BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-028173
Article Type:	Research
Date Submitted by the Author:	25-Nov-2018
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Keywords:	bladder cancer, diagnostic performance, Narrow band imaging, photodynamic diagnosis, white light-guided cystoscopy

Diagnostic Accuracy of Image Technique Based Transurethral Resection for Non-muscle Invasive Bladder Cancer

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Abstract

Objective To explore diagnostic accuracy of image technique based transurethral resection for bladder cancer, with white light-guided cystoscopy (WLC) as reference standard.

Design Systematic review and meta-analysis.

Data sources PubMed/MEDLINE, Web of Science, the Cochrane Library, Central Register of Controlled Trials and Embase from inception through 31st March 2018.

Methods We included studies reporting diagnostic performance of PDD with 5-ALA, PDD with HAL, or NBI, with WLC as reference standard in patient or lesion level. Study risk of bias was assessed using the Quality Assessment of Diagnostic Studies-2 (QUADAS-2). We pooled data using random-effect diagnostic meta-analysis and relevant sensitivity analyses were undertaken.

Results: 26 studies recruiting a total of 3979 patients were identified in this diagnostic meta-analysis. Pooled sensitivity (SSY), specificity (SPY), diagnostic odds ratio (DOR) and area under the receiver operating characteristic curve (AUROC) values were calculated per groups of NBI, HAL and 5-ALA in lesions or patient level. NBI showed significant diagnostic superiority compared with WLC in lesion level (SSY 0.94, 95% CI, 0.82-0.98; SPY 0.79, 95% CI, 0.73-0.85; DOR 40.09, 95% CI, 20.08-80.01; AUROC 0.88, 95% CI, 0.85-0.91). The DOR for NBI showed highest (358.71, 95% CI, 44.50-2891.71) in patient level. Sensitivity analyses were performed on studies with low to moderate RoB and at least 100 patients at lesion level. These results showed consistency with those obtained in our overall analysis.

Conclusions Pooled data indicates image technique based transurethral resection (NBI, HAL and 5-ALA) show diagnostic superiority than WLC. Moreover, NBI could potentially be the most promising diagnostic intervention with best diagnostic accuracy outcomes. Novel Imaging technologies still need to compete with the diagnostic and prognostic outcome of WLC while offering advantages in terms of cost, and reliability.

Key words: bladder cancer, diagnostic performance, Narrow band imaging, photodynamic diagnosis, white light-guided cystoscopy

Strengths and limitations of this study

- This is the first systematic review and diagnostic meta-analysis exploring diagnostic accuracy of image technique based transurethral resection compared with WLC.
- Our study include the stringent methodology used to synthesize the evidence obtained, such as adhering to PRISMA guidelines, using standardized definitions of diagnostic performance analysis and applying QUADAS-2 tool for RoB assessment.
- The majority of studies had a low or moderate risk of bias. All studies clearly reported methodology for the index test and reference standard, and were not considered a significant source of potential bias.
- The further sensitivity analysis was based on relatively few studies, but we used random-effect models to compensate for clinical and methodological diversity among studies.
- The lack of data on important clinical variables, such as grade and stage of disease, primary vs recurrent disease and intravesical instillation settings, may introduce clinical heterogeneity and prevent further sensitivity analyses. We attempted to minimize biases by standardizing data extraction and performing several sensitivity analyses.

Introduction

Bladder cancer is a prevalent malignancy with an estimated 166,583 newly diagnosed cases and 58,742 deaths in Europe in 2012, among which about 75% of patients present with non-muscle invasive bladder cancer (NMIBC) [1-3]. Today, white light cystoscopy (WLC) is the gold-standard technique for detection of bladder cancer. However, the accuracy of WLC in detecting disease is unsatisfactory. The detection reliability of smaller tumors or carcinoma in situ (CIS) may be missed, which leads to that recurrence is remarkably common with up to 30% of patients having tumor identified at the first-check cystoscopy at 3 months and 50% of patients developing a recurrence within the first year [4 5]. Thus, different optical imaging techniques have emerged as an adjunct to WLC to improve visualization of tumors by means of contrast enhancement.

Photodynamic diagnosis (PDD) is performed using blue-violet (380-440nm) light after intravesical instillation of 5-aminolevulinic acid (5-ALA) or hexaminolevulinic acid (HAL). The effect of 5-ALA induced fluorescence on tumor detection in the urinary bladder has been assessed to be an efficient method of mapping the entire mucosa to detect urothelial tumors and flat CIS lesions [6-8]. HAL is the lipophilic hexylester of 5-ALA and has been commercially available since 2006, and has been established as the preferred intravesical agent for detection of NMIBC. However, intravesical inflammation compromised the specificity and priori instillation contributed technical complexity and cost.

