverse events: adverse events of any grade measured by CTCAE and within 90 days of initial TURBT.
- Surgical complications, non-serious: measured within 90 days of initial TURBT according to the Clavien-Dindo classification.

Had we been unable to obtain the necessary information to analyze time-to-event outcomes for time to disease recurrence, time to disease progression, and time to death from bladder cancer, we would instead have analyzed these outcomes as dichotomous outcomes up to 12 months (short term) or 13 to 24 months (longer term) after randomization.

We have presented a summary of findings table reporting the following outcomes listed according to priority.

- Time to disease recurrence
- Time to disease progression
- Surgical complications, serious
- Time to death from bladder cancer
- Any adverse events
- Surgical complications, non-serious

Thresholds for clinical relevance of outcomes

- Time to disease recurrence: we assumed the effect to be of clinical relevance if the observed absolute difference was 5% or greater at 12 months follow-up.
- Time to disease progression: we assumed the effect to be of clinical relevance if the observed absolute difference was 2% or greater at 12 months follow-up.
- Surgical complications, serious: we assumed the effect to be of clinical relevance if the observed absolute difference was 2% or greater at initial TURBT or re-resection.
- Time to death from bladder cancer: we assumed the effect to be of clinical relevance if the observed absolute difference was 2% or greater at 12 months follow-up.
- Adverse events of any grade: we assumed the effect to be of clinical relevance if the observed difference was 5% or greater at 12 months follow-up.
- Surgical complications, non-serious: we assumed the effect to be of clinical relevance if the observed difference was 5% or greater at initial TURBT or re-resection.

These thresholds were established based on the input of the clinical experts on the author team considering the relative importance of a given outcome and the expected control event rate.

Search methods for identification of studies

We performed a comprehensive search with no restrictions on language of publication or publication status. We re-ran searches approximately every three to six months, most recently on March 17, 2021.

Electronic searches

We searched the following databases.

- Cochrane Library (via Wiley; 1970 to 17 March 2021; Appendix 1)
  - Cochrane Database of Systematic Reviews (CDSR)
  - Cochrane Central Register of Controlled Trials (CENTRAL; Issue 3 of 12, March 2021)
- MEDLINE (via Ovid; 1946 to 17 March 2021; Appendix 2)
- Embase (1947 to 17 March 2021; Appendix 3)
- Web of Science Core Collection (1900 to 17 March 2021; Appendix 4)
- Scopus (2004 to 17 March 2021; Appendix 5)
- LILACS (Latin American and Caribbean Health Sciences Information database; 1982 to 17 March 2021; Appendix 6)
- OpenGrey (1997 to 17 March 2021; Appendix 7)

We searched the following trial registers.

- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov/; 2000 to 17 March 2021; Appendix 8)
- World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch/; 2007 to 17 March 2021; Appendix 9)

Our electronic searches also included abstract proceedings of the European Association of Urology (EAU), American Urological Association (AUA), American Society of Clinical Oncology (ASCO), and American Society of Clinical Oncology Genitourinary (ASCO-GU) meetings that are included in the above databases.

Searching other resources

We attempted to identify other potentially eligible trials or ancillary publications by searching the reference lists of retrieved included trials, reviews, meta-analyses, and health technology assessment reports. We also contacted study authors of the included trials to identify any further studies that we may have missed. We contacted drug/device manufacturers for ongoing or unpublished trials.

Data collection and analysis

Selection of studies

We first used the reference management software EndNote to identify and remove duplicate records (EndNote 2019). We used the reference management software Covidence for the study selection process (Covidence). Two of three review authors (PM, AK or JV) independently scanned the titles and abstracts of the remaining records to determine which studies should be assessed further. We investigated all articles deemed potentially relevant as full text. Using Covidence, we categorized the full-text studies as 'included studies' or 'excluded studies.' Any discrepancies were resolved through consensus or through recourse to a third review author (PD). We have presented an adapted PRISMA flowchart documenting the process of study selection and the total number of identified, included, and excluded studies (Liberati 2009). We listed all articles excluded after full-text screening along with the reasons for their exclusion in the 'Characteristics of excluded studies' table.

Data extraction and management

For each included study, two of three review authors (PM, AK or JV) independently extracted key participant and intervention data using a data extraction form based on guidelines provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019a). A second review author (AK and JV) checked these data. Any disagreements were resolved by consensus or by consulting a third review author (PD) if required.

We extracted the following data.

- Study information: author, title, source, publication date, publication type, language, duplicate publications, source of funding, authors' conflicts of interest.
- Study characteristics: study design, randomization method, number of study centers, country of study centers, inclusion and

exclusion criteria, subgroup analysis, statistical methods, period of enrollment, follow-up period.

- Participant characteristics: number of participants, number of participants per study arm, age, gender, ethnicity, clinical stage of disease (presentation, focality, tumor size), number of participants recruited/allocated/evaluated.
- Intervention/comparator information: name, dosage, frequency, duration of treatment, adjuvant therapy, re-intervention, follow-up.
- Outcomes: according to our predefined primary and secondary outcomes (including tumor stage and grade), events of intervention/comparator, timing of outcome measurement, number of re-resections.

We extracted outcome data relevant to this review as needed for calculation of summary statistics and measures of variance. For dichotomous outcomes, we attempted to obtain the numbers of events and totals for population of a 2 x 2 table, as well as summary statistics with corresponding measures of variance. For continuous outcomes, we attempted to obtain means and standard deviations or data necessary to calculate this information. For time-to-event outcomes, we attempted to obtain hazard ratios (HRs) with corresponding measures of variance or data necessary to calculate this information.

Information about potentially relevant ongoing studies including trial identifier is presented in the 'Characteristics of ongoing studies' table.

We contacted authors of the included studies if relevant data were missing.

Dealing with duplicate and companion publications

In the event of duplicate publications, companion documents, or multiple reports of a primary study, we maximized the yield of information by mapping all publications to unique studies and collating all available data. We used the most complete data set aggregated across all known publications. In case of doubt, we gave priority to the publication reporting the longest follow-up associated with our primary or secondary outcomes.

Assessment of risk of bias in included studies

Two review authors (PM and AK) independently assessed the risk of bias of each included study. Any disagreements were resolved by consensus or by consultation with a third review author (PD).

We assessed risk of bias using Cochrane's risk of bias assessment tool (Higgins 2011b; Higgins 2021), which includes the following domains.

- 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

For each study, we judged the risk of bias for each domain as being low, high, or unclear, according to the guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b; Higgins 2021). We have presented a risk of bias summary figure to illustrate these findings.

For performance bias (blinding of participants and personnel) and detection bias (blinding of outcome assessment), we evaluated the risk of bias separately for each outcome, and grouped outcomes according to whether they were measured subjectively or objectively in the risk of bias tables.

Performance bias

- We considered all outcomes similarly susceptible to performance bias.

Detection bias

- We considered all outcomes similarly susceptible to detection bias.

We also assessed attrition bias (incomplete outcome data) on an outcome-specific basis, and presented the judgement for each outcome separately when reporting our findings in the risk of bias tables. We collapsed reporting for outcomes with identical judgments. We considered a < 10% rate of attrition as low; 10% to 20% as unclear; and ≥ 20% in at least one trial arm as high risk of bias.

We assessed reporting bias on a per-study basis. We classified the risk of bias for this domain as low only if we are able to identify an a priori protocol, and the reporting of outcomes and their analyses matched what the investigators had prespecified.

We further summarized the risk of bias across domains for each outcome in each included study, as well as across studies and domains for each outcome, in accordance with the approach for summary assessments of risk of bias presented in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019b). We used the risk of bias assessment on a per-study basis to inform the preplanned sensitivity analyses.

Measures of treatment effect

We expressed dichotomous data as risk ratios (RRs) with 95% confidence intervals (CIs). We expressed time-to-event data as hazard ratios (HRs) with 95% CIs.

Unit of analysis issues

The unit of analysis was the individual participant. Should we identify trials for inclusion with more than two intervention groups in further updates of this review, we will address these in accordance with guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019b). For studies with more than two intervention groups (multi-arm studies), we will only consider interventions that address the review objective for a pairwise comparison in our analysis (Higgins 2019b). In the event of repeated reporting of outcome measurements (e.g. at different time points), we used the data representing the longest follow-up.

Dealing with missing data

Where feasible, we attempted to obtain missing data from study investigators. If this information was available, we performed an intention-to-treat (ITT) analysis. If it was not, we performed a modified intention-to-treat (mITT) analysis, adhering to ITT principles with the exception that participants with missing

outcome data were excluded. If mITT analysis was not possible, we performed the analysis as-treated and per-protocol population (Higgins 2019c). This was rated as a potential source of bias. 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 (LOCF)) if used by the study authors. We did not impute missing data for this review.

Assessment of heterogeneity

In the event of substantial clinical, methodological, or statistical heterogeneity unexplained by subgroup analyses, we did not report outcome results as the pooled effect estimate in a meta-analysis, instead providing a narrative description of the results of each study.

We identified heterogeneity (inconsistency) by visual inspection of the forest plots to assess the amount of overlap of CIs, and by using the I^2 statistic, which quantifies inconsistency across studies to assess the impact of heterogeneity on the meta-analysis (Higgins 2002; Higgins 2003). We interpreted the I^2 statistic as follows (Deeks 2019):

- 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.

In the case of heterogeneity, we attempted to determine the potential causes by examining individual study and subgroup characteristics.

Assessment of reporting biases

In order to identify missing trial data, we searched for completed but not reported trials in the above-mentioned trial registers.

We attempted to obtain study protocols to assess for selective outcome reporting.

If we include 10 or more studies investigating a given outcome in further updates of the review, we will use funnel plots to assess small-study effects. There are several possible explanations for asymmetry of a funnel plot, including true heterogeneity of effect with respect to trial size, poor methodological design (and hence bias of small trials), and publication bias. We will therefore use care in our interpretation of the results.

Data synthesis

Unless there was good evidence for homogeneous effects across studies, we summarized data using a random-effects model (Wood 2008). We interpreted random-effects meta-analyses with due consideration of the whole distribution of effects. In addition, we performed statistical analyses according to the statistical guidelines provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019a). We used the Mantel-Haenszel method for dichotomous outcomes and the generic inverse-variance method for time-to-event outcomes. We used Review Manager 5 software to perform the analyses (Review Manager 2020).

Subgroup analysis and investigation of heterogeneity

We expected the following characteristics to introduce clinical heterogeneity, and therefore planned to carry out subgroup analyses with investigation of interactions for each comparison group by:

- setting: primary versus recurrent bladder cancer;
- multifocality: solitary versus multiple lesions of bladder cancer;
- tumor size: tumor size 3 cm or less versus greater than 3 cm;
- stage: positive cytology and/or history of CIS (in the case of recurrent disease).

Our rationale for these subgroup analyses was as follows.

- Setting: according to the European Organisation for Research and Treatment of Cancer (EORTC) criteria (Sylvester 2006), the setting of primary versus recurrent (primary versus ≤ 1 recurrence versus > 1 recurrence) bladder cancer predicts recurrence and progression; it may represent an effect modifier.
- Multifocality: according to the EORTC criteria (Sylvester 2006), the number of tumors (1 versus 2 to 7 versus ≥ 8) predicts recurrence and progression; it may represent an effect modifier.
- Tumor size: according to the EORTC criteria (Sylvester 2006), tumor size (< 3 cm versus ≥ 3 cm) predicts recurrence and progression; it may represent an effect modifier.
- Stage: compared to other histological types, the detection of CIS is particularly difficult due to its flat growth within the cell level; the effect of blue light versus white light may vary based on participant risk of harboring CIS.

At the request of several external peer referees, we performed one additional post hoc subgroup analysis:

- use of 5-ALA versus HAL as photodynamic agent in combination with TURBT.

We used the test for subgroup differences in Review Manager 5 to compare subgroup analyses if the number of studies was sufficient (Review Manager 2020).

Sensitivity analysis

We planned to perform sensitivity analyses to explore the influence of the following factors (where applicable) on effect sizes.

- Restricting the analyses by taking into account risk of bias, excluding studies at 'high risk' overall.
- Restricting the analyses by taking into account the procedure for re-resection, excluding studies in which all participants underwent re-resection on a routine basis (rather than selectively based on high-risk criteria concordant with current guidelines such as visible tumor left behind, pT1 high-grade tumors). Routine re-resection may potentially mitigate any benefits of blue light (Bogdan 2021; Doisy 2019; Tadrist 2021).

Summary of findings and assessment of the certainty of the evidence

We have presented the overall certainty of the evidence for each outcome according to the GRADE approach, which takes into account five criteria not only related to internal validity (risk of bias, inconsistency, imprecision, publication bias), but also to external validity, such as directness of results (Guyatt 2008). For each

comparison, two review authors (PM; AK or JV) independently rated the certainty of evidence for each outcome as 'high,' 'moderate,' 'low,' or 'very low' using GRADEpro GDT (GRADEpro GDT). Any discrepancies were resolved through consensus or by arbitration from a third review author (PD) if necessary. For each comparison, we have presented a summary of the evidence for the main outcomes in a summary of findings table, which provides key information regarding the best estimate of the magnitude of the effect in relative terms and absolute differences for each relevant comparison of alternative management strategies; numbers of participants and studies addressing each important outcome; and a rating of the overall confidence in effect estimates for each outcome (Guyatt 2011; Schünemann 2019). If meta-analysis was not possible, we presented the results in a narrative summary of findings table.

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

1. Time to disease recurrence
2. Time to disease progression
3. Surgical complications, serious
4. Time to death from bladder cancer
5. Adverse events
6. Surgical complications, non-serious

We used a minimally contextualized approach that focused on absolute effect size estimates for the interpretation of the results, Hultcrantz 2017, which we have reported using proposed language for GRADE narratives (Santesso 2020).

RESULTS

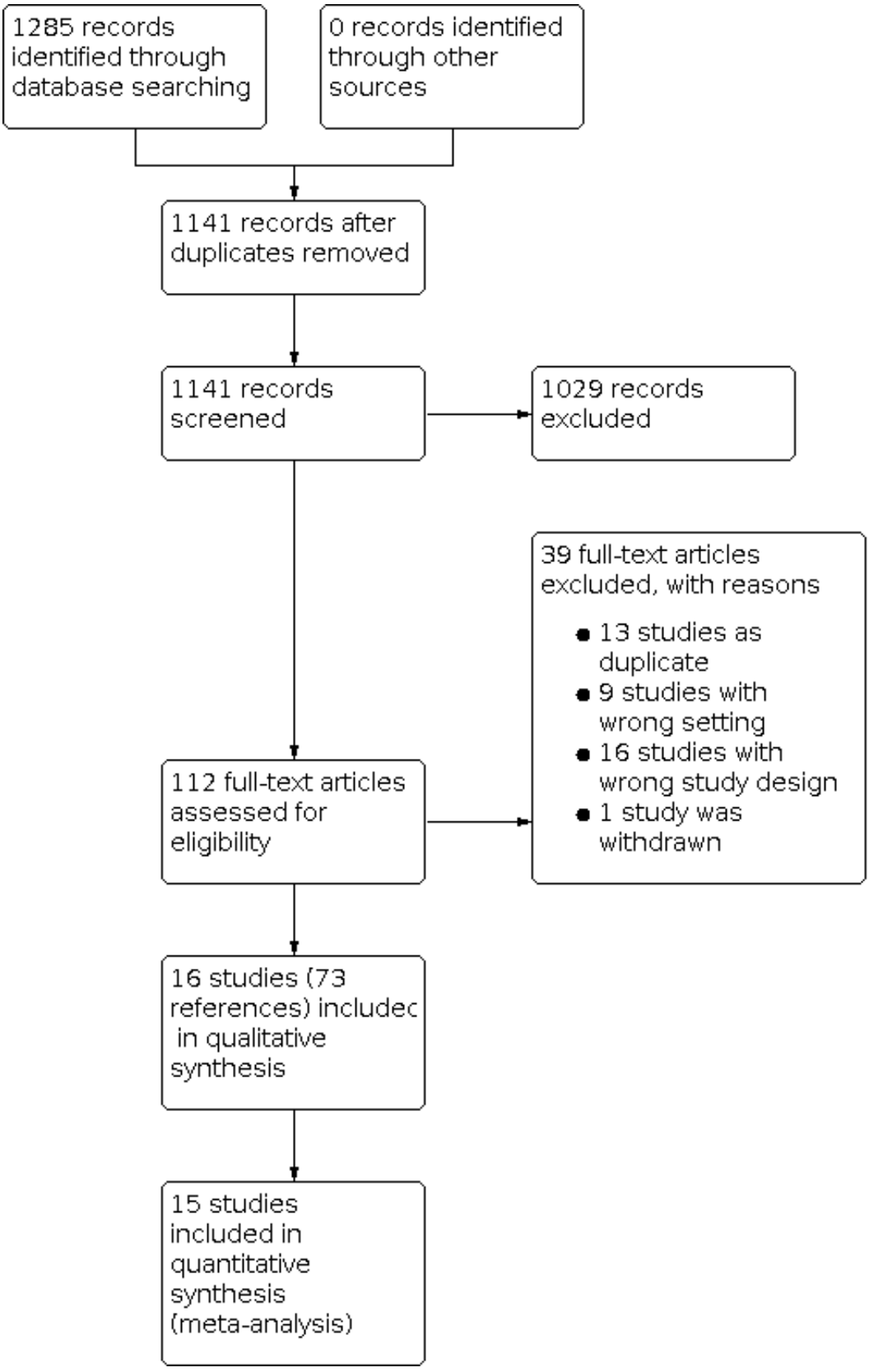
Description of studies

We initially identified 1285 references following our database search, of which 144 were excluded as duplicates. After title and abstract screening, we retrieved the full texts for 112 studies which we assessed for inclusion in the review.

Results of the search

Sixteen studies ultimately met the inclusion criteria for assessment of the study question. The process of study selection is presented in a PRISMA flow diagram (see Figure 1).

Figure 1.



Included studies

We identified 16 trials that were eligible for inclusion (Babjuk 2005; Drăgoescu 2017; Filbeck 2002; Geavlete 2010; Geavlete 2012; Gkritsios 2014; Hermann 2011; Karaolides 2012; Kriegmaier 2002; Neuzillet 2014; O'Brien 2013; Riedl 2001; Rolevich 2017; Schumacher 2010; Stenzl 2010).

