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

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[Intervention Protocol]

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

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

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

BACKGROUND

Description of the condition

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

People with bladder cancer most often present with blood in the urine, but tumors can also be found during the work-up for other symptoms, such as irritative voiding symptoms. The prevalence of bladder cancer ranges between 13% and 35% in people presenting with macroscopic hematuria, and between 5% and 10% in those with microscopic hematuria (Sun 2015). People who are found to have bladder tumors on diagnostic testing, then undergo transurethral resection of bladder tumor (TURBT) to confirm and treat the pathology; in other words, to remove the tumor(s).

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

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

Description of the intervention

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

How the intervention might work

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

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

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

Adverse effects of the intervention

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

Why it is important to do this review

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

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

OBJECTIVES

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

METHODS

Criteria for considering studies for this review

Types of studies

We will include all relevant randomized controlled trials, in which individual participants are randomized.

We will exclude quasi-experimental studies, given the lack of random assignment at the individual-level. Given the nature of the interventions in question, we will exclude cross-over trials from our review, since both the comparator and the experimental interventions involve removal of bladder tumors, and this will present a serious carry-over effect (Higgins 2011). Cluster-randomized trials are also an inappropriate study design in the context of our research question, as individual allocation of the interventions is both feasible and desirable. Given that individually randomized trials are more appropriate, we will exclude cluster-randomized trials from our review (Puffer 2005).

Types of participants

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

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

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

If studies include multiple participant groups or interventions, we will only include the subset of participants of interest. If multiple articles are published by the same group with the same participant cohort, we will merge and analyze relevant data from each article as one study.

Types of interventions

We plan to investigate the following comparisons. Concomitant interventions will have to be the same in the experimental and comparator groups to establish fair comparisons.

Experimental interventions

WLC- and NBI- guided TURBT

Comparator intervention

WLC-guided TURBT

Comparisons

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

Types of outcome measures

Measurement of outcomes assessed in this review will not be used as an eligibility criterion.

Primary outcomes

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

Secondary outcomes

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

Method and timing of outcome measurement

Primary outcomes

1. Time to disease recurrence: from the time of random sequence generation to time of any recurrence of bladder cancer, based on TURBT, regardless of tumor stage or grade
2. Time to disease progression: from the time of random sequence generation to time of progression of bladder cancer. Progression will be defined as an increase in tumor stage, or grade from the histopathology at the time of TURBT, or both.
3. Adverse event, major: Clavien-Dindo grade III, IV, or V (Clavien 2009), within 90 days of initial TURBT

Secondary outcomes

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

If data on the time to disease recurrence, time to disease progression, or time to death from bladder cancer are incomplete and cannot be analyzed as time-to-event outcomes, we will analyze them as dichotomous outcomes, up to 12 months (short-term), or 13 to 24 months (long-term) after randomization.

Thresholds for clinical relevance of outcomes

Primary outcomes

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

Secondary outcomes

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

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

Search methods for identification of studies

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

Electronic searches

We will search for relevant studies in the following ten databases from their respective date of inception, using the search strategies outline in the Appendices.

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

We will incorporate additional relevant key words found during these searches into our search strategies, and document changes accordingly.

Searching other resources

We will attempt to identify other potentially eligible studies by searching the reference lists of included publications. We will also contact study authors of included publications to identify any further studies that we may have missed. We will contact device manufacturers for ongoing or unpublished trials.

Data collection and analysis

Selection of studies

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

Data extraction and management

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

We will extract the following data:

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

We will extract relevant outcomes data needed to calculate summary statistics and measures of variance. For dichotomous outcomes, we will obtain numbers of events and totals to populate a 2 x 2 table, and calculate summary statistics with corresponding measures of variance. For continuous outcomes, we will obtain means and standard deviations or data necessary to calculate this information. For time-to-event outcomes, we will extract hazard ratios with corresponding measures of variance or data necessary to calculate this information.

Potentially relevant ongoing studies will be presented in the table 'Characteristics of ongoing studies'.

Dealing with duplicate and companion publications

In the event of duplicate publications, companion documents, or multiple reports of a primary study, we will maximize yield of information by mapping all publications to a unique study ID and

collating all available data. We will use the most complete dataset, aggregated across all known publications. In case of doubt, we will give priority to the publication reporting the longest follow-up associated with our primary or secondary outcomes.

Assessment of risk of bias in included studies

Two review authors (LL, ST) will independently assess the risk of bias of each included study, using the Cochrane 'Risk of bias' assessment tool (Higgins 2011). They will resolve disagreements by consensus, or through arbitration by a third review author (GL). We will determine if risk of bias is low, high, or unclear, and present our findings in a 'Risk of bias' summary figure. We will assess for the following biases:

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

We will evaluate the risk of performance bias and detection bias separately for each outcome. We will group outcomes according to whether they were measured subjectively or objectively in the 'Risk of bias' tables.

Performance bias - susceptible

- We will consider that all outcomes are similarly susceptible to performance bias

Detection bias - susceptible

- Time to disease recurrence (time-to-event outcome)
- Time to disease progression (time-to-event outcome)
- Time to death from bladder cancer (time-to-event outcome)

Detection bias - not susceptible

- Adverse event, minor: (Clavien-Dindo grade I or II; dichotomous outcome)
- Adverse event, major: (Clavien-Dindo grade III, IV, or V; dichotomous outcome)

We will assess Incomplete outcome data, or attrition bias on an outcome-specific basis. We will consider the rate of attrition as low (less than 10%), unclear (between 10% and 20%), and high (greater than or equal to 20%).