Narrow band imaging (NBI) is a new image-processing modality filtering white light down to two narrow band widths of 415 and 540 nm with advantage of avoiding the need for intravesical contrast administration [9]. Hemoglobin absorbs these wavelengths preferentially, which results in dark neovascularized bladder cancer that strongly contrast with light background of normal mucosa to improve detection rates. The effectiveness of NBI for increasing tumor detection has been confirmed in several studies [10-12]. Overall, NBI yield a 9.9% increased detection rate on patient level and a 19.2% increase on lesion level in a recent meta-

analysis, while subgroup analysis showed NBI was associated with 53% reduction in recurrence rate at 3 months and 19% at 12months compared with WLC[13]. However, NBI may result in increased false-positives, especially for patients with prior intravesical instillations [14].

Although several studies demonstrated the diagnostic superiority of novel image technique-assisted transurethral resection. It is still uncertain that which technique could better improve diagnosis accuracy of bladder cancer detection. In this study, the specific objective was to perform a systematic review and diagnosis meta-analysis assessing the diagnostic performance of PDD using 5-ALA, PDD using HAL, and NBI against the reference standard of WLC for NMIBC.

Methods

The diagnostic meta-analysis was conducted based on the Meta-analysis of Observational Studies in Epidemiology statement[15]. When an included primary study did not match the Standards for Reporting of Diagnostic Accuracy statement, we gathered the information by the authors[16].

Literature search

All studies reporting the diagnostic performance of PDD with 5-ALA, PDD with HAL, or NBI, with WLC as reference standard, were retrieved from multiple databases including PubMed/MEDLINE, Web of Science, the Cochrane Library, Central Register of Controlled Trials and Embase up to 31st March 2018. The following MeSH free and combined terms which were adjusted for the different databases terms were used: “photodynamic diagnoses, PDD, hexaminolevulinate, HAL, 5-aminolevulinate acid, 5-ALA, narrow imaging, NBI, white light cystoscopy, bladder cancer, bladder tumor and BCa.” The review was performed according to Preferred Reporting Items for Systematic Reviews (PRISMA)[17] and Standards for Reporting Diagnostic Accuracy Studies (STARD)[18]. The search was restricted to English-language publications. At least two reviewers (CHC and HH) screened all abstracts and full-text articles independently. Disagreement

was resolved by consensus via discussion with an independent arbiter (JH).

Inclusion and exclusion criteria

Inclusion criteria included the following elements: 1) Population: Patients with suspected NMIBC in the primary setting (i.e. primary diagnosis), or patients with previously confirmed NMIBC undergoing surveillance (i.e. diagnosis of recurrent tumors); 2) Reference standard: All patients must have had WLC as the reference standard, with positive or negative cases being denoted by the presence or absence of NMIBC confirmed by histopathological examination; 3) Diagnostic performance should be compared in intra-patient groups. 4) Diagnostic performance outcomes: Diagnostic Odds Ratios (DOR) and Area Under the Receiver Operating Characteristic Curve (AUROC) in patient or lesion level. When two or more studies reported on a group of patients at the same institution during an overlapping time period, only the article with the latest data set was included, unless different outcomes were reported or different subgroup analyses were performed.

Articles were excluded if the full-text article was not written in English. Abstracts, conference articles, historical overviews, case studies, reviews, and meta-analysis were not considered. Studies that failed to report on sensitivity and/or specificity data as compared with WLC were excluded. For missing or unclear data, we contacted the authors to get more information.

Study Quality

The Quality Assessment of Diagnostic Studies-2 (QUADAS-2) [19] and the Strength Of Recommendation Taxonomy (SORT) numerical scale were applied on included studies[20]. Both checklist were performed independently by two authors (YZ and CHC); disagreement was resolved by discussion or with an independent arbiter (JH). We arbitrarily defined “low RoB” as at least 3 domains scoring “low” across both categories without any domains scoring “high” across either category; “moderate RoB” as at least 2 domains scoring “low” across both categories and without any domain scoring “high” across either

category; all other scoring patterns were defined as “high” RoB.