Full-text publications in the English language were available for all of the included trials. All studies were RCTs; nine were single center, and seven were multicenter. The studies were conducted between 2001 and 2017. In 5 studies participants with primary NMIBC were included, and in 11 studies participants with primary or recurrent NMIBC were included. Inclusion of participants with suspicion of bladder cancer was based on positive urinary cytology, sonography, cystoscopy, or computed tomography. The trials compared white light TURBT to blue light TURBT using 5-ALA and HAL as photoactive compound in seven and nine studies, respectively. Only one study used 50 mL solvent as a comparator in a placebo-controlled setting. Predefined outcomes of the studies were broad and included time to disease recurrence, time to disease progression, time to death from bladder cancer, cancer-specific survival, overall survival, recurrence rate, progression rate, detection rate, residual tumor rate, false-positive rate, surgical complications, and adverse events of any grade. Nine trials reported no funding; four trials reported receiving funding from pharmaceutical companies; and three trials received funding through national government institutions. Nine studies reported conflict of interest statements, of which five declared to have none.

For a detailed description of included studies see Characteristics of included studies, Table 1, and Table 2.

Ongoing studies

We identified two ongoing trials addressing our objective (Boström 2018; Tandogdu 2019). At the time of publication of this review, the study of Boström 2018 was recruiting. Regarding the study of Tandogdu 2019, the manuscript was prepared, but no published data were available yet. We reached out to the authors of both studies.

For a detailed description of ongoing studies see Characteristics of ongoing studies.

Excluded studies

During title and abstract screening we excluded 1029 records that did not meet our inclusion criteria. We excluded 39 studies after full-text screening. Reasons for exclusion included wrong study setting (e.g. surveillance after TURBT; 9 publications); duplicate records (13 publications); wrong study design (e.g. non-randomized; 16 studies); and study withdrawn before accrual of any participants (1 study; NCT00785694). For a detailed description of excluded studies see Characteristics of excluded studies.

Risk of bias in included studies

For details see the risk of bias sections in Characteristics of included studies, Figure 2, and Figure 3.

Figure 2.

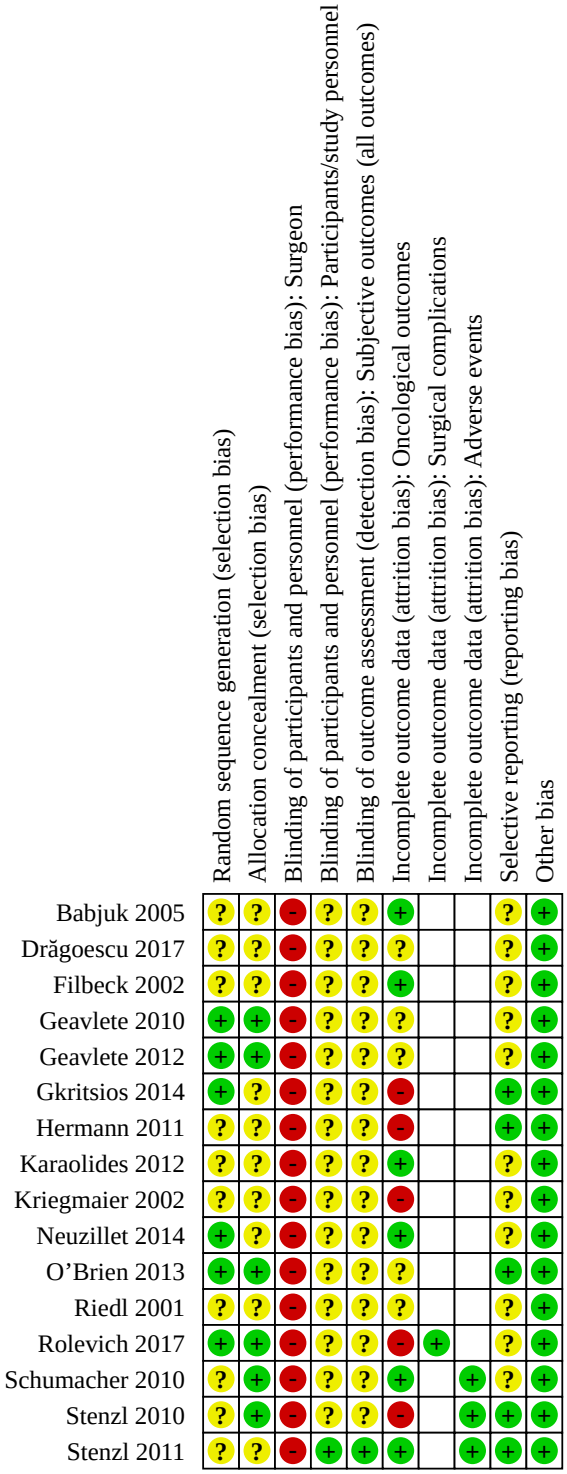
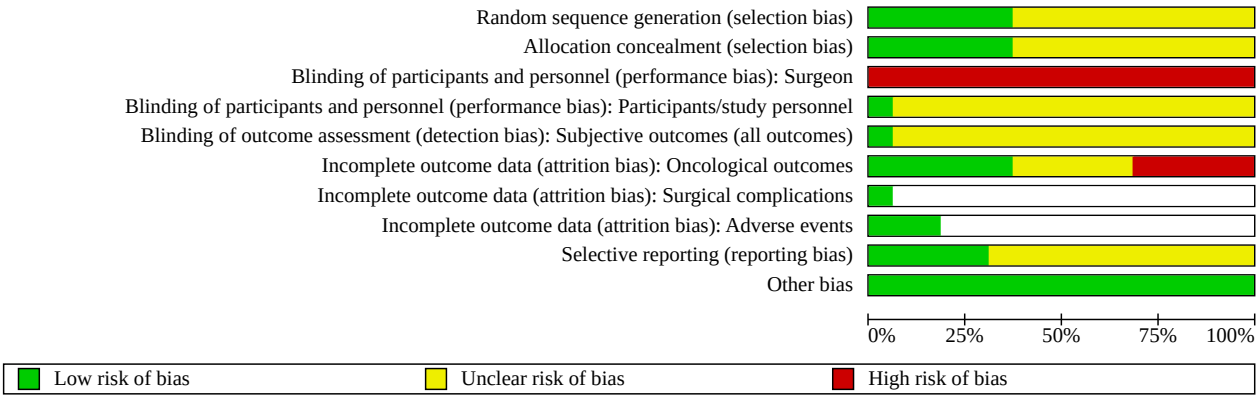


Figure 3.



Allocation

Random sequence generation

We assessed the majority of studies (10 of 16) as at unclear risk of bias for sequence generation (Babjuk 2005; Drăgoescu 2017; Filbeck 2002; Hermann 2011; Karaolides 2012; Kriegmaier 2002; Riedl 2001; Schumacher 2010; Stenzl 2010; Stenzl 2011). We rated the remaining six studies as low risk of bias (Geavlete 2010; Geavlete 2012; Gkritsios 2014; Neuzillet 2014; O'Brien 2013; Rolevich 2017)

Allocation concealment

Similar to above, we judged the majority of studies (10 of 16) as at unclear risk of bias for allocation concealment (Babjuk 2005; Drăgoescu 2017; Filbeck 2002; Gkritsios 2014; Hermann 2011; Karaolides 2012; Neuzillet 2014; Riedl 2001; Stenzl 2010). We rated the remaining six studies as low risk of bias. (Geavlete 2010; Geavlete 2012; O'Brien 2013; Rolevich 2017; Schumacher 2010; Stenzl 2010).

Blinding

Performance bias: blinding of surgeon

Due to the nature of the intervention, in none of the included studies was the surgeon blinded, therefore all studies were rated as high risk of bias for this domain.

Performance bias: blinding of participants and other study personnel

Only one study reported blinding of participants and other study personnel; we judged this study to be at low risk of bias (Stenzl 2011). We assessed all other studies as at unclear risk of bias.

Detection bias: surgical complications

Subjective outcomes (all other outcomes)

One study reported blinding of outcome assessors adequately and was assessed as at low risk of bias (Stenzl 2011).

Objective outcomes (surgical complications)

We judged all studies to be at low risk of bias for the objective outcome of surgical complications.

Incomplete outcome data

We rated the risk of attrition bias on a per-outcome basis but grouped outcomes with identical ratings together.

Oncological outcomes

We identified six studies where randomized participants were included adequately in the analysis for oncological outcomes (Babjuk 2005; Filbeck 2002; Karaolides 2012; Neuzillet 2014; Schumacher 2010; Stenzl 2011). We judged risk of bias to be unclear for five studies due to attrition rates of 10% to 20% (Drăgoescu 2017; Geavlete 2010; Geavlete 2012; O'Brien 2013; Riedl 2001). We judged four studies to be at high risk of bias for this domain (Gkritsios 2014; Hermann 2011; Rolevich 2017; Stenzl 2010).

Surgical complications

One study reported the outcome surgical complications (Rolevich 2017). All participants were included in the analysis, therefore we rated the study as at low risk of bias.

Any adverse events

Only three studies reported this outcome (Schumacher 2010; Stenzl 2010; Stenzl 2011). In all of these studies the vast majority of randomized participants (> 90% per arm) were included in the analysis, therefore we judged the risk of attrition bias to be low.

Selective reporting

We failed to identified protocols for the majority of studies (11 of 16); we rated these studies as at unclear risk of reporting bias (Babjuk 2005; Drăgoescu 2017; Filbeck 2002; Geavlete 2010; Geavlete 2012; Karaolides 2012; Kriegmaier 2002; Neuzillet 2014; Riedl 2001; Rolevich 2017; Schumacher 2010). We identified study protocols for four of the included studies (Gkritsios 2014; Hermann 2011; O'Brien 2013; Stenzl 2010). One additional study protocol was provided by the trial sponsor (Stenzl 2011). The reported primary and secondary outcomes corresponded to how they were planned, therefore we rated these five studies as at low risk of reporting bias.

Other potential sources of bias

We identified no other potential sources of bias.

Effects of interventions

See: **Summary of findings 1** Blue light compared to white light for transurethral resection of NMIBC

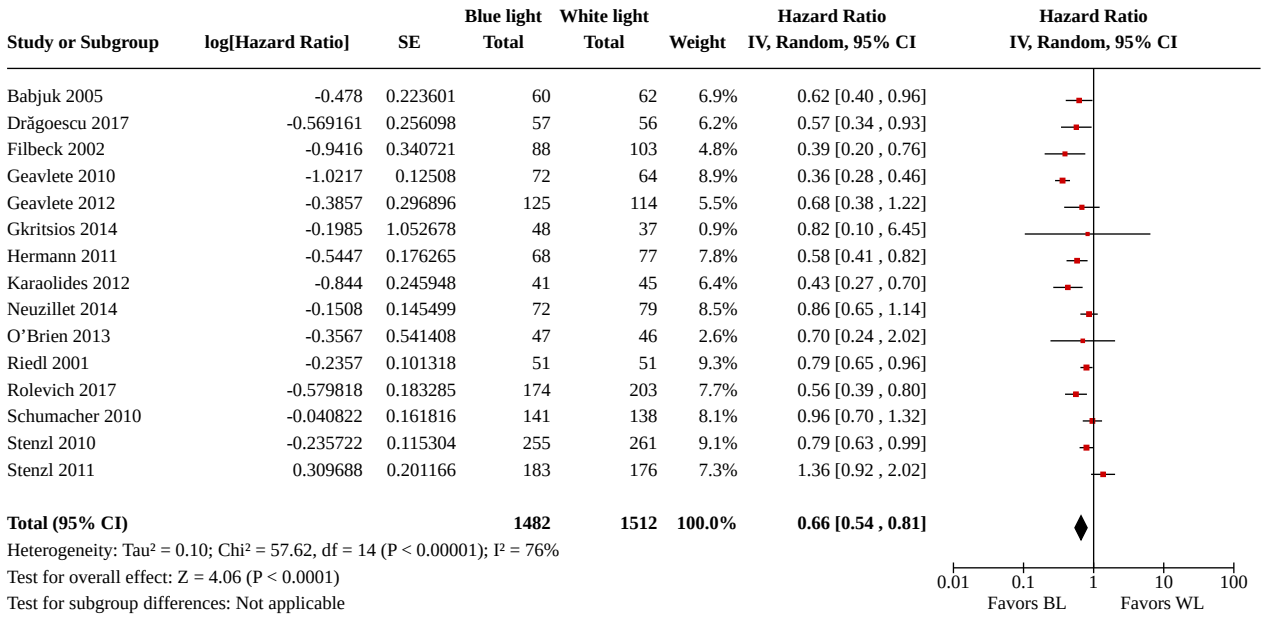
See also Summary of findings 1.

Primary outcomes

Time to disease recurrence

Blue light TURBT may reduce the risk of disease recurrence over time compared to white light TURBT (hazard ratio (HR) 0.66, 95% confidence interval (CI) 0.54 to 0.81; 15 studies; 2994 participants; low-certainty evidence; Analysis 1.1; Figure 4), depending on baseline risk. For participants with low-risk NMIBC with a baseline risk of 15.0% according to EORTC risk categories (Sylvester 2006), this corresponds to 48 fewer (66 fewer to 27 fewer) recurrences per 1000, which falls below our predefined threshold for minimal clinically important difference (MCID) of 50 per 1000. For participants with intermediate- and high-risk NMIBC with baseline risks of 38.0% and 61.0% according to EORTC risk categories (Sylvester 2006), this corresponds to 109 (152 fewer to 59 fewer) and 147 (211 fewer to 76 fewer) fewer recurrences per 1000 participants, respectively, when compared to white light TURBT. We downgraded the certainty of the evidence by one level each for study limitations as well as clinically relevant inconsistency.

Figure 4.



For two studies, all the information for the analysis was contained in the publications (Drăgoescu 2017; Rolevich 2017); for nine studies the HR and P value (if not provided) were calculated with the Parmar method (Geavlete 2010; Geavlete 2012; Gkritsios 2014; Hermann 2011; Karaolides 2012; Neuzillet 2014; O'Brien 2013; Riedl 2001; Stenzl 2011); and for the remaining four studies we performed data reconstruction due to digitalization of Kaplan-Meier curves and HRs and CIs were calculated by the Tierney method (Babjuk 2005; Filbeck 2002; Schumacher 2010; Stenzl 2010).

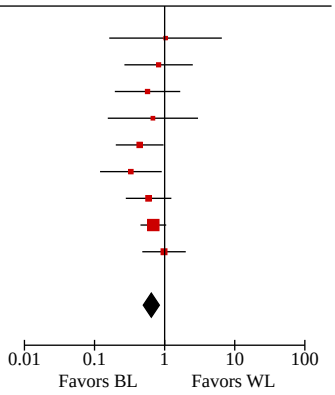
Time to disease progression

Blue light TURBT may reduce the risk of disease progression over time compared to white light TURBT (HR 0.65, 95% CI 0.50 to 0.84; 9 studies; 2200 participants; low-certainty evidence; Analysis 1.2; Figure 5), depending on the baseline risk. For people with low- and intermediate-risk NMIBC with assumed baseline risks of 0.2% and 5% based on EORTC risk categories (Sylvester 2006), this corresponds to 2 (1 fewer to 0 fewer) and 50 fewer (25 fewer to 8 fewer) progressions per 1000 people at 12 months, respectively, when compared to white light TURBT, which falls below our predefined threshold for MCID of 20 per 1000. For people with high-risk NMIBC with an assumed baseline risk of 17.0% per EORTC risk categories (Sylvester 2006), this corresponds to 170 fewer (81 fewer to 25 fewer) progressions per 1000 participants at 12 months. We downgraded the certainty of the evidence by one level each for risk of bias (the majority of studies had an unclear method of randomization, unclear allocation concealment, and lacked an a prior protocol) and imprecision.

Figure 5.

Study or Subgroup	log[Hazard Ratio]	SE	Blue light Total	White light Total	Weight	Hazard Ratio IV, Random, 95% CI
Babjuk 2005	0.029559	0.943226	60	62	2.0%	1.03 [0.16 , 6.54]
Drăgoescu 2017	-0.198451	0.572803	57	56	5.5%	0.82 [0.27 , 2.52]
Geavlete 2012	-0.562119	0.547997	125	114	6.0%	0.57 [0.19 , 1.67]
O'Brien 2013	-0.385662	0.756092	47	46	3.2%	0.68 [0.15 , 2.99]
Riedl 2001	-0.820981	0.399747	51	51	11.3%	0.44 [0.20 , 0.96]
Rolevich 2017	-1.108663	0.516834	174	203	6.8%	0.33 [0.12 , 0.91]
Schumacher 2010	-0.527633	0.381668	141	138	12.4%	0.59 [0.28 , 1.25]
Stenzl 2010	-0.371064	0.215436	255	261	39.0%	0.69 [0.45 , 1.05]
Stenzl 2011	-0.020203	0.364067	183	176	13.7%	0.98 [0.48 , 2.00]
Total (95% CI)			**1093**	**1107**	**100.0%**	**0.65 [0.50 , 0.84]**

Heterogeneity: Tau² = 0.00; Chi² = 4.55, df = 8 (P = 0.80); I² = 0%
Test for overall effect: Z = 3.25 (P = 0.001)
Test for subgroup differences: Not applicable



For one study, all the information for the analysis was contained in the publication (Rolevich 2017); for six studies the HR and P value (if not provided) were calculated with the Parmar method (Babjuk 2005; Drăgoescu 2017; Geavlete 2010; O'Brien 2013; Riedl 2001; Stenzl 2010); and for two studies we performed data reconstruction due to digitalization of Kaplan-Meier curves and HRs and CIs were calculated by the Tierney method (Schumacher 2010; Stenzl 2011).

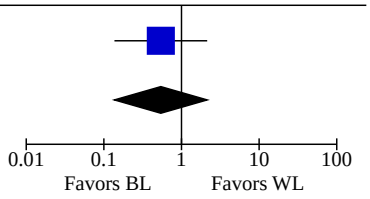
Surgical complications, serious

Blue light TURBT may have little or no effect on serious surgical complications (risk ratio (RR) 0.54, 95% CI 0.14 to 2.14; 1 study; 525 participants; low-certainty evidence; Analysis 1.3; Figure 6). Assuming a risk of serious complications of 2.2% in the white light group, this corresponds to 10 fewer (19 fewer to 25 more) surgical complications per 1000 participants with blue light TURBT, which falls below our predefined threshold for MCID of 20 per 1000. We judged the certainty of evidence to be low (downgraded one level for risk of bias and one level for imprecision).

Figure 6.