We will assess selective reporting bias on a study-specific basis. We will only consider the risk of selective reporting bias as low if we can identify an a priori protocol, and if the analyses and outcomes match what the investigators preplanned.

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

Measures of treatment effect

We will express outcomes with dichotomous data with risk ratios, with 95% confidence intervals (CIs). We will express outcomes with time-to-event data with hazard ratios with 95% CIs.

Unit of analysis issues

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

Dealing with missing data

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

We will conduct intention-to-treat analysis whenever possible. If intention-to-treat analysis is not possible, we will conduct as-treated and per-protocol population analyses. We will consider this a potential source of bias.

Assessment of heterogeneity

In the event of substantial clinical, methodological, or statistical heterogeneity, unexplained by subgroup analyses, we will not include such results in the pooled effect estimate in meta-analysis. Instead, we will provide a narrative description of the results of each study.

Using forest plots,

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

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

The importance of the observed the I^2 statistic will depends on the magnitude and direction of effects, and the strength of evidence for heterogeneity. If we identify heterogeneity, we will attempt to determine possible reasons for it by examining individual study and subgroup characteristics.

Assessment of reporting biases

We will attempt to obtain study protocols to assess for selective outcome reporting. If at least 10 studies are available for meta-analysis, we will assess for publication bias by creating and visually inspecting funnel plots.

Data synthesis

If there are sufficient studies available for meta-analysis, we will conduct a meta-analysis with a random-effects model for pooling

data (Wood 2008). We will conduct statistical analyses according to the statistical guidelines contained in the *Cochrane Handbook for Systematic Reviews of Interventions* (Li 2020). We will analyze dichotomous outcomes with the Mantel-Haenszel method and continuous outcomes with the inverse variance method. We will analyze time-to-event outcomes using the generic inverse variance method. We will use Review Manager 5 software to conduct all analyses (Review Manager 2020).

Subgroup analysis and investigation of heterogeneity

Certain tumor characteristics may impact outcomes. If there are sufficient data, we will conduct the following subgroup analyses:

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

The rationale underlying these subgroup analyses is as follows:

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

Sensitivity analysis

If there are sufficient studies, we will conduct sensitivity analyses to evaluate differences in methodology that could impact the results of meta-analyses. We will conduct sensitivity analysis by 1) excluding studies with high risk of bias (Deeks 2020), and 2) by excluding studies in which all participants underwent re-resection on a routine basis, since routine re-resection may mitigate potential benefits of NBI.

Summary of findings and assessment of the certainty of the evidence

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

We will present a 'Summary of findings' table reporting the following outcomes listed according to a priority rating established by the clinicians on our team with the input of external experts.

1. Time to disease recurrence
2. Time to disease progression
3. Adverse event, major
4. Time to death from bladder cancer
5. Adverse event, minor

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APPENDICES

Appendix 1. Cochrane Library search strategy

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

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

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

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

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

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

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

#8 nbi:ti,ab,kw

#9 #6 OR #7 OR #8

#10 #5 AND #9

Appendix 2. International Pharmaceutical Abstracts search strategy

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

2 NMIBC.tw.

3 TURBT.tw.

4 1 or 2 or 3

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

6 NBI.tw.

7 5 or 6

8 4 and 7

Appendix 3. MEDLINE Ovid search strategy

1 exp urinary bladder neoplasms/

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

3 NMIBC.tw.

4 TURBT.tw.

5 1 or 2 or 3 or 4

6 exp narrow band imaging/

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

8 NBI.tw.

9 6 or 7 or 8

10 5 and 9

11 randomized controlled trial.pt.

12 controlled clinical trial.pt.

13 randomized.ab.

14 placebo.ab.

15 drug therapy.fs.

16 randomly.ab.

17 trial.ab.

18 groups.ab.

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

20 exp animals/ not humans.sh.

21 19 not 20

22 10 and 21

Appendix 4. Embase search strategy

#1 'bladder tumor'/exp

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

#3 nmibc:ab,ti

#4 turbt:ab,ti

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

#6 'narrow band imaging'/exp

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

#8 nbi:ab,ti

#9 #6 OR #7 OR #8

#10 #5 AND #9

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

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

#13 #11 NOT#12

#14 #10 AND #13

Appendix 5. Web of Science search strategy

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

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

#3 #1 AND #2

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

#5 #3 AND #4

Appendix 6. Scopus search strategy

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

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

#3 #1 AND #2

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

#5 #3 AND #4

Appendix 7. Open Grey literature search strategy

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

Appendix 8. ClinicalTrials.gov search strategy

#1 Bladder Cancer

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

#3 1 AND 2

Appendix 9. WHO search strategy

#1 bladder cancer AND narrow band imaging

#2 bladder cancer AND NBI

#3 bladder cancer AND narrow-band imaging

#4 bladder cancer AND narrowband imaging

#5 1 OR 2 OR 3 OR 4

Appendix 10. LILACS search strategy

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

HISTORY

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CONTRIBUTIONS OF AUTHORS

1. Draft the protocol: LL, ST, EG, LH, PM, PD, GL
2. Study selection: n.a.
3. Extract data from studies: n.a.
4. Enter data into RevMan: n.a.
5. Carry out the analysis: n.a.
6. Interpret the analysis: n.a.
7. Disagreement resolution: n.a.

DECLARATIONS OF INTEREST

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