Data Extraction

The following data were extracted from the selected studies: 1) study characteristics (first author, study design, number of patients, follow-up); 2) intervention characteristics (index tests, duration of follow-up, schedule and nature of WLC); 3) patient characteristics (age, sex, NMIBC patients, tumor lesions, disease grade and stage, disease setting, duration of follow-up); 4) diagnostic performance measure (sensitivity: SSY; specificity: SPY; negative predictive value: NPV; positive predictive value: PPV; false positive rate: FPR; false negative rate: FNR). Data was extracted from each study at lesion or patient level to assess 5-ALA, HAL and NBI as the index test using WLC as the reference standard, with positive or negative disease as determined by histopathological examination.

The Primary outcomes of SSY, SPY, NPV, PPV, FPR and FNR for individual studies were calculated with the following standard definitions. SSY was defined as the proportion of index test-positive patients or lesions out of all cases of WLC-positive findings. SPY referred to the proportion of index test-negative patients or lesions out of all cases of WLC-negative findings. NPV was defined as the proportion of true negatives (i.e. negative index test and negative WLC) out of all index test-negative cases or lesions; PPV was defined as the proportion of true positives (i.e. positive index test and positive WLC) out of all index test-positive cases or lesions. FNR was defined as the proportion of index test-negative cases or lesions out of all cases of WLC-positive findings (i.e. 1 – SSY); FPR was defined as the proportion of index test-positive cases or lesions out of all cases of WLC-negative findings (i.e. 1 – SPY). FP cases or lesions referred to patients who had index test-positive findings whilst WLC found negative findings.

Statistical analysis

Separate meta-analyses were performed for the currently new technology-assisted cystoscopy in NMIBC patients to best summarize the totality of the available evidence. The pooled estimates for DOR and AUROC

with 95% confidence intervals (CIs) of the compared end points were used in our diagnostic meta-analysis. The AUROC is an overall summary measure index of the diagnostic accuracy. A perfect test will have an AUROC close to 1 and a poor test has AUROC close to 0.5[21]. We formulated forest plots of the summary measures of accuracy and examined the heterogeneity of the summary measures of sensitivity and specificity with a random effects model. The publication bias was assessed using Deeks' funnel plot, and statistical significance was determined with Deeks' asymmetry test[22 23]. A two-sided p value of less than 0.05 was considered significant. The diagnostic meta-analysis was performed using Stata 13.0 (StataCorp, College Station, TX, USA). Results were plotted on Summary Receiver Operating Curve (SROC) using RevMan 5.2 software. To explore the effect of heterogeneity on the results, sensitivity analyses were planned based on disease grade (low grade vs high grade), stage (pTa vs pT1), setting (primary vs recurrent tumours), number of participants (studies with n>100 patients only), and on studies with low to moderate RoB.

Results

Search and Study Selection

The flow diagram summarizing the literature screening and inclusion process is presented in Figure 1. Of the 652 potentially relevant articles identified in the database search, 271 studies were excluded for duplication. We excluded 278 studies when screening titles and abstracts: 32 editorials or letters, 24 reviews or meeting abstracts, 85 non-comparative studies and 137 papers on an obviously different topic. During the screening of 103 full-text articles, 36 studies were excluded for not being relevant to this review and another 41 studies were excluded for not having within-patient comparisons. Finally, 26 studies[12 24-48] were included in the diagnostic meta-analysis.

Study Demographics

The characteristics of the 26 studies included in this meta-analysis are summarized in Table 1. The

interventions were 5-ALA-based PDD in 9 studies, HAL-based PDD in 8 studies, and NBI in 9 studies. The studies were published from 1994 to 2016, and the sample size ranged from 12 to 605 participants, with a median sample size of 95.5. The mean or median age in the studies was quite similar. Likewise, the male/female ratio showed no differences. Most enrolled patients in included studies were NMIBC.

Lesion level analysis

All studies used non-standardized definitions to calculate their diagnostic outcomes, in which case the results of included studies were recalculated using standard definitions with the raw data provided (Supplementary Table 1). The diagnostic meta-analysis results were presented in lesion-level and patient-level analyses. Based on lesion level, the forest plot of estimates of DOR for NBI, HAL and 5-ALA compared with WLC were showed in Figure 2, the pooled DOR for NBI, HAL and 5-ALA were 40.09 (95% CI, 20.08-80.01, Figure 2A), 78.14 (95% CI, 31.42-194.28, Figure 2C) and 18.14 (95% CI, 4.28-76.87, Figure 2E). The SROC curves for NBI, HAL and 5-ALA were showed in Figure 3A, the AUROC of NBI, HAL and 5-ALA were 0.88 (95% CI, 0.85-0.91), 0.94 (95% CI, 0.92-0.96) and 0.82 (95% CI, 0.79-0.85). Importantly, the results of the SSY and SPY for each intervention are shown in Supplementary Figures 1-3. The pooled estimates for the SSY data for NBI, HAL and 5-ALA were 0.94 (95% CI, 0.82-0.98, Supplementary Figure 1A), 0.95 (95% CI, 0.91-0.98, Supplementary Figure 2A) and 0.90 (95% CI, 0.71-0.97, Supplementary Figure 3A), whereas the SPY data for NBI, HAL and 5-ALA were 0.79 (95% CI, 0.73-0.85, Supplementary Figure 1B), 0.81 (95% CI, 0.74-0.87, Supplementary Figure 2B) and 0.69 (95% CI, 0.57-0.79, Supplementary Figure 3B), presenting superiority compared with WLC. The DOR value and AUROC of NBI, HAL and 5-ALA presented excellent diagnostic performance.