Study or Subgroup	Blue light Events	Blue light Total	White light Events	White light Total	Weight	Risk Ratio M-H, Random, 95% CI
Rolevich 2017	3	252	6	273	100.0%	0.54 [0.14 , 2.14]
Total (95% CI)		**252**		**273**	**100.0%**	**0.54 [0.14 , 2.14]**
Total events:	3		6			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.87 (P = 0.38)
Test for subgroup differences: Not applicable



Secondary outcomes

Time to death from bladder cancer

Blue light TURBT may have little or no effect on the risk of death from bladder cancer over time (HR 0.55, 95% CI 0.19 to 1.61; 1 study; 407 participants; low-certainty evidence; Analysis 1.4). Assuming a risk of bladder cancer of 2.2% in the white light group, this corresponds to 22 deaths from bladder cancer per 1000 participants with white light TURBT and 10 fewer (17 fewer to 13 more) deaths from bladder cancer per 1000 participants with blue light TURBT, which falls below our predefined threshold for MCID of 20 per 1000. We judged the certainty of evidence to be low (downgraded one level for risk of bias and one level for imprecision).

Any adverse events

We are very uncertain as to whether blue light TURBT reduces the incidence of adverse events of any grade as we assessed the certainty of the evidence as low (RR 1.09, 95% CI 0.88 to 1.33; 3 studies; 1375 participants; low-certainty evidence; Analysis 1.5). Assuming a risk of any adverse event of 39.7% in the white light group, this corresponds to 397 adverse events of any grade per 1000 participants with white light TURBT and 36 more (48 fewer to 131 more) any adverse events per 1000 participants with blue light TURBT, which falls below our predefined threshold for MCID of 50 per 1000. We judged the certainty of evidence to be low (downgraded one level for risk of bias and one level for imprecision).

Surgical complications, non-serious

No analysis was possible as this outcome was not reported by any study.

Subgroup analyses

I. Primary versus recurrent bladder cancer

Time to disease recurrence

The pooled effect size in participants with primary bladder tumor (HR 0.79, 95% CI 0.60 to 1.03; 2 studies; 368 participants) was similar to that of participants with recurrent disease (HR 0.80, 95% CI 0.67 to 0.95; 2 studies; 422 participants; Analysis 2.1). All comparisons were across studies and did not suggest a potential subgroup effect (P = 0.95).

Time to disease progression

We were unable to perform this analysis due to lack of reported data.

Surgical complications, serious

We were unable to perform this analysis due to lack of reported data.

II. Solitary versus multiple lesions of bladder cancer

Time to disease recurrence

The pooled effect size in participants with a solitary bladder tumor (HR 0.60, 95% CI 0.38 to 0.95; 3 studies; 230 participants) was similar to that of participants with multiple tumors (HR 0.53, 95% CI 0.31 to 0.90; 3 studies; 241 participants; Analysis 3.1). All comparisons were across studies, and we did not find any suggestion of a potential subgroup effect (P = 0.74).

Time to disease progression

We were unable to perform this analysis due to lack of reported data.

Surgical complications, serious

No additional analysis was possible as the primary analysis (Analysis 1.3) included only one study (Rolevich 2017).

III. Tumor size 3 cm or less versus greater than 3 cm

No analysis was possible as no data were reported by any included study.

IV. Positive cytology and/or history of CIS (in the case of recurrent disease)

No analysis was possible as no data were reported by any included study.

V. 5-ALA versus HAL (post hoc subgroup analysis)

Time to disease recurrence

The pooled effect size of studies using 5-ALA (HR 0.76, 95% CI 0.57 to 1.00; 6 studies; 1430 participants) was similar to that of studies using HAL (HR 0.60, 95% CI 0.45 to 0.78; 9 studies; 1564 participants; Analysis 4.1). All comparisons were across studies, and we did not find any suggestion of a potential subgroup effect (P = 0.23).

Time to disease progression

The pooled effect size of studies using 5-ALA (HR 0.72, 95% CI 0.47 to 1.11; 5 studies; 1239 participants) was similar to that of studies using HAL (HR 0.69, 95% CI 0.48 to 0.98; 4 studies; 961 participants; Analysis 4.2). All comparisons were across studies, and we did not find any suggestion of a potential subgroup effect (P = 0.87).

Surgical complications, serious

No subgroup analysis was possible as the analysis (Analysis 1.3) included only one study (Rolevich 2017).

Sensitivity analyses

I. Sensitivity analysis by studies at high risk of bias overall

No analysis was possible as no study was judged to be at low risk of bias.

II. Sensitivity analysis by re-resection

We were able to perform sensitivity analyses by excluding studies in which all participants underwent re-resection on a routine basis for the three primary outcomes of this review.

Time to disease recurrence

The effect size (HR 0.64, 95% CI 0.56 to 0.74; 9 studies; 1776 participants; Analysis 5.1) was similar to that of the primary analysis (HR 0.66, 95% CI 0.54 to 0.81; 15 studies; 2994 participants).

Time to disease progression

The effect size (HR 0.64, 95% CI 0.46 to 0.90; 6 studies; 1460 participants; Analysis 5.2) as similar to that of the primary analysis (HR 0.65, 95% CI 0.50 to 0.84; 9 studies; 2200 participants).

Surgical complications, serious

No additional analysis was possible as the primary analysis (Analysis 1.3) included only one study (Rolevich 2017).

DISCUSSION

Summary of main results

We identified 16 RCTs including a total of 4325 participants that compared blue light-enhanced TURBT with white light-based TURBT in the treatment of primary or recurrent non-muscle invasive bladder cancer. Of 4352 randomized participants, 3283 could be included in the analysis. Of the randomized participants, 2169 received a blue light TURBT and 2183 participants received a white light TURBT.

Blue light may reduce the risk of disease recurrence over time (low-certainty evidence) and may also reduce the risk of disease progression over time (low-certainty evidence). For both outcomes, the magnitude of this treatment effect in absolute terms depends greatly on the baseline risk as reflected by the EORTC prognostic group. Meanwhile, blue light may have little to no effect on the incidence of serious surgical complications (low-certainty evidence).

We also found that blue light may have little to no effect on the risk of death from bladder cancer over time (low-certainty evidence), and we are very uncertain of the effect on adverse events of any

grade (low-certainty evidence). We do not know the effect of blue light on non-serious surgical complications as none of the included trials reported this outcome.

None of our predefined subgroup analysis suggested evidence for a subgroup effect. We also did not find any evidence of a subgroup effect when comparing 5-ALA versus HAL.

A sensitivity analysis based on risk of bias was not possible. Our analytic results appeared robust to a sensitivity analysis that excluded studies in which all participants underwent a re-resection on a routine basis.

Overall completeness and applicability of evidence

This Cochrane Review is based on 16 RCTs including participants with primary or recurrent non-muscle invasive bladder cancer (stage Ta, T1, and carcinoma in situ), which represents a population of patients routinely managed in clinical practice.

The studies included in this review were published between 2001 and 2017. During this period, technological progress has led to improvements in the instruments used for visualization and resection. Unfortunately, not all of the included studies described the equipment used in detail. Accordingly, the influence of the equipment used on the results of the included studies remains unclear. Examples of this include the recently US Food and Drug Administration-approved use of flexible cystoscopes for blue light visualization (used for surveillance) as well as the type of white light cystoscopy equipment used (i.e. high-definition versus standard-definition camera systems).

Aside from the studies' comparable intervention of blue light to white light TURBT, there were differences in the implementation of the individual studies. Both 5-ALA and HAL were used as the fluorescent agent, and furthermore only one study used a solvent as a placebo instillation. There were also differences in the postoperative instillation regimen. Administrations of mitomycin C as well as epirubicin or doxorubicin were used. Due to the heterogeneity of the treatments used, we could not consider these data in our analysis, which may have affected the results. Another difference was whether a re-TURBT was performed, and if so, at what point in time. In most of the studies, the time between five and seven weeks after the initial TURBT was chosen, but re-TURBT was rarely performed again under blue light. Overall, all of these differences reflect clinical heterogeneity that may have impacted our study results.

We were unable to address whether blue light TURBT may obviate the need for routine re-resection (Doisy 2019; Tadrist 2021). In addition, we did not address the issue of cost consequences or effectiveness, which is relevant given the required capital investment and personnel-intensive workflow alterations (Klaassen 2017; Witjes 2014a).

A major source of heterogeneity in the included studies was the postoperative use of intravesical chemotherapy (e.g. postoperative mitomycin installation) as well as the initiation of intravesical induction therapy. These agents are known to impact outcomes (Han 2021; Hwang 2019; Shepherd 2017), and were applied differently in the included studies, therefore representing a potential source of bias.

Lastly, this review indicates a paucity of published, direct trial-derived evidence on adverse events related to the installation of the photodynamic agent used for blue light cytoscopy. A sponsor-supported study on the issue of safety specific to HLA has been published using pooled trial data (Witjes 2014). It reported no serious adverse events related to the agent, but did not permit trial-specific data attribution and verification that would have permitted inclusion in the review.

Quality of the evidence

We rated the certainty of evidence as low throughout all endpoints. Reasons for downgrading of the evidence included concerns over study limitations for risk of bias, inconsistency, and imprecision.

- Study limitations: a majority of studies did not provide assurance of allocation concealment (thereby raising concerns over selection bias); very few studies explicitly reported blinding of study participants and personnel or outcome assessors; and more than half of the included studies had substantial attrition of participants. This was in part due to purposeful exclusion of participants at various time points in the course of each study due to a diagnosis of muscle invasive bladder cancer or histopathological findings without malignancy. Different ways of dealing with excluded participants may have distorted the study results. For example, participants with a diagnosis of muscle invasive bladder cancer who subsequently underwent cystectomy may have experienced surgical complications or adverse events that were not accounted for. In addition, few studies had an a priori protocol that was retrievable, which made it difficult to judge the risk of reporting bias. It is notable that much fewer studies reported on serious surgical complications and adverse events than on time to recurrence or progression. All of these issues prompted us to consistently rate down the certainty of evidence by one level.
- Inconsistency: we downgraded the certainty of evidence by one level for the outcome time to disease recurrence in accordance with GRADE guidance considering not only the I^2 value, but also the clinical implications of using a minimally contextualized approach (Hultcrantz 2017).
- Imprecision: we downgraded most of the outcomes by one level for imprecision, as CIs for the pooled effect sizes were consistent with both no effect and clinically important reduction.

Potential biases in the review process

In order to minimize potential bias in the review process, we performed a sensitive search strategy in multiple databases. Despite a comprehensive and unrestricted search, we may have missed studies (unpublished, non-English). Two review authors independently performed literature screening, data extraction, and risk of bias assessment.

Some studies did not provide hazard ratios for the outcomes time to disease recurrence and time to disease progression. We therefore calculated hazard ratios either with Parmar method (Parmar 1998), or conducted data reconstruction via digitalization of Kaplan-Meier curves and by Tierney method (Tierney 2007). Both methods can only reconstruct hazard ratios according to the information available, which may have resulted in bias.

The subgroup analysis comparing 5-ALA versus HAL was conducted post hoc (as described in Differences between protocol and review section) and was motivated by the comments of several peer referees suggesting that HAL may have superior oncological outcomes (Gakis 2015). Interpreting the results in accordance with Cochrane guidance, we did not find evidence to support a subgroup effect.

Agreements and disagreements with other studies or reviews

Relatively few higher-quality systematic reviews exist on this topic, which are described as follows.

- Mowatt 2011 published a systematic review and meta-analysis that addressed both the diagnostic accuracy of photodynamic cystoscopy as well as its clinical effectiveness compared to white light. Based on a literature search up to 2008, the review identified four RCTs with 709 participants (Babjuk 2005; Filbeck 2002; Kriegmaier 2002; Riedl 2001), and reported a substantially reduced risk of recurrence (RR 0.37, 95% CI 0.20 to 0.69) and greater progression-free survival (RR 1.37, 95% CI 1.18 to 1.59) compared to white light. The authors did not rate the certainty of evidence. The risk of bias assessment also reported unclear allocation concealment and failure to blind participants, personnel, or outcome assessors.
- Rink 2013 reported a similar systematic review that assessed both diagnostic accuracy and comparative effectiveness and identified a total of 13 randomized trials (date of last search October 2012), but double-counted several studies that had presented both initial results as well as longer-term follow-up. The authors also provided no meta-analysis of their own.
- Tran 2017 reported an evidence report by the Canadian Agency for Drugs and Technologies with a search date of up to 2016. Their findings suggested both short-term (based on 10 RCTs) and long-term (based on 12 RCTs) reduced risk of recurrence, but no reduced risk of progression. The results of subgroup analyses for both outcomes favored HAL over 5-ALA, but the tests of interaction were not significant, thereby indicating chance as a potential explanation for these findings. The strength of evidence was described as low and moderate, respectively.
- Chou 2017 reported the most recent high-quality systematic review on this topic to date; however, the latest search date is reported as September 2015, and the review only included studies published as full text, thereby raising concerns about publication bias. Since publication of Chou 2017, one study has published extended follow-up data (Drăgoescu 2017), and results of one additional study have become available (Rolevich 2017). In addition, our review adds an analysis based on time-to-event outcomes using HR both for time to recurrence and progression, whereas Chou 2017 used RR that were analyzed as short- (less than three months), intermediate- (three months to less than one year), and long-term (one year or more). Whereas the interpretation of Chou 2017 focused on the presence or absence of statistical significance, we applied a minimally contextualized approach to GRADE (Hultcrantz 2017), with predefined thresholds of what we considered the MCID for each outcome. Lastly, we were able to provide a more nuanced interpretation of our results by applying the relative effect size measures to different baseline risk groups. As a result, our findings provide more support for the notion that blue light cystoscopy-guided TURBT extends time to progression, but that any clinically important effect may be limited to individuals stratified as high risk.
- Sari 2021, a recent systematic review and network meta-analysis, sought to also assess whether a single intravesical chemotherapy installation added to the therapeutic effectiveness of blue light and narrow band imaging-assisted TURBT compared to white light. The findings were consistent with ours in that blue light cystoscopy-assisted TURBT outperformed white light, and the positive effect was accentuated by intravesical chemotherapy, as one might have expected. Missing from this review, however, was any attempt to rate the certainty of evidence. Also, narrow band imaging-assisted TURBT appeared to outperform blue light. While this is outside the scope of our review, it is the topic of an ongoing companion review, Lai 2021, of this study.

AUTHORS' CONCLUSIONS

Implications for practice

The findings of this review suggest a favorable impact of blue light transurethral bladder tumor resection (TURBT) on the risk of disease recurrence and progression; however, whether this risk reduction is clinically relevant greatly depends on the baseline risk of patients. Time to death from bladder cancer may not be impacted. We did not find an increase in severe surgical complications with blue light cystoscopy, and we did not find any trial evidence on other, non-surgical adverse events.

We expect findings of the review to help further inform evidence-based guidelines by major professional organizations such as the American Urological Association (AUA) and the European Association of Urology (EAU). Current EAU guidelines, EAU 2021, make a conditional recommendation for the use of "methods to improve tumor visualization" referring to both blue light cytoscopy and narrow band imaging, but further qualify this by "if available." The latest AUA guidelines, AUA 2016, (amended in 2020) state that clinicians "should offer" blue light cytoscopy (moderate recommendation) without further qualifiers to "increase detection and decrease recurrence." Baseline risk as defined by risk category may be an important criterion to help guide the use of blue light technology in clinical practice.

Implications for research

Although we identified 16 randomized controlled trials addressing the objective of the review, the certainty of the evidence is low, therefore future high-quality trials are likely to change our results. Future studies should be conducted with greater methodological rigor with regard to safeguards against selection, performance, and detection bias; have a published a priori protocol; and ensure greater completeness of follow-up. Authors should extend follow-up and plan ahead to address questions with regard to participant subgroups.

Future studies should also take into account recent technological developments such as digital imaging technology or LED (light-emitting diode) illumination. It remains unclear how such innovations in white light technology may alter the assessment of the comparative effectiveness of blue light technology. To identify the most effective treatment option for individuals with non-muscle invasive bladder cancer, head-to-head trials comparing white light, blue light, and other therapeutic

options, such as narrow band imaging, should be conducted. Furthermore, surveillance strategies combining blue light and flexible cystoscopy should be examined.

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Sari 2021

Sari Motlagh R, Mori K, Laukhtina E, Aydh A, Katayama S, Grossmann NC, et al. Impact of enhanced optical techniques at time of transurethral resection of bladder tumour, with or without single immediate intravesical chemotherapy, on recurrence rate of non-muscle-invasive bladder cancer: a systematic review and network meta-analysis of randomized trials. *BJU International* 2021;**128**(3):280-9.

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Schmidt S, Kunath F, Coles B, Draeger DL, Krabbe LM, Dersch R, et al. Intravesical bacillus calmette-guérin versus mitomycin C for Ta and T1 bladder cancer. *Cochrane Database of Systematic Reviews* 2020, Issue 1. Art. No: CD011935. [DOI: 10.1002/14651858.CD011935.pub2]

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Schünemann HJ, Higgins JPT, Vist GE, Glasziou P, Akl EA, Skoetz N, et al. Chapter 14: Completing 'Summary of findings' tables and grading the certainty of the evidence. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). Cochrane Handbook for Systematic Reviews of

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Witjes JA, Gomella LG, Stenzl A, Chang SS, Zaak D, Grossman HB. Safety of hexaminolevulinate for blue light cystoscopy in bladder cancer. A combined analysis of the trials used for registration and postmarketing data. *Urology* 2014;**84**(1):122-6.

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Witjes 2018

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Wood L, Egger M, Gluud LL, Schulz KF, Juni P, Altman DG, et al. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. *BMJ* 2008;**336**(7644):601-5. [DOI: 10.1136/bmj.39465.451748.AD]

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Zaak D, Karl A, Stepp H, Tritschler S, Tilki D, Burger M, et al. Fluorescence cystoscopy at bladder cancer: present trials [Die fluoreszenzzystoskopie beim harnblasenkarzinom: aktueller stellenwert]. *Urologe A* 2007;**46**(11):1519-27. [DOI: 10.1007/s00120-007-1563-7]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Babjuk 2005

Study characteristics	
Methods	• randomized, parallel unblinded • single center/Czech Republic
Participants	Study setting • primary and recurrent • only Ta/T1 Eligibility criteria • patients with suspected primary or recurrent superficial BCa planned for TURBT Non-eligibility criteria • surgical or instillation therapy within 3 months

Babjuk 2005 *(Continued)*

	Intervention cohort • participants recruited: 64 • unifocal/multifocal tumors: 15/45 Comparator cohort • participants recruited: 64 • unifocal/multifocal tumors: 24/38
Interventions	Intervention: WLC + BLC followed by BL-TURBT Comparator: WLC followed by WL-TURBT Adjuvant instillation therapy: NA
Outcomes	Outcome(s)* • recurrence-free survival • recurrence rate • progression rate (to muscle invasive disease) Results • median follow-up: 24 months • RFS was 17.1 months in intervention group vs 8.1 months in comparator group • RFS rate was 40% in intervention group vs 28% in comparator group
Funding sources	Grant of Czech Health Ministry
Declarations of interest	NA
Contact of study author	Date of contact attempt to first study author: 30 November 2020 Contact status: reply by author; original study data no longer available
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The patients were randomly assigned to two groups." Comment: method of sequence generation unclear
Allocation concealment (selection bias)	Unclear risk	Quote: "The patients were randomly assigned to two groups." Comment: allocation concealment unclear
Blinding of participants and personnel (performance bias) Surgeon	High risk	Quote: NA Comment: surgeon unblinded
Blinding of participants and personnel (performance bias) Participants/study personnel	Unclear risk	Quote: NA Comment: unclear whether study participants and other study personnel were blinded

Babjuk 2005 *(Continued)*

Blinding of outcome assessment (detection bias) Subjective outcomes (all outcomes)	Unclear risk	Quote: NA Comment: unclear whether study personnel were blinded
Incomplete outcome data (attrition bias) Oncological outcomes	Low risk	Quote: "six [participants] (two in group A and four in group B) were excluded after histological examination, as in two there was no histological evidence of TCC, in three there was muscle invasion, and in one there was a multiple T1G3 tumour with concomitant carcinoma in situ (CIS) treated with immediate cystectomy." Comment: loss to follow-up was < 10%, and variation in loss to follow-up between groups was low
Selective reporting (reporting bias)	Unclear risk	Quote: NA Comment: no protocol available
Other bias	Low risk	Quote: NA Comment: no other bias identified

Drăgoescu 2017

Study characteristics	
Methods	• randomized, parallel-group trial • single center/Romania
Participants	Study setting • primary Eligibility criteria • patients with primitive NMIBC diagnosed Non-eligibility criteria • NR Intervention cohort • participants recruited: 57 • unifocal/multifocal tumors: 27/30 Comparator cohort • participants recruited: 56 • unifocal/multifocal tumors: 30/26
Interventions	Intervention: WLC + BLC followed by BL-TURBT Comparator: WLC followed by WL-TURBT Adjuvant instillation therapy: 30 to 50 mg mitomycin C, doxorubicin, farmorubicin within 6 hours after surgery
Outcomes	Outcome(s)

Drăgoescu 2017 *(Continued)*

- recurrence-free survival
- detection rate
- progression rate
- cancer-related death

Results

- median follow-up: 72.1 months
- RFS was 38.6 months in intervention group vs 32.3 months in comparator group (P = 0.2)
- 5-year recurrence rate was 49.1% in intervention group vs 67.9% in comparator group
- detection rate: 26.3% more in intervention group
- progression rate was 8.7% in intervention group vs 10.7% in comparator group

Funding sources	National Scientific Research Council (CNCSIS) within the National Exploratory Research Project Program (PCE–2)
Declarations of interest	None
Contact of study author	Date of contact attempt to first study author: 30 November 2020 Contact status: no reply to date
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "the study designed as a prospective randomized clinical trial." Comment: method of sequence generation unclear
Allocation concealment (selection bias)	Unclear risk	Quote: "distribution of patients in both groups was conducted in a randomized single blind manner." Comment: allocation concealment unclear
Blinding of participants and personnel (performance bias) Surgeon	High risk	Quote: NA Comment: surgeon unblinded
Blinding of participants and personnel (performance bias) Participants/study personnel	Unclear risk	Quote: NA Comment: unclear whether study participants and other study personnel were blinded
Blinding of outcome assessment (detection bias) Subjective outcomes (all outcomes)	Unclear risk	Quote: NA Comment: unclear whether study personnel were blinded
Incomplete outcome data (attrition bias) Oncological outcomes	Unclear risk	Quote: "between 2009 and 2011, 113 patients with primary NMIBC were enrolled in our prospective study and randomized in two parallel groups: 57 patients in the study group (PDD) and 56 patients in the control group (WLC)." Comment: loss to follow-up was < 10%

Drăgoescu 2017 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Quote: NA Comment: no protocol available
Other bias	Low risk	Quote: NA Comment: no other bias identified

Filbeck 2002

Study characteristics	
Methods	• randomized • single center/Germany
Participants	Study setting • primary and recurrent Eligibility criteria • patients with suspected primary or recurrent BCa on preoperative endoscopy Non-eligibility criteria • NR Intervention cohort • participants recruited: 151 • unifocal/multifocal tumors: 55/33 Comparator cohort • participants recruited: 150 • unifocal/multifocal tumors: 79/24
Interventions	Intervention: BL-TURBT Comparator: WL-TURBT Adjuvant instillation therapy: NA
Outcomes	Outcome(s) • recurrence-free survival • residual tumor rate Results • median follow-up: 24 months • RFS rate was 57% in comparator group vs 28% in intervention group (P < 0.001)
Funding sources	NR
Declarations of interest	NR
Contact of study author	Date of contact attempt to first study author: 30 November 2020

Filbeck 2002 *(Continued)*

	Contact status: no reply to date
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "patients in whom bladder carcinoma was suspected on preoperative endoscopy were randomized to 2 treatment arms" Comment: method of sequence generation unclear
Allocation concealment (selection bias)	Unclear risk	Quote: "patients in whom bladder carcinoma was suspected on preoperative endoscopy were randomized to 2 treatment arms" Comment: allocation concealment unclear
Blinding of participants and personnel (performance bias) Surgeon	High risk	Quote: NA Comment: surgeon unblinded
Blinding of participants and personnel (performance bias) Participants/study personnel	Unclear risk	Quote: NA Comment: unclear whether study participants and other study personnel were blinded
Blinding of outcome assessment (detection bias) Subjective outcomes (all outcomes)	Unclear risk	Quote: NA Comment: unclear whether study personnel were blinded
Incomplete outcome data (attrition bias) Oncological outcomes	Low risk	Quote: "In the white light arm 103 patients were evaluable and 47 were excluded from further analysis because no tumor was identified (22), a muscle invasive urothelial tumor was diagnosed or cystectomy was indicated (23) or followup was refused after initial resection (2 with a stage pTa grade 1 and stage pT1 grade 2 tumor, respectively). Of the 151 patients randomized to the fluorescence diagnosis arm 88 were evaluable, while 63 were excluded from study due to no positive tumor finding (38), muscle invasive disease and/or an indication for cystectomy (23) and loss to followup (2 with stage pTa grade 2 disease)." Comment: most of excluded patients did not meet initial eligibility criteria; those that did and were excluded were few and were similar between groups
Selective reporting (reporting bias)	Unclear risk	Quote: NA Comment: no protocol available
Other bias	Low risk	Quote: NA. Comment: no other bias identified

Geavlete 2010

Study characteristics	
Methods	• randomized • single center/Romania
Participants	Study setting • primary Eligibility criteria • patients with suspicion of BCa based on positive urinary cytology and ultrasound Non-eligibility criteria • massive hematuria • moderate to severe leukocyturia • prior intravesical instillations earlier than 3 months • suspicion of upper urinary tract disease Intervention cohort • participants recruited: 223 • unifocal/multifocal tumors: NR Comparator cohort • participants recruited: 223 • unifocal/multifocal tumors: NR
Interventions	Intervention: WLC + BLC followed by WL-TURBT + BL-TURBT Comparator: WLC followed by WL-TURBT Adjuvant instillation therapy: mitomycin C (no further information on dosage)
Outcomes	Outcome(s)* • recurrence rate • detection rate Results • median follow-up: 6 weeks • RFS rate was 11.1% in intervention group vs 31.2% in comparator group
Funding sources	NR
Declarations of interest	NR
Contact of study author	Date of contact attempt to first study author: 30 November 2020 Contact status: no reply to date
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Geavlete 2010 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "randomized by means of sealed envelopes containing consecutive numbers" Comment: method of sequence generation clearly described
Allocation concealment (selection bias)	Low risk	Quote: "randomized by means of sealed envelopes containing consecutive numbers" Comment: allocation concealment clearly described
Blinding of participants and personnel (performance bias) Surgeon	High risk	Quote: NA Comment: surgeon unblinded
Blinding of participants and personnel (performance bias) Participants/study personnel	Unclear risk	Quote: NA Comment: unclear whether study participants and other study personnel were blinded
Blinding of outcome assessment (detection bias) Subjective outcomes (all outcomes)	Unclear risk	Quote: "to ensure the complete objectivity of the evaluation, the urologists performing the Re-TURBTs were unaware of the diagnostic and treatment modality initially applied in each case." Comment: blinding of study personnel reported only at the time point of re-re-section
Incomplete outcome data (attrition bias) Oncological outcomes	Unclear risk	Quote: "In the blue-light group, 78.9% of the patients were diagnosed with NMIBC, 14.3% presented muscle-invasive bladder tumors, and no tumor was found in 6.7% of the cases. In the white-light arm, these categories of patients represented 71.3%, 14.8%, and 13.9% of the series, respectively." Comment: 78.9% and 71.3% correspond to 176 and 159 participants in the blue and white light groups, respectively. However, only percentages and not raw numbers are provided for follow-up outcomes, so it was not possible to discern whether percentages reflect number of initially randomized participants or number of participants remaining at follow-up.
Selective reporting (reporting bias)	Unclear risk	Quote: NA Comment: no protocol available
Other bias	Low risk	Quote: NA Comment: no other bias identified

Geavlete 2012

Study characteristics	
Methods	• randomized • single center/Romania
Participants	Study setting • primary and recurrent

Geavlete 2012 *(Continued)*

	Eligibility criteria • patients with suspected NMIBC based on positive urinary cytology and ultrasound Non-eligibility criteria • massive hematuria • moderate to severe leukocyturia • prior intravesical instillations earlier than ≤ 3 months • suspicion of upper urinary tract disease Intervention cohort • participants recruited: 181 • unifocal/multifocal tumors: 53/89 Comparator cohort • participants recruited: 181 • unifocal/multifocal tumors: NR
Interventions	Intervention: WLC + BLC followed by WL-TURBT + BL-TURBT Comparator: WLC followed by WL-TURBT Adjuvant instillation therapy: mitomycin C (no further information on dosage)
Outcomes	Outcome(s)* • recurrence rate • detection rate • progression rate • postoperative treatment modification • false-positive rate Results • median follow-up: 24 months • RFS rate was 31.2% in intervention group vs 45.6% in comparator group • recurrence rate at 24 months was 35.4% in intervention group vs 54.0% in comparator group • detection rate was 92.2% in intervention group vs 80.3% in comparator group (P = 0.046) • progression rate at 24 months was 4.0% in intervention group vs 7.0% in comparator group (P = 0.123)
Funding sources	NR
Declarations of interest	1 author: received honoraria from GE Healthcare when spoke at a company-sponsored symposia
Contact of study author	Date of contact attempt to first study author: 30 November 2020 Contact status: no reply to date
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomized by means of sealed envelopes, thus ensuring allocation concealment by the 'sequentially-numbered, opaque, sealed envelopes' method"

Geavlete 2012 *(Continued)*

		Comment: method of sequence generation clearly described
Allocation concealment (selection bias)	Low risk	Quote: "randomized by means of sealed envelopes, thus ensuring allocation concealment by the 'sequentially-numbered, opaque, sealed envelopes' method" Comment: allocation concealment clearly described
Blinding of participants and personnel (performance bias) Surgeon	High risk	Quote: "in each case, the urologist performing the procedure was informed on whether HAL-BLC would be available only after finishing the WLC to ensure maximum attention to the standard investigation" Comment: surgeon unblinded
Blinding of participants and personnel (performance bias) Participants/study personnel	Unclear risk	Quote: NA Comment: unclear whether study participants and other study personnel were blinded
Blinding of outcome assessment (detection bias) Subjective outcomes (all outcomes)	Unclear risk	Quote: "to ensure the complete objectivity of the evaluation, the urologists performing the follow-up of WLCs were unaware of the diagnostic and treatment modality initially applied in each case" Comment: blinding of study personnel reported only at the time point of WLCs
Incomplete outcome data (attrition bias) Oncological outcomes	Unclear risk	Quote: "during the follow-up period, 17 patients in the HAL-BLC arm and 13 in the WLC arm did not complete the 2 years protocol and were consequently excluded from the trial." Comment: unclear rate (10% to 20%) of participants lost to follow-up
Selective reporting (reporting bias)	Unclear risk	Quote: NA Comment: no protocol available
Other bias	Low risk	Quote: NA Comment: no other bias identified

Gkritsios 2014

Study characteristics	
Methods	• randomized • single center/Greece
Participants	Study setting • primary and recurrent Eligibility criteria • patients with suspected or confirmed NMIBC Non-eligibility criteria • patients scheduled for a second TURBT • porphyria

Gkritsios 2014 *(Continued)*

- gross hematuria
- known allergy to HAL
- presence of > 4 solitary tumors
- large tumors (> 3 cm in diameter)

Intervention cohort

- participants recruited: 66
- unifocal/multifocal tumors: NR

Comparator cohort

- participants recruited: 64
- unifocal/multifocal tumors: NR

Interventions	Intervention: WLC + BLC followed by WL-TURBT + BL-TURBT Comparator: WLC followed by WL-TURBT Adjuvant instillation therapy: 50 mg epirubicin
Outcomes	Outcome(s)* • recurrence-free survival • detection rate • recurrence rate • false-positive rate • adverse events • surgeon opinion on whether blue light "helped them with patient" Results • median follow-up: 40 months • RFS was 31.0 months in intervention group vs 27.0 months in comparator group • recurrence rate within 40 months was 37.5% in intervention group vs 45.9% in comparator group (P = 0.507) • surgeon opinion: in 34 out of the 54 participants (63%, 95% CI 50.1 to 75.8) blue light was helpful
Funding sources	NR
Declarations of interest	NR
Contact of study author	Date of contact attempt to first study author: 30 November 2020 Contact status: no reply to date
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomization plan was produced with the use of an electronic randomization plan generator (randomization.com), with the method of randomly permuted blocks" Comment: method of sequence generation clearly described

Gkritsios 2014 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Quote: "randomization plan was produced with the use of an electronic randomization plan generator (randomization.com), with the method of randomly permuted blocks" Comment: method of sequence generation clearly described
Blinding of participants and personnel (performance bias) Surgeon	High risk	Quote: NA Comment: surgeon unblinded
Blinding of participants and personnel (performance bias) Participants/study personnel	Unclear risk	Quote: NA Comment: unclear whether study participants and other study personnel were blinded
Blinding of outcome assessment (detection bias) Subjective outcomes (all outcomes)	Unclear risk	Quote: NA Comment: unclear whether study personnel were blinded
Incomplete outcome data (attrition bias) Oncological outcomes	High risk	Quote: "excluded from follow-up n=6 and n=13, respectively (see figure 1)" Comment: high rate (≥ 20%) of participants lost to follow-up
Selective reporting (reporting bias)	Low risk	Quote: NA Comment: reporting according to the protocol (UMIN000008176) of primary and secondary outcome measures
Other bias	Low risk	Quote: NA Comment: no other bias identified

Hermann 2011

Study characteristics	
Methods	• randomized, comparative • multicenter (2 centers)/Denmark
Participants	Study setting • primary and recurrent • only Ta/T1 Eligibility criteria • patients with suspicion of BCa based on cystoscopy Non-eligibility criteria • porphyria • gross hematuria • known allergy to HAL Intervention cohort

Hermann 2011 *(Continued)*

	• participants recruited: 115 • unifocal/multifocal tumors: 44/24 (0 to 1: 44/2 to 7: 24/> 8: 0) Comparator cohort • participants recruited: 118 • unifocal/multifocal tumors: 48/29 (0 to 1: 48/2 to 7: 29/> 8: 0)
Interventions	Intervention: WLC + WL-TURBT followed by BL-TURBT Comparator: WLC followed by WL-TURBT Adjuvant instillation therapy: NA
Outcomes	Outcome(s)* • recurrence-free survival • recurrence rate • detection rate • adverse events Results • median follow-up: 12 months • true- (and false-) positive detection rate was 64% (25%) of intervention group and 83% (16%) of comparator group • RFS rate was 47.3% in intervention group and 30.5% in comparator group (P = 0.05)
Funding sources	Photocure ASA; financial support by the Juchum and the Boemske Foundations
Declarations of interest	NR
Contact of study author	Date of contact attempt to first study author: 30 November 2020 Contact status: reply by author; provided full study report in co-operation with the sponsor
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "eligible patients were randomized just before surgery to one of two treatment groups" Comment: method of sequence generation unclear
Allocation concealment (selection bias)	Unclear risk	Quote: "eligible patients were randomized just before surgery to one of two treatment groups" Comment: allocation concealment unclear
Blinding of participants and personnel (performance bias) Surgeon	High risk	Quote: NA Comment: surgeon unblinded
Blinding of participants and personnel (performance bias)	Unclear risk	Quote: NA

Hermann 2011 *(Continued)*

Participants/study personnel		Comment: unclear whether study participants and other study personnel were blinded
Blinding of outcome assessment (detection bias) Subjective outcomes (all outcomes)	Unclear risk	Quote: NA Comment: unclear whether study personnel were blinded
Incomplete outcome data (attrition bias) Oncological outcomes	High risk	Quote: "thirteen patients were excluded from the HAL group and one from the white light group (Fig. 2). Fourteen patients were lost to follow-up." Comment: high rate (≥ 20%) of participants lost to follow-up, which was also substantially different between groups
Selective reporting (reporting bias)	Low risk	Quote: NA Comment: reporting according to the protocol (NCT00412971) of primary outcome measures (tumor recurrence rates, recurrence-free survival within 1 year) and secondary outcome measures (additional lesion found by blue light-cystoscopy, false-positive detection rate)
Other bias	Low risk	Quote: NA Comment: no other bias identified

Karaolides 2012

Study characteristics	
Methods	• randomized • single center/Greece
Participants	Study setting • primary and recurrent Eligibility criteria • patients with suspicion of BCa based on ultrasound, CT imaging, endoscopic finding, positive cytology Non-eligibility criteria • upper urinary tract disease • documented recurrence of BCa within the last 12 months • intravesical chemotherapy or immunotherapy instillations within the last 3 months Intervention cohort • participants recruited: 49 • unifocal/multifocal tumors: 18/23 Comparator cohort • participants recruited: 53 • unifocal/multifocal tumors: 26/19
Interventions	Intervention: WLC + BLC followed by WL-TURBT + BL-TURBT Comparator: WL-TURBT