Patient level analysis

As for patient level analysis, the AUROC, SSY and SPY could not be calculated as few studies included. Figure 2 showed the forest plots of DOR for NBI, HAL and 5-ALA. For NBI, the highest DOR

were reached. The DOR for NBI and HAL were 358.71 (95% CI, 44.50-2891.71, Figure 2B) and 59.95 (95% CI, 24.30-147.92, Figure 2D), present better performance compared with WLC. The SROC curves for NBI, HAL and 5-ALA were showed in Figure 3B. However, the DOR for 5-ALA was 79.52 (95% CI, 0.94-6759.92, Figure 2F), without statistic difference.

Sensitivity Analyses

Sensitivity analyses were performed on studies with low to moderate RoB and at least 100 patients at lesion level. The diagnostic performance results for studies with low to moderate RoB and at least 100 patients were demonstrated at Supplementary Table 2. The forest plot of estimates of pooled DOR for NBI, HAL and 5-ALA with low to moderate RoB were showed in Supplementary Figure 4; while forest plot of estimates of pooled DOR for NBI, HAL and 5-ALA with at least 100 patients were showed in Supplementary Figure 5. These results showed consistency with those obtained in our overall analysis.

RoB of included studies

The comparison-adjusted funnel plots of the diagnostic meta-analysis were not suggestive of any publication bias, showed in Figure 4. QUADAS-2 tool was applied for RoB assessment of included studies in our meta-analysis (Supplementary Figure 6). Overall, 69% (18/26) of the studies were judged as having low or unclear RoB across most domains. All studies clearly reported methodology for the index test and reference standard, and were not considered a significant source of potential bias. The risk of bias in the patient selection in 3 studies were deemed high due to the absence of consecutive inclusion of patients；4 studies were at high RoBs for the flow and timing.

Discussion

Our systematic review indicated that pooled diagnostic accuracy of NBI, HAL or 5-ALA showed excellent diagnostic performance compared with WLC. NBI could potentially be the most promising

diagnostic intervention for NMIBC patients with advantages in terms of simplicity, cost and reliability. In this study, we have summarized the diagnostic performance of new technique-assisted cystoscopy strategies for NMIBC. Our diagnostic meta-analysis was further undertaken to estimate diagnostic performance of NBI, HAL and 5-ALA compared with WLC. Since virtually all of the techniques assessed in this review based on the reference standard of WLC, new technique-assisted cystoscopy showed diagnostic superiority than conventional WLC. In this context, adoption of these strategies in bladder cancer diagnosis practice is essential. The present results do strongly suggest that new imaging-based technologies, in particular NBI, are promising diagnostic intervention for bladder cancer detection in clinical practice.

PDD and NBI both aim at improving the visualization of bladder tumors. Several studies [12 49 50] have shown the superiority of PDD or NBI over WLC alone in tumor detection. Further meta-analysis enrolling 2807 patients found a 21% increase in tumor detection with PDD over WLC in the pooled estimates for patients and biopsies[51]. NBI, another optical enhancement technology, improve diagnostic accuracy by increasing contrast of superficial vasculature between normal mucosa and tumor tissue. Previous studies reported significant detection improvement in bladder tumors with NBI cystoscopy compared with standard WLC [12 14]. Our former meta-analysis indicated that NBI provides an additional 17% of patients and an additional 24% of tumors compared with WLC [52]. However, these studies did not use standardized diagnostic accuracy definitions. Our diagnostic meta-analysis applied standard diagnostic accuracy definitions and further pooled estimates demonstrated new technique assisted cystoscopy showed significant diagnostic superiority than conventional WLC, demonstrating the sub-optimal performance of WLC in diagnosing NMIBC.