Karaolides 2012 *(Continued)*

	Adjuvant instillation therapy: 50 mg epirubicin
Outcomes	Outcome(s)* • recurrence-free survival • recurrence rate Results • median follow-up: 18 months • RFS was 13.6 months in intervention group vs 7.0 months in comparator group • recurrence-free rate at 18 months was 82.5% in intervention group vs 50.6% in comparator group (P < 0.001)
Funding sources	NR
Declarations of interest	NR
Contact of study author	Date of contact attempt to first study author: 30 November 2020 Contact status: no reply to date
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "patients with suspected bladder cancer were randomized" Comment: method of sequence generation unclear
Allocation concealment (selection bias)	Unclear risk	Quote: "patients with suspected bladder cancer were randomized" Comment: allocation concealment unclear
Blinding of participants and personnel (performance bias) Surgeon	High risk	Quote: NA Comment: surgeon unblinded
Blinding of participants and personnel (performance bias) Participants/study personnel	Unclear risk	Quote: NA Comment: unclear whether other study personnel were blinded
Blinding of outcome assessment (detection bias) Subjective outcomes (all outcomes)	Unclear risk	Quote: NA Comment: unclear whether study personnel were blinded
Incomplete outcome data (attrition bias) Oncological outcomes	Low risk	Quote: excluded from follow-up n = 1 and n = 1, respectively (see Figure 1) Comment: low rate of participants (< 10%) lost to follow-up
Selective reporting (reporting bias)	Unclear risk	Quote: NA Comment: no protocol available

Karaolides 2012 *(Continued)*

Other bias	Low risk	Quote: NA Comment: no other bias identified

Kriegmaier 2002

Study characteristics	
Methods	• randomized, phase III • multicenter (8 centers)/Austria, Germany
Participants	Study setting • primary and recurrent Eligibility criteria • patients suspicious for primary BCa or tumor recurrence Non-eligibility criteria • NR Intervention cohort • participants recruited: 83 • unifocal/multifocal tumors: NR Comparator cohort • participants recruited: n = 82 • unifocal/multifocal tumors: NR
Interventions	Intervention: PDD-TURBT Comparator: WL-TURBT Adjuvant instillation therapy: NA
Outcomes	Outcome(s) • residual tumor • detection rate Results • median follow-up: 2 weeks • RFS rate was 67.3% in intervention group vs 46.9% in comparator group (P < 0.031)
Funding sources	NR
Declarations of interest	NR
Contact of study author	Date of contact attempt to first study author: 30 November 2020 Contact status: no reply to date
Notes	

Kriegmaier 2002 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "the randomization procedure was stratified according to participating centers and further by the potentially prognostically relevant risk score, defined according to the results of European Organization for the Research and Treatment of Cancer studies 30831, 30790 and 30782 as 1—recurrence, 2—early recurrence at less than 12 months, 3—bacillus Calmette-Guerin therapy less than 12 months in duration and 4—a history of carcinoma in situ" Comment: method of sequence generation unclear
Allocation concealment (selection bias)	Unclear risk	Quote: "the randomization procedure was stratified according to participating centers and further by the potentially prognostically relevant risk score, defined according to the results of European Organization for the Research and Treatment of Cancer studies 30831, 30790 and 30782 as 1—recurrence, 2—early recurrence at less than 12 months, 3—bacillus Calmette-Guerin therapy less than 12 months in duration and 4—a history of carcinoma in situ" Comment: allocation concealment unclear
Blinding of participants and personnel (performance bias) Surgeon	High risk	Quote: NA Comment: surgeon unblinded
Blinding of participants and personnel (performance bias) Participants/study personnel	Unclear risk	Quote: NA Comment: unclear whether study participants and other study personnel were blinded
Blinding of outcome assessment (detection bias) Subjective outcomes (all outcomes)	Unclear risk	Quote: NA Comment: unclear whether study personnel were blinded
Incomplete outcome data (attrition bias) Oncological outcomes	High risk	Quote: NA Comment: loss to follow-up was > 20%
Selective reporting (reporting bias)	Unclear risk	Quote: NA Comment: no protocol available
Other bias	Low risk	Quote: NA Comment: no other bias identified

Neuzillet 2014

Study characteristics

Methods	• randomized • multicenter (2 centers)/France

Neuzillet 2014 *(Continued)*

Participants	Study setting • primary Eligibility criteria • patients with primary NMIBC based on cystoscopy and positive urinary cytology Non-eligibility criteria • suspicion of MIBC, upper urinary tract disease, or massive hematuria Intervention cohort • participants recruited: 72 • unifocal/multifocal tumors: NR/NR Comparator cohort • participants recruited: 79 • unifocal/multifocal tumors: NR/NR
Interventions	Intervention: WLC + WL-TURBT followed by BLC + BL-TURBT Comparator: WLC followed by WL-TURBT Adjuvant instillation therapy: NA
Outcomes	Outcome(s) • recurrence rate • detection rate Results • median follow-up: 6 weeks • Recurrence rate: 20 participants with BLC and 26 participants with WLC • Detection rate: average difference on first TURBT for BLC vs WLC was + 0.4 (P = 0.35); in second TURBT + 0.54 (P = 0.19)
Funding sources	NA
Declarations of interest	NA
Contact of study author	Date of contact attempt to first study author: 30 November 2020 Contact status: no reply to date
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "based on a computer-generated random sequence (1:1), sequentially numbered individual sealed envelopes were prepared by an independent statistician with the group the relevant patient was to be assigned, i.e., a first TURB with WLC and PDD (hexaminolevulinate [HAL]arm) or WLC alone (control arm). Randomization was done the day before the first TURB." Comment: method of sequence generation clearly described

Neuzillet 2014 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Quote: "based on a computer-generated random sequence (1:1), sequentially numbered individual sealed envelopes were prepared by an independent statistician with the group the relevant patient was to be assigned, i.e., a first TURB with WLC and PDD (hexaminolevulinate [HAL]arm) or WLC alone (control arm). Randomization was done the day before the first TURB" Comment: allocation concealment unclear
Blinding of participants and personnel (performance bias) Surgeon	High risk	Quote: NA Comment: surgeon unblinded
Blinding of participants and personnel (performance bias) Participants/study personnel	Unclear risk	Quote: NA Comment: unclear whether study participants and other study personnel were blinded
Blinding of outcome assessment (detection bias) Subjective outcomes (all outcomes)	Unclear risk	Quote: NA Comment: unclear whether study personnel were blinded
Incomplete outcome data (attrition bias) Oncological outcomes	Low risk	Quote: "excluded from follow-up n=2 and n=2, respectively (see figure)" Comment: low rate of participants (< 10%) lost to follow-up
Selective reporting (reporting bias)	Unclear risk	Quote: NA Comment: no protocol available
Other bias	Low risk	Quote: NA Comment: no other bias identified

O'Brien 2013

Study characteristics	
Methods	• randomized, non-blinded • single center/United Kingdom
Participants	Study setting • primary Eligibility criteria • patients with suspected new NMIBC Non-eligibility criteria • suspicion of MIBC • previous BCa • porphyria • pregnancy

O'Brien 2013 *(Continued)*

	• sensitivity 5-ALA Intervention cohort • participants recruited: 129 • unifocal/multifocal tumors: 55/70/not stated: 4 Comparator cohort • participants recruited: 120 • unifocal/multifocal tumors: 36/79/not stated: 5
Interventions	Intervention: WLC + BLC followed by WL-TURBT + BL-TURBT Comparator: WLC followed by WL-TURBT Adjuvant instillation therapy: 40 mg mitomycin C in 40 mL saline
Outcomes	Outcome(s) • recurrence-free survival Results • median follow-up: 12 months • RFS rate at 12 months was 16% in intervention group and 22% in comparator group
Funding sources	NR
Declarations of interest	2 authors: speaker for GE Healthcare; 1 author: speaker for Photocure; 1 author: speaker for Ipsen
Contact of study author	Date of contact attempt to first study author: 30 November 2020 Contact status: no reply to date
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomization was performed in the urology department of Guy's Hospital by means of sealed envelopes in blocks of 20" Comment: method of sequence generation clearly described
Allocation concealment (selection bias)	Low risk	Quote: "randomization was performed in the urology department of Guy's Hospital by means of sealed envelopes in blocks of 20" Comment: allocation concealment clearly described
Blinding of participants and personnel (performance bias) Surgeon	High risk	Quote: NA Comment: surgeon unblinded
Blinding of participants and personnel (performance bias) Participants/study personnel	Unclear risk	Quote: NA Comment: unclear whether study participants and other study personnel were blinded

O'Brien 2013 *(Continued)*

Blinding of outcome assessment (detection bias) Subjective outcomes (all outcomes)	Unclear risk	Quote: NA Comment: unclear whether study personnel were blinded
Incomplete outcome data (attrition bias) Oncological outcomes	Unclear risk	Quote: "excluded from follow-up see figure 3" Comment: unclear rate (10% to 20%) of participants lost to follow-up
Selective reporting (reporting bias)	Low risk	Quote: NA Comment: reporting according to the protocol (ISRCTN14275387) of primary outcome measure (recurrence rate of bladder tumor at 3 months and 12 months postsurgery) and secondary outcome measures (analysis of histology)
Other bias	Low risk	Quote: NA Comment: no other bias identified

Riedl 2001

Study characteristics	
Methods	• randomized • multicenter (2 centers)/Austria, Germany
Participants	Study Setting • primary Eligibility criteria • pts with suspected BCa on prior cystoscopy, ultrasound or cytology Non-eligibility criteria • NR Intervention cohort • participants recruited: NR • unifocal/multifocal tumors: 19/32 Comparator cohort • participants recruited: NR • unifocal/multifocal tumors: 31/20
Interventions	Intervention: BL-TURBT Comparator: WL-TURBT Adjuvant instillation therapy: NA
Outcomes	Outcome(s)* • recurrence free survival • detection rate

Riedl 2001 *(Continued)*

	Results • median follow-up: 60 months • RFS was 42.0 months in intervention group vs. 39.0 months in comparator group • detection rate in second TURBT was 16% in intervention vs. 39% in comparator group
Funding sources	NR
Declarations of interest	NR
Contact of study author	Date of contact attempt to first study author: 30 November 2020 Contact status: reply by author; no original study data available any more
Notes	none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "each center had an individual randomization code formulated before initiation of the study." Comment: method of sequence generation unclear.
Allocation concealment (selection bias)	Unclear risk	Quote: "each center had an individual randomization code formulated before initiation of the study". Comment: allocation concealment unclear.
Blinding of participants and personnel (performance bias) Surgeon	High risk	Quote: NA Comment: surgeon unblinded.
Blinding of participants and personnel (performance bias) Participants/study personnel	Unclear risk	Quote: NA Comment: unclear whether study participants and other study personnel were blinded.
Blinding of outcome assessment (detection bias) Subjective outcomes (all outcomes)	Unclear risk	Quote: NA Comment: unclear whether study personnel were blinded.
Incomplete outcome data (attrition bias) Oncological outcomes	Unclear risk	Quote: "Of the 115 patients (56 from 1 center and 59 from the other center) initially randomized for the study 13 were excluded after primary transurethral resection because of muscle invasive bladder cancer on microscopic examination." Comment: unclear rate (10-20%) of randomized participants were excluded.
Selective reporting (reporting bias)	Unclear risk	Quote: NA Comment: no protocol available.
Other bias	Low risk	Quote: NA

Riedl 2001 *(Continued)*

	Comment: no other bias identified.

Rolevich 2017

Study characteristics	
Methods	• randomized, factorial design • single center/Republic of Belarus
Participants	Study setting • primary and recurrent Eligibility criteria • patients with suspected primary or recurrent NMIBC • age at least 18 years • adequate physiologic bladder capacity • estimated life expectancy of at least 3 years Non-eligibility criteria • ureterohydronephrosis • treatment of NMIBC in the previous 6 months Intervention cohort • participants recruited: 252 • unifocal/multifocal tumors: 82/92 (0 to 1: 82/2 to 7: 74/> 8: 18) Comparator cohort • participants recruited: 273 • unifocal/multifocal tumors: 89/114 (0 to 1: 89/2 to 7: 87/> 8: 27)
Interventions	Intervention: WLC + BLC followed by BL-TURBT + doxorubicin or BL-TURBT only Comparator: WLC followed by WL-TURBT + doxorubicin or WL-TURBT only Adjuvant instillation therapy: 50 mg doxorubicin
Outcomes	Primary • recurrence-free survival Secondary • progression-free survival • overall survival • cancer-specific survival • safety Results • median follow-up: 60 months • RFS was 54.0 months in intervention group vs 65.0 months in comparator group (HR 0.76, 95% CI 0.54 to 1.07; P = 0.11) • PFS was 54.0 months in intervention group vs 65.0 months in comparator group (HR 0.65, 95% CI 0.28 to 1.52; P = 0.32)

Rolevich 2017 *(Continued)*

- safety: 3 complications in the intervention group vs 6 complications in the comparator group

Funding sources	Belarusian Ministry of Health
Declarations of interest	None
Contact of study author	Date of contact attempt to first study author: 30 November 2020 Contact status: reply by author: 19 January 2021
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomization was performed by the computer software generating random numbers with equal allocation ratio" Comment: method of sequence generation clearly described
Allocation concealment (selection bias)	Low risk	Quote: "The procedure was done in the central randomization office via telephone or local network interface, which allowed concealment of generated random sequence." Comment: allocation concealment clearly described
Blinding of participants and personnel (performance bias) Surgeon	High risk	Quote: NA Comment: surgeon unblinded
Blinding of participants and personnel (performance bias) Participants/study personnel	Unclear risk	Quote: NA Comment: unclear whether study participants and other study personnel were blinded
Blinding of outcome assessment (detection bias) Subjective outcomes (all outcomes)	Unclear risk	Quote: "The follow-up was arranged mostly by a local healthcare provider outside the study center, which resulted in blinding to the patients' treatment arm allocation." Comment: blinding of study personnel reported only at the time point of follow-up
Incomplete outcome data (attrition bias) Oncological outcomes	High risk	Quote: "a total of 525 bladder cancer patients entered the study, of these, 377 patients (72 %) were eligible for efficacy analysis (Fig. 1)" Comment: high rate (≥ 20%) of participants lost to follow-up
Incomplete outcome data (attrition bias) Surgical complications	Low risk	Quote: NA Comment: all randomized participants taken into account in analysis
Selective reporting (reporting bias)	Unclear risk	Quote: NA Comment: no protocol available
Other bias	Low risk	Quote: NA

Rolevich 2017 *(Continued)*

	Comment: no other bias identified

Schumacher 2010

Study characteristics	
Methods	• randomized, phase III • multicenter (5 centers)/Sweden
Participants	Study setting • primary and recurrent Eligibility criteria • patients with suspected NMIBC based on at least 1 documented cystoscopy Non-eligibility criteria • WHO general health status score of > 2 • porphyria • hypersensitivity to porphyrins • renal or hepatic impairment, or both Intervention cohort • participants recruited: 153 • unifocal/multifocal tumors: 53/66/NA: 6/no tumor: 16 Comparator cohort • participants recruited: 147 • unifocal/multifocal tumors: 58/61/NA: 2/no tumor: 17
Interventions	Intervention: WLC + BLC followed by WL-TURBT + BL-TURBT Comparator: WLC followed by WL-TURBT Adjuvant instillation therapy: NA
Outcomes	Outcome(s)* • recurrence-free survival • progression-free survival • detection rate • adverse events Results • median follow-up: 24 months • RFS at 12 months was 55.1% (95% CI 46.1 to 63.2) in the intervention group vs 55.9% (95% CI 46.8 to 64.0) in the control group (log-rank test, P = 0.689) • PFS at 12 months was 91.1% (95% CI 82.8 to 95.5) in the intervention group vs 89.1% (95% CI 81.0 to 93.9) in the control group (log-rank test, P = 0.979) • adverse events occurred in 28% of participants in the intervention group vs 17.5% in the control group
Funding sources	Medac GmbH, Germany

Schumacher 2010 *(Continued)*

Declarations of interest	None
Contact of study author	Date of contact attempt to first study author: 30 November 2020 Contact status: no reply to date
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "the urologist telephoned the randomisation office and stated the person-number, age, gender, and risk group. These data made block randomisation possible, and the urologist was informed whether FL should be used or not" Comment: method of sequence generation unclear
Allocation concealment (selection bias)	Low risk	Quote: "the urologist telephoned the randomisation office and stated the person-number, age, gender, and risk group. These data made block randomisation possible, and the urologist was informed whether FL should be used or not." Comment: allocation concealment clearly described
Blinding of participants and personnel (performance bias) Surgeon	High risk	Quote: NA Comment: surgeon unblinded
Blinding of participants and personnel (performance bias) Participants/study personnel	Unclear risk	Quote: NA Comment: unclear whether study participants and other study personnel were blinded
Blinding of outcome assessment (detection bias) Subjective outcomes (all outcomes)	Unclear risk	Quote: "all pathologists were unaware of whether or not FL was used" Comment: unclear whether all study personnel were blinded
Incomplete outcome data (attrition bias) Oncological outcomes	Low risk	Quote: "of the 300 patients, 21 (7%) were excluded from the full-analysis set. Reasons for exclusion were radical cystectomy based on the results of the primary TUR (4.7%) and no first cystoscopy (2.3%)." Comment: low rate (< 10%) of participants lost to follow-up
Incomplete outcome data (attrition bias) Adverse events	Low risk	Quote: "adverse events were reported in 22.9% of patients and occurred more often in the FL group (28%) than in the WL group (17.5%)" Comment: all randomized participants taken into account in analysis
Selective reporting (reporting bias)	Unclear risk	Quote: NA Comment: no protocol available
Other bias	Low risk	Quote: NA

Schumacher 2010 *(Continued)*

Comment: no other bias identified

Stenzl 2010

Study characteristics	
Methods	• randomized • multicenter (28 centers)/USA, Canada, Europe
Participants	Study setting • primary and recurrent • only Ta/T1 Eligibility criteria • patients with suspected Ta and/or T1 based on outpatient cystoscopy • presence of > 1 initial or recurrent papillary tumor or recurrence within 12 months of a previous BCa Non-eligibility criteria • gross hematuria • BCG or chemotherapy within 3 months before initial TURBT Intervention cohort • participants recruited: 382 • unifocal/multifocal tumors: NR/NR Comparator cohort • participants recruited: 384 • unifocal/multifocal tumors: NR/NR
Interventions	Intervention: 1) WLC + mapping -> 2nd randomization -> 2) BLC + mapping followed by BL-TURBT Comparator: WLC followed by WL-TURBT Adjuvant instillation therapy: NA
Outcomes	Outcome(s)* • recurrence-free survival • progression-free survival • detection rate • adverse events Results • median follow-up: 9 months • RFS was 55.1 months in intervention group vs 53.0 months in comparator group • RFS was 47% in intervention group and 56% in comparator group within 9-month surveillance period • 31 participants in the intervention group vs 46 participants in the control group had disease progression • adverse events occurred in 202 participants in the intervention group vs 193 participants in the control group
Funding sources	Photocure ASA, Norway

Stenzl 2010 *(Continued)*

Declarations of interest	3 authors: financial interest and/or other relationship with Photocure ASA and others
Contact of study author	Date of contact attempt to first study author: 30 November 2020 Contact status: reply by author: 1 December 2020, reply by sponsor: 22 December 2020
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomization was performed centrally, and was stratified for patients presenting with initial and recurrent bladder cancer" Comment: method of sequence generation unclear
Allocation concealment (selection bias)	Low risk	Quote: "randomization was performed centrally, and was stratified for patients presenting with initial and recurrent bladder cancer" Comment: allocation concealment clearly described
Blinding of participants and personnel (performance bias) Surgeon	High risk	Quote: NA Comment: surgeon unblinded
Blinding of participants and personnel (performance bias) Participants/study personnel	Unclear risk	Quote: NA Comment: unclear whether study participants and other study personnel were blinded
Blinding of outcome assessment (detection bias) Subjective outcomes (all outcomes)	Unclear risk	Quote: NA Comment: unclear whether study personnel were blinded
Incomplete outcome data (attrition bias) Oncological outcomes	High risk	Quote: excluded from follow-up see figure 2 Comment: high rate (≥ 20%) of participants lost to follow-up
Incomplete outcome data (attrition bias) Adverse events	Low risk	Quote: "a similar level of AEs was experienced by patients in both groups (table 5)" Comment: all participants taken into account in intention-to-treat analysis
Selective reporting (reporting bias)	Low risk	Quote: NA Comment: reporting according to the protocol (NCT00233402) of primary outcome measures (detection rate, recurrence-free survival within 9 months) and secondary outcome measures (false-positive lesions of blue light, CIS lesion detected only by blue light)
Other bias	Low risk	Quote: NA Comment: no other bias identified

Stenzl 2011

Study characteristics	
Methods	• randomized, double-blind, placebo-controlled • multicenter (8 centers)/Austria, Germany
Participants	Study setting • primary Eligibility criteria • patients with suspected NMIBC based on cystoscopy sonography, x-ray, or cytology with Papanicolaou test > II Non-eligibility criteria • general health status > 2 according to the WHO score (Eastern Cooperative Oncology Group) • porphyria • hypersensitivity to porphyrins • renal impairment • hepatic impairment • leukocytes < 3500/µL • platelets < 100,000/µL • lymph node metastasis or other metastasis • other current malignancies (not including basalioma) • pregnancy (planned or existent) • breastfeeding • no safety in contraception • simultaneous participation in other clinical trials • mental disorders Intervention cohort • participants recruited: 192 • unifocal/multifocal tumors: 104/79 Comparator cohort • participants recruited: 189 • unifocal/multifocal tumors: 112/64
Interventions	Intervention: WLC + BLC followed by BL-TURBT Comparator: WLC followed by WL-TURBT Adjuvant instillation therapy: NA
Outcomes	Outcome(s) • recurrence-free survival • recurrence rate • progression-free survival • detection rate • adverse events Results • median follow-up: 12 months

Stenzl 2011 *(Continued)*

- RFS was 64.0% in intervention group vs 72.8% in comparator group
- PFS was 89.4% in intervention group vs 89.0% in comparator group

Funding sources	medac Gesellschaft fur klinische Spezialpräparate mbH, Hamburg, Germany
Declarations of interest	NR
Contact of study author	Date of contact attempt to first study author: 30 November 2020 Contact status: reply by author: 15 January 2021
Notes	Study protocol was provided by the sponsor.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomization was stratified according to 2 categories of the potentially prognostic and relevant European Organization for Research and Treatment of Cancer risk score describing the probability of tumor recurrence and/or tumor progression" Comment: method of sequence generation unclear
Allocation concealment (selection bias)	Unclear risk	Quote: "this randomized, double-blind, placebo-controlled study comprising 381 patients was conducted at 8 urology centers in Austria and Germany over a period of 27 months" Comment: method of allocation concealment unclear
Blinding of participants and personnel (performance bias) Surgeon	High risk	Quote: "the study was designed as a double-blind trial. During the whole trial, neither the patient, the physicians involved in performing transurethral resections, nor the sponsor staff were aware of the study arm administered. This included anyone determining subject eligibility, evaluating endpoints, or assessing compliance with the protocol. For this trial, 2 independent teams of investigators were required. The first team was responsible for patient registration as well as for the first and second transurethral resections. The second team was responsible for evaluating the primary study endpoint within the control cystoscopies and did not know whether the original procedure had been carried out under white light or fluorescent light." Comment: surgeon unblinded; blinding of surgeon within follow-up control cystoscopies
Blinding of participants and personnel (performance bias) Participants/study personnel	Low risk	Quote: "the study was designed as a double-blind trial. During the whole trial, neither the patient, the physicians involved in performing transurethral resections, nor the sponsor staff were aware of the study arm administered. This included anyone determining subject eligibility, evaluating endpoints, or assessing compliance with the protocol. For this trial, 2 independent teams of investigators were required. The first team was responsible for patient registration as well as for the first and second transurethral resections. The second team was responsible for evaluating the primary study endpoint within the control cystoscopies and did not know whether the original procedure had been carried out under white light or fluorescent light." Comment: study participants and other study personnel were blinded
Blinding of outcome assessment (detection bias)	Low risk	Quote: "the study was designed as a double-blind trial. During the whole trial, neither the patient, the physicians involved in performing transurethral resections, nor the sponsor staff were aware of the study arm administered. This in-

Stenzl 2011 *(Continued)*

Subjective outcomes (all outcomes)		cluded anyone determining subject eligibility, evaluating endpoints, or assessing compliance with the protocol. For this trial, 2 independent teams of investigators were required. The first team was responsible for patient registration as well as for the first and second transurethral resections. The second team was responsible for evaluating the primary study endpoint within the control cystoscopies and did not know whether the original procedure had been carried out under white light or fluorescent light." Comment: study personnel were blinded
Incomplete outcome data (attrition bias) Oncological outcomes	Low risk	Quote: participants excluded from follow-up see figure 1. Comment: low rate (< 10%) of participants lost to follow-up
Incomplete outcome data (attrition bias) Adverse events	Low risk	Quote: "Of the 370 patients who underwent cystoscopy with 5-ALA or the corresponding placebo (safety population), 123 (33.2%) reported adverse events (white light, 33.9%; fluorescent light, 32.6%) (Table 5)." Comment: all randomized participants taken into account in analysis
Selective reporting (reporting bias)	Low risk	Quote: NA Comment: reporting of primary and secondary outcome measures according to protocol
Other bias	Low risk	Quote: NA Comment: no other bias identified

*No definition of primary and secondary endpoints.
5-ALA: 5-aminolevulinic acid
BCa: bladder cancer
BCG: Bacillus Calmette-Guerin
BLC: blue light cystoscopy
BL-TURBT: blue light transurethral resection of bladder tumor
CI: confidence interval
CIS: carcinoma in situ
CT: computed tomography
HAL: hexaminolevulinic acid
HR: hazard ratio
MIBC: muscle invasive bladder cancer
NA: not available
NMIBC: non-muscle invasive bladder cancer
NR: not reported
PDD-TURBT: photodynamic diagnosis-assisted transurethral resection of bladder tumor
PFS: progression-free survival
RFS: recurrence-free survival
TURBT: transurethral resection of bladder tumor
WHO: World Health Organization
WLC: white light cystoscopy
WL-TURBT: white light transurethral resection of bladder tumor

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

Study	Reason for exclusion
Daneshmand 2018	Wrong setting (surveillance)

Study	Reason for exclusion
Daniltchenko 2004	Duplicate
Doehn 2014	Wrong setting (diagnostic test accuracy)
Doisy 2019	Wrong study design (cross-over trial)
Drejer 2020	Wrong setting (surveillance)
DRKS00000142	Wrong setting (wrong comparator)
EUCTR2004-002259-15-AT	Duplicate
EUCTR2012-000559-15-FI	Duplicate
EUCTR2013-003898-98-IT	Duplicate
EUCTR2015-000436-15-DK	Wrong setting (surveillance)
Filbeck 2003	Duplicate
Fradet 2007	Wrong setting (surveillance)
Gallagher 2017	Wrong study design (non-randomized trial)
Geavlete 2009	Wrong study design (non-randomized trial)
ISRCTN14275387	Duplicate
JPRN-UMIN000001337	Wrong study design (non-randomized trial)
JPRN-UMIN000008176	Duplicate
JPRN-UMIN000009093	Wrong study design (non-randomized trial)
JPRN-UMIN000010798	Wrong study design (non-randomized trial)
JPRN-UMIN000031471	Wrong study design (non-randomized trial)
JPRN-UMIN000035712	Wrong study design (non-randomized trial)
Lipiński 2008	Wrong study design (non-randomized trial)
Lykke 2015	Wrong study design (non-randomized trial)
Madej 2009	Wrong study design (non-randomized trial)
NCT00052637	Wrong study design (non-randomized trial)
NCT00412971	Duplicate
NCT00785694	Withdrawn study (rejected ethics approval in UK and Netherlands)
NCT01166230	Duplicate
Otto 2009	Duplicate

Study	Reason for exclusion
Rolevich 2019	Wrong study design (post hoc analysis)

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

Boström 2018

Study name	Treatment of Ta bladder cancer in high risk of recurrence—fluorescence cystoscopy with optimized adjuvant mitomycin-C (FinnBladder 9)
Methods	• randomized • multicenter/Finland
Participants	Estimated enrollment • 400 participants Study setting • primary/recurrent • only Ta Eligibility criteria • number of primary tumors ≥ 2, or size of solitary primary tumor ≥ 3 cm, or recurrent papillary tumors • histologically proven Ta bladder cancer • histological grade 1 to 2 (WHO 1973 grading system) or PUNLMP or low-grade (WHO 2004 grading system) bladder cancer Non-eligibility criteria • grade 3 tumors (WHO 1973 grading system) or high-grade tumors (WHO 2004 grading system) • CIS • suspicion or evidence of papillary tumors or CIS of the upper urinary tract • non-transitional cell carcinoma • suspicion or previous history of the patient not tolerating intravesical instillations • known allergy to mitomycin C or hexaminolevulinate
Interventions	1. No adjuvant instillations • Intervention: blue light TURBT with no adjuvant instillations • Comparator: white light TURBT with no adjuvant instillations 2. Adjuvant instillations (6 weekly optimized mitomycin C instillations) • Intervention: blue light TURBT with adjuvant instillations • Comparator: white light TURBT with adjuvant instillations
Outcomes	Primary outcomes • bladder cancer recurrence at 2 years Secondary outcomes • bladder cancer progression to T2 or higher • progression, recurrence, or side effects preventing completion of the trial • treatment failure (progression, recurrence, or side effects preventing completion of the trial) • death due to bladder cancer or other reasons

Boström 2018 *(Continued)*

	Other outcomes • analysis of cost-effectiveness
Starting date	August 2012
Contact information	Date of contact attempt to first study author: 28 June 2021 Contact status: reply by author 8 July 2021; study still recruiting; date of anticipated publication 2022 to 2023
Notes	clinicaltrials.gov/ct2/show/NCT01675219

Tandogdu 2019

Study name	PHOTOdynamic versus white light-guided treatment of non-muscle invasive bladder cancer: randomised trial of clinical and cost-effectiveness
Methods	• randomized • multicenter
Participants	Estimated enrollment • 533 participants Study setting • primary • only intermediate/high risk Eligibility criteria • visual/ultrasound/CT diagnosis of intermediate-/high-risk NMIBC • white light visual appearances of intermediate- or high-risk disease (3-centimeter tumor size, 2 or more tumors, or flat velvety erythematous changes alerting a clinical suspicion of CIS) • suspicion of papillary bladder tumour > 3 cm based on ultrasound or CT scanning (without hydronephrosis) Non-eligibility criteria • visual evidence of low-risk NMIBC (solitary tumor < 3 cm) • visual evidence of MIBC on preliminary cystoscopy, i.e. non-papillary or sessile mass (attached directly by its base without a stalk) • upper tract (kidney or ureteric) tumors on imaging • any other malignancy in the past 2 years (except non-melanomatous skin cancer cured by excision, adequately treated CIS of the cervix, ductal/lobular CIS of the breast, or prostate cancer in patients who have a life expectancy of > 5 years upon trial entry) • evidence of metastases • porphyria or known hypersensitivity to porphyrins
Interventions	Intervention: blue light TURBT Control: white light TURBT
Outcomes	Primary outcomes • bladder cancer recurrence at 3 years • analysis of cost-effectiveness

Tandogdu 2019 *(Continued)*

	Secondary outcomes • progression rate at 3 years • safety • health-related quality of life • cancer-specific survival
Starting date	September 2014
Contact information	Date of contact attempt to first study author: 28 July 2021 Contact status: reply by author 28 July 2021; manuscript is currently being prepared
Notes	www.isrctn.com/ISRCTN84013636

CIS: carcinoma in situ
CT: computerized tomography
MIBC: muscle invasive bladder cancer
NMIBC: non-muscle invasive bladder cancer
PUNLMP: papillary urothelial neoplasm of low malignant potential
TURBT: transurethral resection of bladder tumor
WHO: World Health Organization

DATA AND ANALYSES

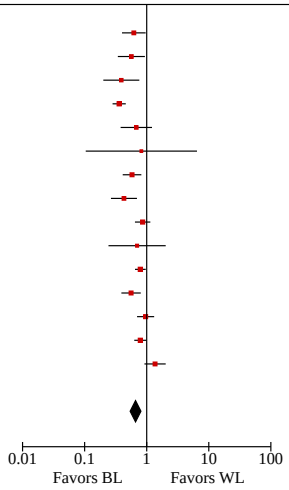
Comparison 1. Blue light versus white light

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Time to disease recurrence	15	2994	Hazard Ratio (IV, Random, 95% CI)	0.66 [0.54, 0.81]
1.2 Time to disease progression	9	2200	Hazard Ratio (IV, Random, 95% CI)	0.65 [0.50, 0.84]
1.3 Surgical complications, serious	1	525	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.14, 2.14]
1.4 Time to death from bladder cancer	1	407	Hazard Ratio (IV, Random, 95% CI)	0.55 [0.19, 1.61]
1.5 Adverse events	3	1375	Risk Ratio (IV, Random, 95% CI)	1.09 [0.88, 1.33]

Analysis 1.1. Comparison 1: Blue light versus white light, Outcome 1: Time to disease recurrence

Study or Subgroup	log[Hazard Ratio]	SE	Blue light Total	White light Total	Weight	Hazard Ratio IV, Random, 95% CI	Risk of Bias A	B	C	D	E
Babjuk 2005	-0.478	0.223601	60	62	6.9%	0.62 [0.40 , 0.96]	?	?	?	?	+
Drăgoescu 2017	-0.569161	0.256098	57	56	6.2%	0.57 [0.34 , 0.93]	?	?	?	?	+
Filbeck 2002	-0.9416	0.340721	88	103	4.8%	0.39 [0.20 , 0.76]	?	?	?	?	+
Geavlete 2010	-1.0217	0.12508	72	64	8.9%	0.36 [0.28 , 0.46]	+	+	?	?	+
Geavlete 2012	-0.3857	0.296896	125	114	5.5%	0.68 [0.38 , 1.22]	+	+	?	?	+
Gkritsios 2014	-0.1985	1.052678	48	37	0.9%	0.82 [0.10 , 6.45]	+	?	?	+	+
Hermann 2011	-0.5447	0.176265	68	77	7.8%	0.58 [0.41 , 0.82]	?	?	?	+	+
Karaolides 2012	-0.844	0.245948	41	45	6.4%	0.43 [0.27 , 0.70]	?	?	?	?	+
Neuzillet 2014	-0.1508	0.145499	72	79	8.5%	0.86 [0.65 , 1.14]	+	?	?	?	+
O'Brien 2013	-0.3567	0.541408	47	46	2.6%	0.70 [0.24 , 2.02]	+	+	?	+	+
Riedl 2001	-0.2357	0.101318	51	51	9.3%	0.79 [0.65 , 0.96]	?	?	?	?	+
Rolevich 2017	-0.579818	0.183285	174	203	7.7%	0.56 [0.39 , 0.80]	+	+	?	?	+
Schumacher 2010	-0.040822	0.161816	141	138	8.1%	0.96 [0.70 , 1.32]	?	+	?	?	+
Stenzl 2010	-0.235722	0.115304	255	261	9.1%	0.79 [0.63 , 0.99]	?	+	?	+	+
Stenzl 2011	0.309688	0.201166	183	176	7.3%	1.36 [0.92 , 2.02]	?	?	+	+	+
Total (95% CI)			**1482**	**1512**	**100.0%**	**0.66 [0.54 , 0.81]**					

Heterogeneity: Tau² = 0.10; Chi² = 57.62, df = 14 (P < 0.00001); I² = 76%
Test for overall effect: Z = 4.06 (P < 0.0001)
Test for subgroup differences: Not applicable

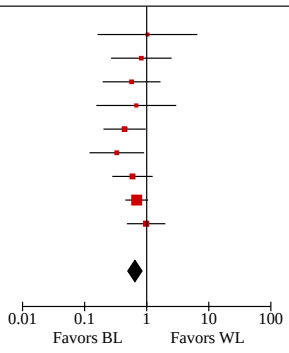


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of outcome assessment (detection bias): Subjective outcomes (all outcomes)
(D) Selective reporting (reporting bias)
(E) Other bias

Analysis 1.2. Comparison 1: Blue light versus white light, Outcome 2: Time to disease progression

Study or Subgroup	log[Hazard Ratio]	SE	Blue light Total	White light Total	Weight	Hazard Ratio IV, Random, 95% CI	Risk of Bias A	B	C	D	E
Babjuk 2005	0.029559	0.943226	60	62	2.0%	1.03 [0.16 , 6.54]	?	?	?	?	+
Drăgoescu 2017	-0.198451	0.572803	57	56	5.5%	0.82 [0.27 , 2.52]	?	?	?	?	+
Geavlete 2012	-0.562119	0.547997	125	114	6.0%	0.57 [0.19 , 1.67]	+	+	?	?	+
O'Brien 2013	-0.385662	0.756092	47	46	3.2%	0.68 [0.15 , 2.99]	+	+	?	+	+
Riedl 2001	-0.820981	0.399747	51	51	11.3%	0.44 [0.20 , 0.96]	?	?	?	?	+
Rolevich 2017	-1.108663	0.516834	174	203	6.8%	0.33 [0.12 , 0.91]	+	+	?	?	+
Schumacher 2010	-0.527633	0.381668	141	138	12.4%	0.59 [0.28 , 1.25]	?	+	?	?	+
Stenzl 2010	-0.371064	0.215436	255	261	39.0%	0.69 [0.45 , 1.05]	?	+	?	+	+
Stenzl 2011	-0.020203	0.364067	183	176	13.7%	0.98 [0.48 , 2.00]	?	?	+	+	+
Total (95% CI)			**1093**	**1107**	**100.0%**	**0.65 [0.50 , 0.84]**					