Study performed by Burger [53] showed that PDD using HAL significantly reduced recurrence rate at 9–12 months compared with WLC-assisted TUR alone. Also, Lee et al performed a meta-analysis[54] evaluating

oncologic outcomes for WLC, PDD- and NBI-assisted TUR, which showed both PDD and NBI reduced recurrence rate compared with WLC. However, therapeutic effectiveness of new technique assisted TUR such as recurrence and progression could not be demonstrated in this review. Future therapeutic efficacy analysis was needed to identify promising intervention.

The strengths of our study include the stringent methodology used to synthesize the evidence obtained, such as adhering to PRISMA guidelines, using standardized definitions of diagnostic performance analysis and applying QUADAS-2 tool for RoB assessment. Moreover, the strict diagnostic meta-analysis and further sensitivity analysis was applied to synthesize diagnostic accuracy for reliable result. However, potential study limitations should be acknowledged. Any biases and inaccuracies within individual studies would be reflected in our analysis. The lack of data on important clinical variables, such as grade and stage of disease, primary vs recurrent disease and intravesical instillation settings, may introduce clinical heterogeneity and prevent further sensitivity analyses. However, we have attempted to minimize biases by applying rigorous selection criteria during the design phase of our study, standardizing data extraction and performing several sensitivity analyses to evaluate the robustness of our findings.

In summary, this meta-analysis provides pooled diagnostic accuracy for NBI, HAL and 5-ALA techniques for NMIBC patients compared with WLC as a reference standard. The results demonstrate that the diagnostic accuracy of NBI, HAL and 5-ALA all superiority than WLC at lesion level in diagnostic meta-analysis. The findings confirm the excellent diagnostic performance of these new imaging-based technologies in diagnosing NMIBC in comparison with the present standard using WLC, although well-designed prospective studies with long-term follow-up may shed more light on their impact on diagnostic and prognostic outcomes.

Abbreviations CI: Confidence intervals; CIS: carcinoma in situ; DOR: Diagnostic odds ratios; DTA: Diagnostic test accuracy; FNR: False negative rate; FPR: False positive rate; IQR: Interquartile range; HAL:

hexylaminolevulinate; NBI: and narrow band imaging; NMIBC: Non-muscle-invasive bladder cancer; NPV: Negative predictive value; PDD: Photodynamic diagnosis; PPV: Positive predictive value; SPY: Specificity; SSY: Sensitivity; SROC: Summary receiver operating curve; AUROC: Area under the receiver operating characteristic curve; TURBT: Transurethral resection of bladder tumors; WLC: White light cystoscopy; 5-ALA: 5-aminolaevulinic acid.

Acknowledgements We would like to thank Prof. J.X. Zhang, Department of Medical Statistics and Epidemiology, School of Public Health, Sun Yat-Sen University, Guangzhou, China, for statistical advice and research comments.

Contributors CHC conceptualized and designed the study, drafted the initial and final manuscript, provided funding support. HH contributed to data collection and extraction, data analysis and interpretation, drafted initial and final manuscript. YZ contributed to article screening, data collection and extraction, assessment of risk of bias and drafting manuscript: HL contributed to article screening, data collection and extraction and assessment of risk of bias. RJ Sylvester led and supervised statistical analysis, provided administrative support. TXL and JH contributed to study conceptualization and design, supervised study implementation, and critically reviewed the manuscript.

Funding This study was funded by the National Natural Science Foundation of China (Grant No. 81572514,81472384, 81472381, 81402106, 81772719, 81772728, 91740119, 91529301); Guangdong Medical Research Fund (A2018330); Science and Technology Program of Guangzhou (Grant No. 201604020156, 201604020177, 201707010116, 201803010098); National Natural Science Foundation of Guangdong (Grant No. 2018A030313564, 2018B030311009, 2018A030310250,2016A030313321, 2015A030311011, 2015A030310122). Yixian Youth project of Sun Yat-sen Memorial Hospital

(YXQH201812).

Competing interests None declared.

Patient consent Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement There are no additional data available.

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Figure legend

Figure 1. The PRISMA flow chart of included studies in DTA analysis.

Figure 2. The Forest Plot of estimates of DOR for NBI (A), HAL (C), 5-ALA (E) in lesion level and estimates of DOR for NBI (B), HAL (D), 5-ALA (F) in patient level.

Figure 3. The SROC curve for NBI, HAL and 5-ALA diagnosing NMIBC in lesion level (A) and patient level (B).

Figure 4. Deeks' funnel plot with asymmetry test for NBI (A), HAL (B) and 5-ALA (C) in lesion level.