Heterogeneity: Tau² = 0.00; Chi² = 4.55, df = 8 (P = 0.80); I² = 0%
Test for overall effect: Z = 3.25 (P = 0.001)
Test for subgroup differences: Not applicable

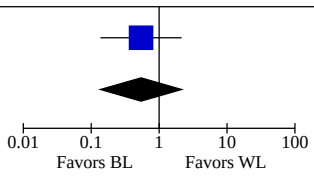


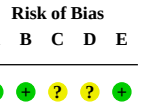
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of outcome assessment (detection bias): Subjective outcomes (all outcomes)
(D) Selective reporting (reporting bias)
(E) Other bias

Analysis 1.3. Comparison 1: Blue light versus white light, Outcome 3: Surgical complications, serious

Study or Subgroup	Blue light Events	Blue light Total	White light Events	White light Total	Weight	Risk Ratio M-H, Random, 95% CI
Rolevich 2017	3	252	6	273	100.0%	0.54 [0.14 , 2.14]
Total (95% CI)		**252**		**273**	**100.0%**	**0.54 [0.14 , 2.14]**
Total events:	3		6			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.87 (P = 0.38)
Test for subgroup differences: Not applicable



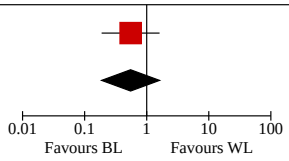


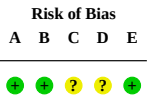
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of outcome assessment (detection bias): Subjective outcomes (all outcomes)
(D) Selective reporting (reporting bias)
(E) Other bias

Analysis 1.4. Comparison 1: Blue light versus white light, Outcome 4: Time to death from bladder cancer

Study or Subgroup	log[Hazard Ratio]	SE	Blue light Total	White light Total	Weight	Hazard Ratio IV, Random, 95% CI
Rolevich 2017	-0.597837	0.548304	191	216	100.0%	0.55 [0.19 , 1.61]
Total (95% CI)			**191**	**216**	**100.0%**	**0.55 [0.19 , 1.61]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.09 (P = 0.28)
Test for subgroup differences: Not applicable



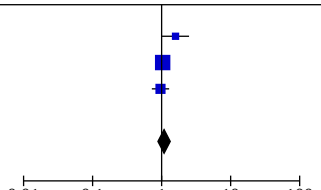


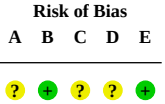
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of outcome assessment (detection bias): Subjective outcomes (all outcomes)
(D) Selective reporting (reporting bias)
(E) Other bias

Analysis 1.5. Comparison 1: Blue light versus white light, Outcome 5: Adverse events

Study or Subgroup	Blue light Events	Blue light Total	White light Events	White light Total	Weight	Risk Ratio IV, Random, 95% CI
Schumacher 2010	39	141	24	138	16.0%	1.59 [1.01 , 2.50]
Stenzl 2010	202	365	193	361	54.5%	1.04 [0.91 , 1.18]
Stenzl 2011	61	187	62	183	29.5%	0.96 [0.72 , 1.29]
Total (95% CI)		**693**		**682**	**100.0%**	**1.09 [0.88 , 1.33]**
Total events:	302		279			

Heterogeneity: Tau² = 0.02; Chi² = 3.64, df = 2 (P = 0.16); I² = 45%
Test for overall effect: Z = 0.78 (P = 0.43)
Test for subgroup differences: Not applicable



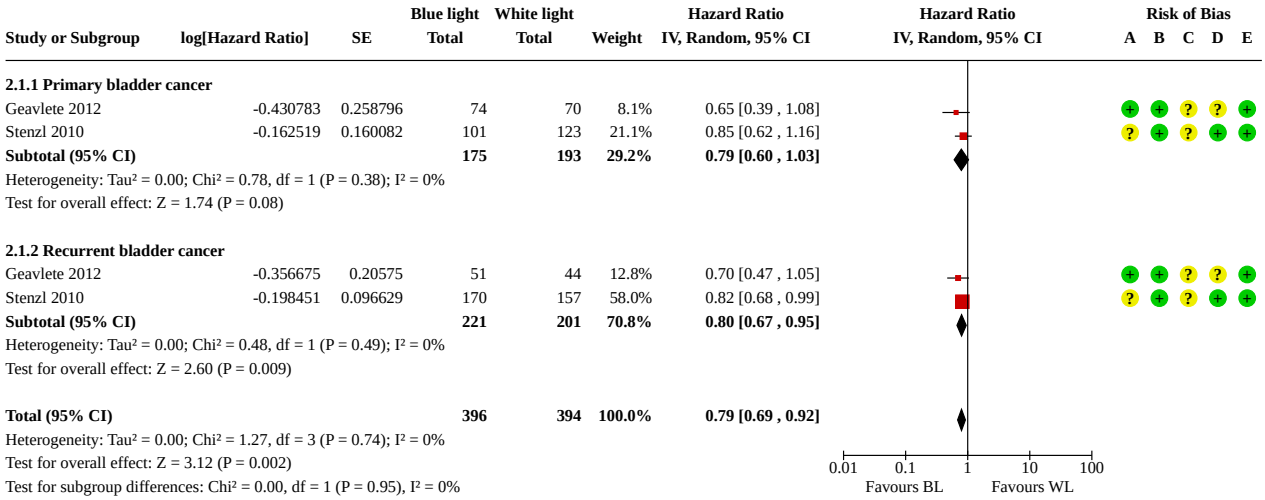


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of outcome assessment (detection bias): Subjective outcomes (all outcomes)
(D) Selective reporting (reporting bias)
(E) Other bias

Comparison 2. Blue light versus white light—subgroup analysis: primary versus recurrent bladder cancer

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Time to disease recurrence	2	790	Hazard Ratio (IV, Random, 95% CI)	0.79 [0.69, 0.92]
2.1.1 Primary bladder cancer	2	368	Hazard Ratio (IV, Random, 95% CI)	0.79 [0.60, 1.03]
2.1.2 Recurrent bladder cancer	2	422	Hazard Ratio (IV, Random, 95% CI)	0.80 [0.67, 0.95]

Analysis 2.1. Comparison 2: Blue light versus white light—subgroup analysis: primary versus recurrent bladder cancer, Outcome 1: Time to disease recurrence

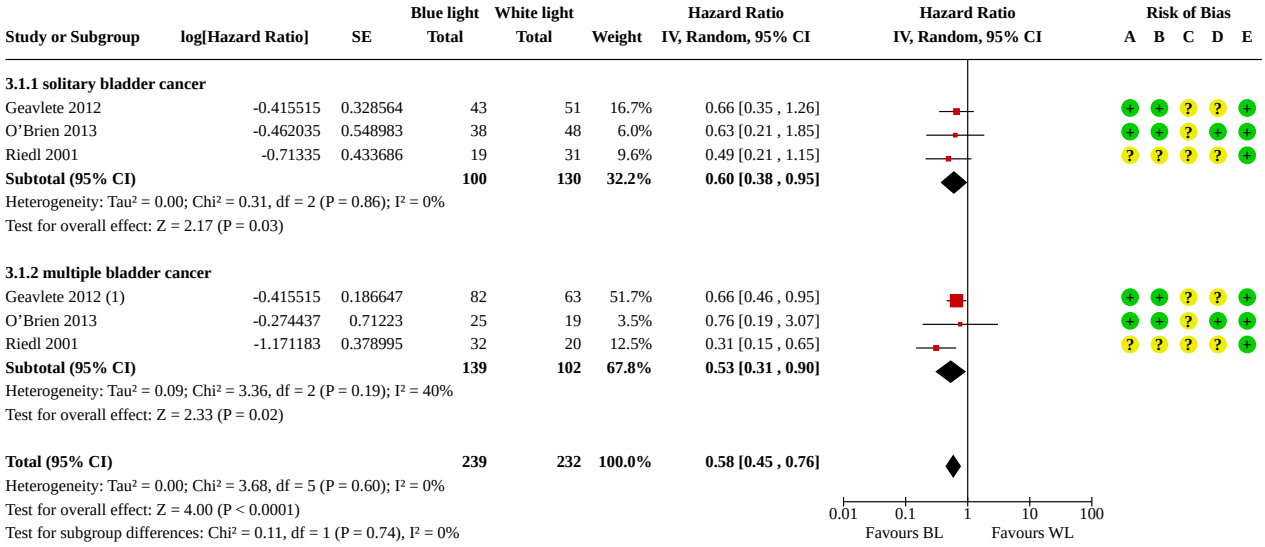


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of outcome assessment (detection bias): Subjective outcomes (all outcomes)
(D) Selective reporting (reporting bias)
(E) Other bias

Comparison 3. Blue light versus white light—subgroup analysis: solitary versus multiple lesions of bladder cancer

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Time to disease recurrence	3	471	Hazard Ratio (IV, Random, 95% CI)	0.58 [0.45, 0.76]
3.1.1 solitary bladder cancer	3	230	Hazard Ratio (IV, Random, 95% CI)	0.60 [0.38, 0.95]
3.1.2 multiple bladder cancer	3	241	Hazard Ratio (IV, Random, 95% CI)	0.53 [0.31, 0.90]

Analysis 3.1. Comparison 3: Blue light versus white light—subgroup analysis: solitary versus multiple lesions of bladder cancer, Outcome 1: Time to disease recurrence



Footnotes

(1) HR and p-value (if not provided) calculated with Parmar method:- Geavlete 2012- O'Brien 2013- Riedl 2001

Risk of bias legend

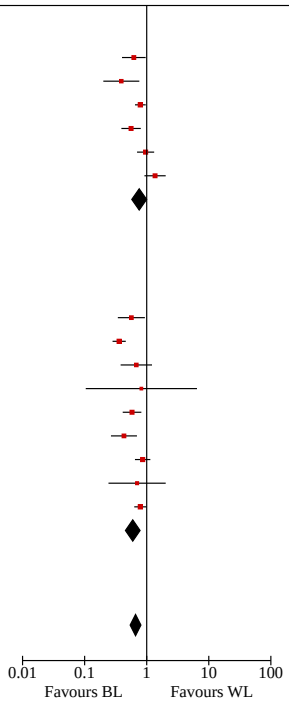
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of outcome assessment (detection bias): Subjective outcomes (all outcomes)
(D) Selective reporting (reporting bias)
(E) Other bias

Comparison 4. Blue light versus white light—subgroup analysis of 5-ALA versus HAL (post hoc)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Time to disease recurrence	15	2994	Hazard Ratio (IV, Random, 95% CI)	0.66 [0.54, 0.81]
4.1.1 5-ALA	6	1430	Hazard Ratio (IV, Random, 95% CI)	0.76 [0.57, 1.00]
4.1.2 HAL	9	1564	Hazard Ratio (IV, Random, 95% CI)	0.60 [0.45, 0.78]
4.2 Time to disease progression	9	2200	Hazard Ratio (IV, Random, 95% CI)	0.77 [0.63, 0.96]
4.2.1 5-ALA	5	1239	Hazard Ratio (IV, Random, 95% CI)	0.72 [0.47, 1.11]
4.2.2 HAL	4	961	Hazard Ratio (IV, Random, 95% CI)	0.69 [0.48, 0.98]

Analysis 4.1. Comparison 4: Blue light versus white light—subgroup analysis of 5-ALA versus HAL (post hoc), Outcome 1: Time to disease recurrence

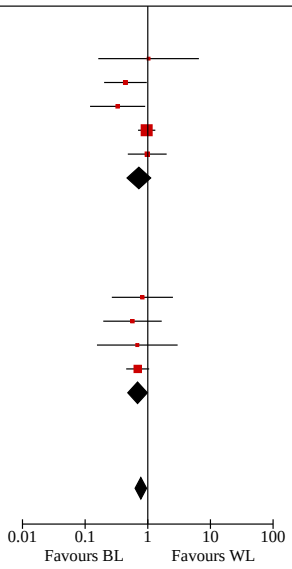
Study or Subgroup	log[Hazard Ratio]	SE	Blue light Total	White light Total	Weight	Hazard Ratio IV, Random, 95% CI	Risk of Bias A B C D E
4.1.1 5-ALA							
Babjuk 2005	-0.478	0.223601	60	62	6.9%	0.62 [0.40 , 0.96]	? ? ? ? +
Filbeck 2002	-0.9416	0.340721	88	103	4.8%	0.39 [0.20 , 0.76]	? ? ? ? +
Riedl 2001	-0.2357	0.101318	51	51	9.3%	0.79 [0.65 , 0.96]	? ? ? ? +
Rolevich 2017	-0.579818	0.183285	174	203	7.7%	0.56 [0.39 , 0.80]	+ + ? ? +
Schumacher 2010	-0.040822	0.161816	141	138	8.1%	0.96 [0.70 , 1.32]	? + ? ? +
Stenzl 2011	0.309688	0.201166	183	176	7.3%	1.36 [0.92 , 2.02]	? ? + + +
Subtotal (95% CI)			**697**	**733**	**44.1%**	**0.76 [0.57 , 1.00]**	
Heterogeneity: Tau² = 0.08; Chi² = 17.79, df = 5 (P = 0.003); I² = 72%							
Test for overall effect: Z = 1.97 (P = 0.05)							
4.1.2 HAL							
Drăgoescu 2017	-0.569161	0.256098	57	56	6.2%	0.57 [0.34 , 0.93]	? ? ? ? +
Geavlete 2010	-1.0217	0.12508	72	64	8.9%	0.36 [0.28 , 0.46]	+ + ? ? +
Geavlete 2012	-0.3857	0.296896	125	114	5.5%	0.68 [0.38 , 1.22]	+ + ? ? +
Gkritsios 2014	-0.1985	1.052678	48	37	0.9%	0.82 [0.10 , 6.45]	+ ? ? + +
Hermann 2011	-0.5447	0.176265	68	77	7.8%	0.58 [0.41 , 0.82]	? ? ? + +
Karaolides 2012	-0.844	0.245948	41	45	6.4%	0.43 [0.27 , 0.70]	? ? ? ? +
Neuzillet 2014	-0.1508	0.145499	72	79	8.5%	0.86 [0.65 , 1.14]	+ ? ? ? +
O'Brien 2013	-0.3567	0.541408	47	46	2.6%	0.70 [0.24 , 2.02]	+ + ? + +
Stenzl 2010	-0.235722	0.115304	255	261	9.1%	0.79 [0.63 , 0.99]	? + ? + +
Subtotal (95% CI)			**785**	**779**	**55.9%**	**0.60 [0.45 , 0.78]**	
Heterogeneity: Tau² = 0.11; Chi² = 30.77, df = 8 (P = 0.0002); I² = 74%							
Test for overall effect: Z = 3.74 (P = 0.0002)							
Total (95% CI)			**1482**	**1512**	**100.0%**	**0.66 [0.54 , 0.81]**	
Heterogeneity: Tau² = 0.10; Chi² = 57.62, df = 14 (P < 0.00001); I² = 76%							
Test for overall effect: Z = 4.06 (P < 0.0001)							
Test for subgroup differences: Chi² = 1.47, df = 1 (P = 0.23), I² = 32.0%							

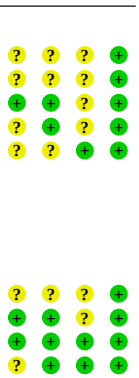


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of outcome assessment (detection bias): Subjective outcomes (all outcomes)
(D) Selective reporting (reporting bias)
(E) Other bias

Analysis 4.2. Comparison 4: Blue light versus white light—subgroup analysis of 5-ALA versus HAL (post hoc), Outcome 2: Time to disease progression

Study or Subgroup	log[Hazard Ratio]	SE	Blue light Total	White light Total	Weight	Hazard Ratio IV, Random, 95% CI
4.2.1 5-ALA						
Babjuk 2005	0.029559	0.943226	60	62	1.3%	1.03 [0.16 , 6.54]
Riedl 2001	-0.820981	0.399747	51	51	7.2%	0.44 [0.20 , 0.96]
Rolevich 2017	-1.108663	0.516834	174	203	4.3%	0.33 [0.12 , 0.91]
Schumacher 2010	-0.040822	0.161816	141	138	44.1%	0.96 [0.70 , 1.32]
Stenzl 2011	-0.020203	0.364067	183	176	8.7%	0.98 [0.48 , 2.00]
Subtotal (95% CI)			**609**	**630**	**65.7%**	**0.72 [0.47 , 1.11]**
Heterogeneity: Tau² = 0.09; Chi² = 6.77, df = 4 (P = 0.15); I² = 41%						
Test for overall effect: Z = 1.48 (P = 0.14)						
4.2.2 HAL						
Drăgoescu 2017	-0.198451	0.572803	57	56	3.5%	0.82 [0.27 , 2.52]
Geavlete 2012	-0.562119	0.547997	125	114	3.8%	0.57 [0.19 , 1.67]
O'Brien 2013	-0.385662	0.756092	47	46	2.0%	0.68 [0.15 , 2.99]
Stenzl 2010	-0.371064	0.215436	255	261	24.9%	0.69 [0.45 , 1.05]
Subtotal (95% CI)			**484**	**477**	**34.3%**	**0.69 [0.48 , 0.98]**
Heterogeneity: Tau² = 0.00; Chi² = 0.21, df = 3 (P = 0.98); I² = 0%						
Test for overall effect: Z = 2.05 (P = 0.04)						
Total (95% CI)			**1093**	**1107**	**100.0%**	**0.77 [0.63 , 0.96]**
Heterogeneity: Tau² = 0.00; Chi² = 7.64, df = 8 (P = 0.47); I² = 0%						
Test for overall effect: Z = 2.38 (P = 0.02)						
Test for subgroup differences: Chi² = 0.03, df = 1 (P = 0.87), I² = 0%						





Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Selective reporting (reporting bias)
(D) Other bias