Table 1 Summary of the characteristics of the included studies

Study	Institution No.	patients	Index test	period	Age, mean (range)	Male (%)	NMIBC (%)	Tumor lesions (n)
Shadpour et al.2016[29]	Unicentre	50	NBI	2012-2013	63.86 ± 10.05	34(68.0)	100	95
Song et al.2016[27]	Unicentre	63	NBI	2012-2013	66(56-76)	39(61.9)	94.1	21
Kobotake et Al.2015[35]	Unicentre	135	NBI	2010-2014	75	110(81.5)	100	120
Ye et al.2015[12]	Multicentre	384	NBI	NR	61(21-79)	267(69.5)	100	167
Shen et al.2012[28]	Unicentre	78	NBI	2009-2010	68 (33–75)	62(79.5)	100	211
Zhu et al. 2012[24]	Unicentre	12	NBI	2009-2010	57(28-73)	9(75.0)	100	9
Tatsugami et Al.2010[26]	Unicentre	104	NBI	2007-2009	70.6 (38-90)	88(84.6)	NR	110
Cauberg et Al.2009[47]	Multicentre	95	NBI	2007-2009	70.6 (38.1-90.2)	70(73.7)	NR	226
Herr et Al.2008[38]	Unicentre	427	NBI	2007	65 (26-90)	316(74.0)	100	NR
Palou et Al.2014[33]	Multicentre	283	HAL	2008-2009	67.5(42-95)	242(85.5)	94.1	621
Lapini et Al.2012[34]	Multicentre	96	HAL	2010-2011	NR	80(83.3)	NR	108
Burgues et Al.2011[55]	Multicentre	305	HAL	2006-2009	66.9(39-93)	270(88.5)	100	600
Ray et al.2010[32]	Unicentre	27	HAL	2005-2006	70(49-82)	21(77.8)	100	NR
Schmidbauer et al.2009[30]	Unicentre	66	HAL	NR	63(38-84)	49(74.2)	93.1	NR
Geavlete et Al.2008[40]	Unicentre	128	HAL	2007-2008	65(36-81)	NR	92.2	NR
Fradet et Al.2006[41]	Multicentre	298	HAL	NR	67±11	223(74.8)	100	113
Jichlinski et Al.2003[36]	Multicentre	52	HAL	2000-2001	72±12	38(73.1)	100	143
Grimbergen et Al.2003[6]	Unicentre	160	5-ALA	1998-2002	67(30-91)	NR	90.0%	390
Filbeck et Al.2002[43]	Unicentre	279	5-ALA	1997-2000	34-89	NR	90.3%	336
Dominicis et	Unicentre	49	5-ALA	NR	60(31-77)	42(85.7)	100	52

Al.2001[45]								
Ehsan et	Unicentre	30	5-ALA	NR	55-89	19(63.3)	NR	NR
Al.2001[44]								
Jeon at	Unicentre	62	5-ALA	1997-1999	61.9(32-80)	57(91.1)	NR	148
Al.2001[37]								
Zaak et	Unicentre	605	5-ALA	NR	65.6(16-99)	472(78.0)	NR	552
Al.2001[25]								
Filbeck et	Unicentre	123	5-ALA	1997	64.5(28-86)	NR	91.9	124
Al.1999[42]								
Riedl et	Unicentre	52	5-ALA	NR	44-79	NR	100	123
Al.1999[31]								
D'hallewin et	Unicentre	16	5-ALA	NR	NR	NR	100	50
Al.1998[46]								

WLC: white light cystoscopy; NT: new technology; 5-ALA: 5-aminolaevulinic acid; HAL: hexylaminolevulinate; NBI: narrow band imaging; NR: not reported.

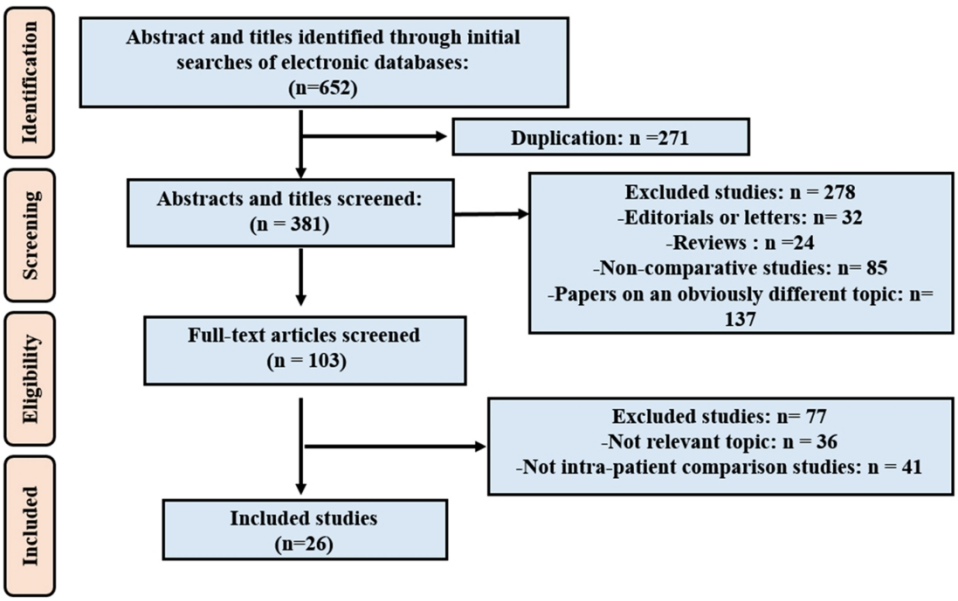

Figure 1. The PRISMA flow chart of included studies in DTA analysis.

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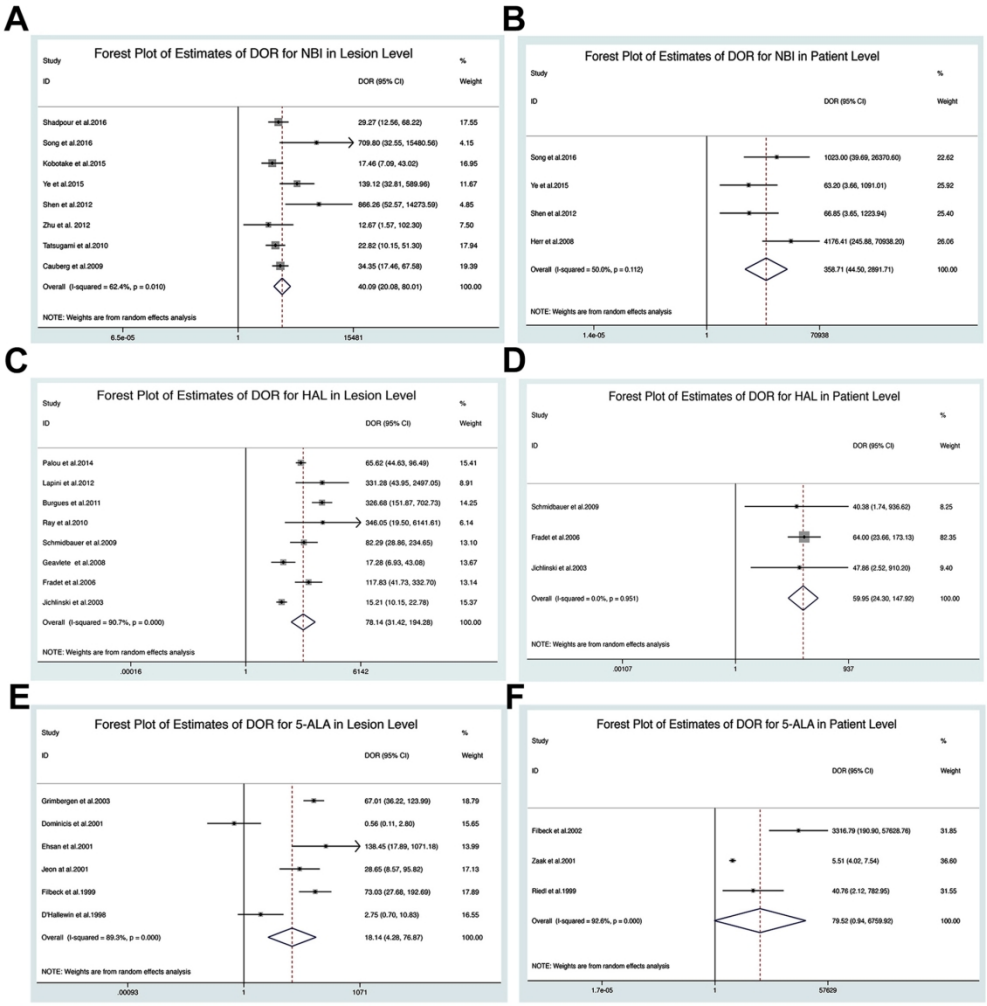

Figure 2. The Forest Plot of estimates of DOR for NBI (A), HAL (C), 5-ALA (E) in lesion level and estimates of DOR for NBI (B), HAL (D), 5-ALA (F) in patient level.