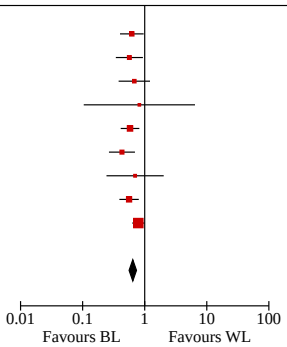
Comparison 5. Blue light versus white light—sensitivity analysis by re-resection

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Time to disease recurrence	9	1776	Hazard Ratio (IV, Random, 95% CI)	0.64 [0.56, 0.74]
5.2 Time to disease progression	6	1460	Hazard Ratio (IV, Random, 95% CI)	0.64 [0.46, 0.90]

Analysis 5.1. Comparison 5: Blue light versus white light—sensitivity analysis by re-resection, Outcome 1: Time to disease recurrence

Study or Subgroup	log[Hazard Ratio]	SE	Blue light Total	White light Total	Weight	Hazard Ratio IV, Random, 95% CI	Risk of Bias A	B	C	D	E
Babjuk 2005	-0.478	0.223601	60	62	9.8%	0.62 [0.40 , 0.96]	?	?	?	?	+
Drăgoescu 2017	-0.569161	0.256098	57	56	7.5%	0.57 [0.34 , 0.93]	?	?	?	?	+
Geavlete 2012	-0.3857	0.296896	125	114	5.5%	0.68 [0.38 , 1.22]	+	+	?	?	+
Gkritsios 2014	-0.1985	1.052678	48	37	0.4%	0.82 [0.10 , 6.45]	+	?	?	+	+
Hermann 2011	-0.5447	0.176265	68	77	15.7%	0.58 [0.41 , 0.82]	?	?	?	+	+
Karaolides 2012	-0.844	0.245948	41	45	8.1%	0.43 [0.27 , 0.70]	?	?	?	?	+
O'Brien 2013	-0.3567	0.541408	47	46	1.7%	0.70 [0.24 , 2.02]	+	+	?	+	+
Rolevich 2017	-0.579818	0.183285	174	203	14.5%	0.56 [0.39 , 0.80]	+	+	?	?	+
Stenzl 2010	-0.235722	0.115304	255	261	36.8%	0.79 [0.63 , 0.99]	?	+	?	+	+
Total (95% CI)			**875**	**901**	**100.0%**	**0.64 [0.56 , 0.74]**					

Heterogeneity: Tau² = 0.00; Chi² = 7.16, df = 8 (P = 0.52); I² = 0%
Test for overall effect: Z = 6.33 (P < 0.00001)
Test for subgroup differences: Not applicable

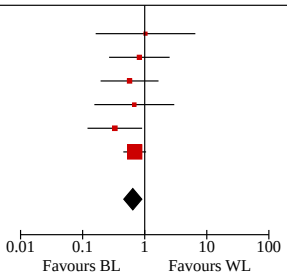


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of outcome assessment (detection bias): Subjective outcomes (all outcomes)
(D) Selective reporting (reporting bias)
(E) Other bias

Analysis 5.2. Comparison 5: Blue light versus white light—sensitivity analysis by re-resection, Outcome 2: Time to disease progression

Study or Subgroup	log[Hazard Ratio]	SE	Blue light Total	White light Total	Weight	Hazard Ratio IV, Random, 95% CI	Risk of Bias A	B	C	D	E
Babjuk 2005	0.029559	0.943226	60	62	3.3%	1.03 [0.16 , 6.54]	?	?	?	?	+
Drăgoescu 2017	-0.198451	0.572803	57	56	8.8%	0.82 [0.27 , 2.52]	?	?	?	?	+
Geavlete 2012	-0.562119	0.547997	125	114	9.6%	0.57 [0.19 , 1.67]	+	+	?	?	+
O'Brien 2013	-0.385662	0.756092	47	46	5.1%	0.68 [0.15 , 2.99]	+	+	?	+	+
Rolevich 2017	-1.108663	0.516834	174	203	10.8%	0.33 [0.12 , 0.91]	+	+	?	?	+
Stenzl 2010	-0.371064	0.215436	255	261	62.4%	0.69 [0.45 , 1.05]	?	+	?	+	+
Total (95% CI)			**718**	**742**	**100.0%**	**0.64 [0.46 , 0.90]**					

Heterogeneity: Tau² = 0.00; Chi² = 2.26, df = 5 (P = 0.81); I² = 0%
Test for overall effect: Z = 2.60 (P = 0.009)
Test for subgroup differences: Not applicable



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of outcome assessment (detection bias): Subjective outcomes (all outcomes)
(D) Selective reporting (reporting bias)
(E) Other bias

ADDITIONAL TABLES

Table 1. Baseline characteristics of included studies

Study name	Trial period (year to year)	Setting/country	Description of participants	Intervention(s) and comparator(s)	Adjuvant instillation*/re-resection	Duration of follow-up (median)	Age (years (mean), range)	Gender (male/female)
Babjuk 2005	2001 to 2005	Single center/Czech Republic	Primary and recurrent NMIBC, only Ta/T1	Intervention: 1 g 5-ALA + BL-TURBT	NA/NA	24 months	67.9 ± NA	43/17
				Comparator: WL-TURBT			67.9 ± NA	39/23
Drăgoescu 2017	2009 to 2011	Single center/Romania	Primary NMIBC	Intervention: 0.85 g HAL + BL-TURBT	Mitomycin C, doxorubicin, farmorubicin/NA	60 months	59.4 ± 9.9	45/12
				Comparator: WL-TURBT			60.3 ± 10.2	43/13
Filbeck 2002	1997 to 2000	Single center/Germany	Primary and recurrent NMIBC	Intervention: 1 g 5-ALA + BL-TURBT	NA/WL-TURBT after 6 weeks	24 months	68.0 (31 to 88)	NA
				Comparator: WL-TURBT			70.0 (32 to 89)	NA
Geavlete 2010	2007 to 2009	Single center/Romania	Primary NMIBC	Intervention: HAL + BL-TURBT	Mitomycin C/ WL-TURBT after 6 weeks	6 weeks	64.0 (32 to 86)	327/119
				Comparator: WL-TURBT				
Geavlete 2012	NA	Single center/Romania	Primary and recurrent NMIBC	Intervention: HAL + BL-TURBT	Mitomycin C/NA	24 months	66.8 (31 to 85)	267/95
				Comparator: WL-TURBT				

Table 1. Baseline characteristics of included studies *(Continued)*

Gkritsios 2014	NA	Single center/Greece	Primary and recurrent NMIBC	Intervention: 0.85 g 5-ALA + BL-TURBT	Epirubicin/NA	40 months	66.0 ± NA	43/11
				Comparator: WL-TURBT			68.2 ± NA	44/6
Hermann 2011	NA	Multicenter/Denmark	Primary and recurrent NMIBC, only Ta/T1	Intervention: 0.85 g 5-ALA + BL-TURBT	NA/NA	12 months	71.0 (35 to 96)	NA
				Comparator: WL-TURBT			69.0 (41 to 92)	NA
Karaolides 2012	2008 to 2010	Single center/Greece	Primary and recurrent NMIBC	Intervention: HAL + BL-TURBT	Epirubicin/NA	18 months	66.3 (37 to 82)	33/8
				Comparator: WL-TURBT			63.8 (39 to 88)	40/5
Kriegmaier 2002	1997 to 1998	Multicenter/Germany, Austria	Primary and recurrent NMIBC	Intervention: 1 g 5-ALA + BL-TURBT	NA/WL-TURBT after 10 to 14 days	2 weeks	69.3 (38 to 88)	53/12
				Comparator: WL-TURBT			69.6 (34 to 94)	45/19
Neuzillet 2014	2009 to 2012	Multicenter/France	Primary NMIBC	Intervention: 0.85 g HAL + BL-TURBT	NA/PDD-TURBT after 6 weeks	6 weeks	74.0 ± 10.3	64/8
				Comparator: WL-TURBT			74.0 ± 10.4	69/10
O'Brien 2013	2005 to 2010	Single center/United Kingdom	Primary NMIBC	Intervention: HAL + BL-TURBT	Mitomycin C/NA	12 months	68.0 (31 to 95)	95/34
				Comparator:			68.0 (29 to 90)	88/32

Table 1. Baseline characteristics of included studies *(Continued)*

				WL-TURBT				
Riedl 2001	1998 to 2000	Multicenter/Germany, Austria	Primary NMIBC	Intervention: 1 g 5-ALA + BL-TURBT	NA/PDD-TURBT after 6 weeks	60 months	67.0 (19 to 86)	36/15
				Comparator: WL-TURBT				37/14
Rolevich 2017	2008 to 2012	Single center/Republic of Belarus	Primary and recurrent NMIBC	Intervention: 1 g 5-ALA + BL-TURBT	Doxorubicin/NA	60 months	NA	134/40
				Comparator: WL-TURBT			NA	156/47
Schumacher 2010	2002 to 2005	Multicenter/Sweden	Primary and recurrent NMIBC	Intervention: 1 g 5-ALA + BL-TURBT	NA/WL-TURBT after 5 to 7 weeks in pts with pT1 G2-3 or T2	24 months	70.1 ± 10.1	103/38
				Comparator: WL-TURBT			68.9 ± 10.8	104/34
Stenzl 2010	NR	Multicenter/USA, Canada, Europe	Primary and recurrent NMIBC, only Ta/T1	Intervention: 0.85 g HAL + BL-TURBT	NA/NA	9 months	68.0 ± 10.8	212/59
				Comparator: WL-TURBT			69.6 ± 10.7	223/57
Stenzl 2011	NR	Multicenter/Germany, Austria	Primary NMIBC	Intervention: 1 g 5-ALA + BL-TURBT	NA/WL-TURBT after 2 to 4 weeks in pts with pT1 G2-3 or T2	12 months	66.0 ± 12.0	259/100
				Comparator: WL-TURBT				

*Only immediate postoperative instillations, no Bacille Calmette-Guerin schedule.
5-ALA: 5-aminolevulinic acid
BL-TURBT: blue light transurethral resection of bladder tumor
HAL: hexaminolevulinic acid

NA: not available
NMIBC: non-muscle invasive bladder cancer
NR: not reported
PDD-TURBT: photodynamic diagnosis-assisted transurethral resection of bladder tumor
pts: participants
WL-TURBT: white light transurethral resection of bladder tumor

Table 2. Participants in the included studies

Study name	Intervention(s) and comparator(s)	Screened/ eligible (N)	Randomized (N)	Analyzed (N): efficacy	Analyzed (N): safety	Finishing trial (N)
Babjuk 2005	Intervention: 1 g 5-ALA + BL-TURBT	128/122	64	60	NA	60
	Comparator: WL-TURBT		64	62	NA	62
Drăgoescu 2017	Intervention: 0.85 g 5-ALA + BL-TURBT	113/113	57	57	NA	57
	Comparator: WL-TURBT		56	56	NA	56
Filbeck 2002	Intervention: 1 g 5-ALA + BL-TURBT	301/191	151	88	NA	88
	Comparator: WL-TURBT		150	103	NA	103
Geavlete 2010	Intervention: HAL + BL-TURBT	NA/446	223	176	NA	NA
	Comparator: WL-TURBT		233	159	NA	NA
Geavlete 2012	Intervention: HAL + BL-TURBT	362/269	181	125	NA	48
	Comparator: WL-TURBT		181	114	NA	37
Gkritsios 2014	Intervention: 0.85 g 5-ALA + BL-TURBT	130/104	66	48	NA	48
	Comparator: WL-TURBT		64	37	NA	37
Hermann 2011	Intervention: 0.85 g 5-ALA + BL-TURBT	223/223	115	68	NA	68
	Comparator: WL-TURBT		118	77	NA	77
Karaolides 2012	Intervention: HAL + BL-TURBT	102/102	49	41	NA	41
	Comparator: WL-TURBT		53	45	NA	45
Kriegmaier 2002	Intervention: 1 g 5-ALA + BL-TURBT	165/129	83	65	NA	65
	Comparator: WL-TURBT		82	64	NA	64

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

Neuzillet 2014	Intervention: 0.85 g 5-ALA + BL-TURBT	151/151	72	72	NA	43
	Comparator: WL-TURBT		79	79	NA	50
O'Brien 2013	Intervention: HAL + BL-TURBT	249/185	129	86	NA	63
	Comparator: WL-TURBT		120	82	NA	67
Riedl 2001	Intervention: 1 g 5-ALA + BL-TURBT	115/102	NA	51	51	NA
	Comparator: WL-TURBT		NA	51	51	NA
Rolevich 2017	Intervention: 1 g 5-ALA + BL-TURBT	525/377	252	174	NA	NA
	Comparator: WL-TURBT		273	203	NA	NA
Schumacher 2010	Intervention: 1 g 5-ALA + BL-TURBT	300/279	153	141	NA	136
	Comparator: WL-TURBT		147	138	NA	134
Stenzl 2010	Intervention: 0.85 g 5-ALA + BL-TURBT	814/766	382	200	421	200
	Comparator: WL-TURBT		384	202	391	202
Stenzl 2011	Intervention: 1 g 5-ALA + BL-TURBT	381/370	192	183	187	NA
	Comparator: WL-TURBT		189	176	183	NA
Intervention total			2169	1635	659	994
Comparator total			2183	1648	625	1011
Grand total			4352	3283	1284	2005

5-ALA: 5-aminolevulinic acid
BL-TURBT: blue light transurethral resection of bladder tumor
HAL: hexaminolevulinic acid
NA: not available
WL-TURBT: white light transurethral resection of bladder tumor

APPENDICES

Appendix 1. Cochrane Library search strategy

#1 MeSH descriptor: [undefined] 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: [Photosensitizing Agents] explode all trees

#7 (photodynamic and diagnosis):ti,ab,kw (Word variations have been searched)

#8 (PDD):ti,ab,kw (Word variations have been searched)

#9 MeSH descriptor: [Fluorescence] explode all trees

#10 (fluorescence):ti,ab,kw (Word variations have been searched)

#11 MeSH descriptor: [Aminolevulinic Acid] explode all trees

#12 (Aminolaevulinate):ti,ab,kw (Word variations have been searched)

#13 (hexaminolevulinate):ti,ab,kw (Word variations have been searched)

#14 (ALA or HAL):ti,ab,kw (Word variations have been searched)

#15 #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14

#16 #5 and #15

Appendix 2. MEDLINE via 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 Photosensitizing Agents/

7 photodynamic.tw. and (diagnosis.fs. or diagnosis.tw.)

8 PDD.tw.

9 exp Fluorescence/

10 fluorescence.tw.

11 exp Aminolevulinic Acid/

12 Aminolaevulinate.tw.

13 hexaminolevulinate.tw.

14 (ALA or HAL).tw.

15 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14

16 5 and 15

17 randomized controlled trial.pt.

18 controlled clinical trial.pt.

19 randomized.ab.

20 placebo.ab.

21 drug therapy.fs.

22 randomly.ab.

23 trial.ab.

24 groups.ab.

25 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24

26 exp animals/ not humans.sh.

27 25 not 26

28 16 and 27

Appendix 3. 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 'photosensitizing agent'/exp

#7 photodynamic:ab,ti AND (diagnosis:lnk OR diagnosis:ab,ti)

#8 pdd:ab,ti

#9 'fluorescence'/exp

#10 'fluorescence':ab,ti

#11 'aminolevulinic acid'/exp

#12 aminolaevulinate:ab,ti

#13 hexaminolevulinate:ab,ti

#14 ala:ab,ti OR hal:ab,ti

#15 #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14

#16 #5 AND #15

#17 '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

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

#19 #17 NOT #18

#20 #16 AND #19

Appendix 4. 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=((("Photosensitizing Agents" OR photodynamic) AND diagnosis) fluorescence OR "Aminolevulinic Acid" OR Aminolaevulinate OR hexaminolevulinate)

#3 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*)

#4 #1 AND #2 AND #3

Appendix 5. Scopus search strategy

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

#2 TITLE-ABS-KEY((("Photosensitizing Agents" OR photodynamic) AND diagnosis) fluorescence OR "Aminolevulinic Acid" OR Aminolaevulinate OR hexaminolevulinate)

#3 ("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*))

#4 #1 AND #2 AND #3

Appendix 6. LILACS search strategy

((mh:("Urinary Bladder Neoplasms")) OR (tw:("bladder cancer" OR "bladder carcinoma" OR "bladder neoplasm" OR "bladder tumor" OR "bladder tumour" OR "NMIBC" OR "TURBT"))) AND ((mh:("Photosensitizing Agents" OR "Fluorescence" OR "Aminolevulinic Acid")) OR (tw:((photodynamic AND diagnosis) OR "PDD" OR "fluorescence" OR "Aminolaevulinate" OR "hexaminolevulinate" OR "ALA" OR "HAL"))) 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")

Appendix 7. OpenGrey literature search strategy

"Bladder Cancer" AND (photodyanmic OR fluorescence)

Appendix 8. ClinicalTrials.gov search strategy

#1 Bladder Cancer

#2 photodyanmic OR fluorescence

#3 1 AND 2

Appendix 9. WHO ICTRP search strategy

1 bladder cancer AND photodynamic

2 bladder cancer AND fluorescence

3 1 OR 2

HISTORY

Protocol first published: Issue 11, 2020

CONTRIBUTIONS OF AUTHORS

- Draft the protocol: PM, PD, VN, AK, JV, MHK
- Study selection: PM, AK, JV, PD
- Data extraction: PM, AK, JV
- Enter data into Review Manager 5: PM
- Carry out the analysis: PM, PD
- Interpret the analysis: PM, PD, VN
- Disagreement resolution: PD

DECLARATIONS OF INTEREST

PM, AK, JV, VN, MHK, and PD report no conflicts of interest.

SOURCES OF SUPPORT

Internal sources

- New Source of support, USA

  Philipp Dahm received salary support from the Minneapolis VA Healthcare system

External sources

- New Source of support, Germany

  Philipp Maisch received salary support as a Cochrane Urology Fellow through the Deutsche Forschungs Gemeinschaft (DFG)

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

This review is based on a published protocol (Maisch 2020). In response to comments arising during the external review, we made the following changes.

- We revised our original definition of progression to correspond to that of the International Bladder Cancer Group (Lamm 2014).
- We reconsidered our risk of bias assessment and now consider all outcomes potentially susceptible to detection bias, as their determination includes judgement on the part of the investigators.
- We added a subgroup analysis for the use of 5-aminolevulinic acid (5-ALA) versus hexaminolevulinic acid (HAL). These have been clearly labeled as post hoc.

INDEX TERMS

Medical Subject Headings (MeSH)

*Carcinoma, Transitional Cell [surgery]; Cystectomy [adverse effects]; Neoplasm Recurrence, Local; *Urinary Bladder Neoplasms [surgery]

MeSH check words

Humans