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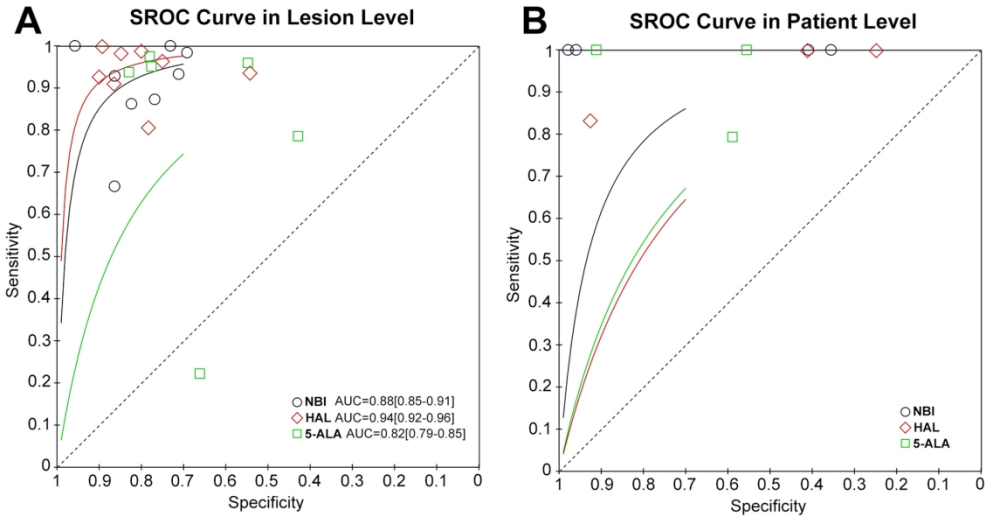

Figure 3. The SROC curve for NBI, HAL and 5-ALA diagnosing NMIBC in lesion level (A) and patient level (B).

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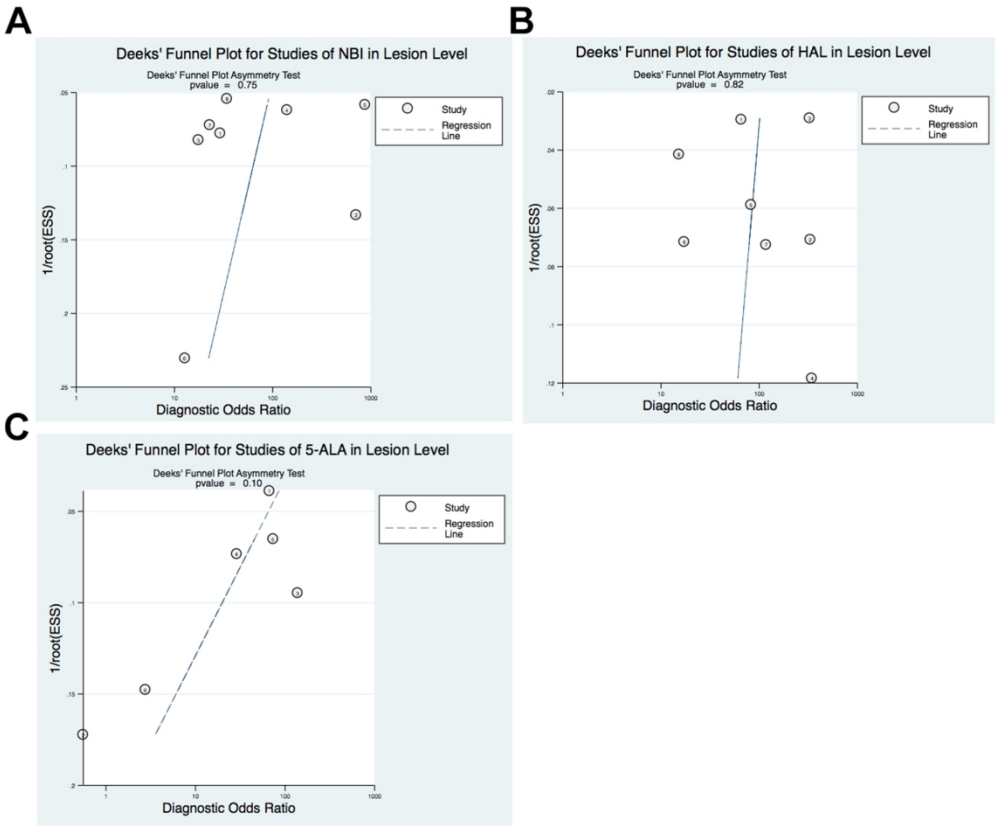
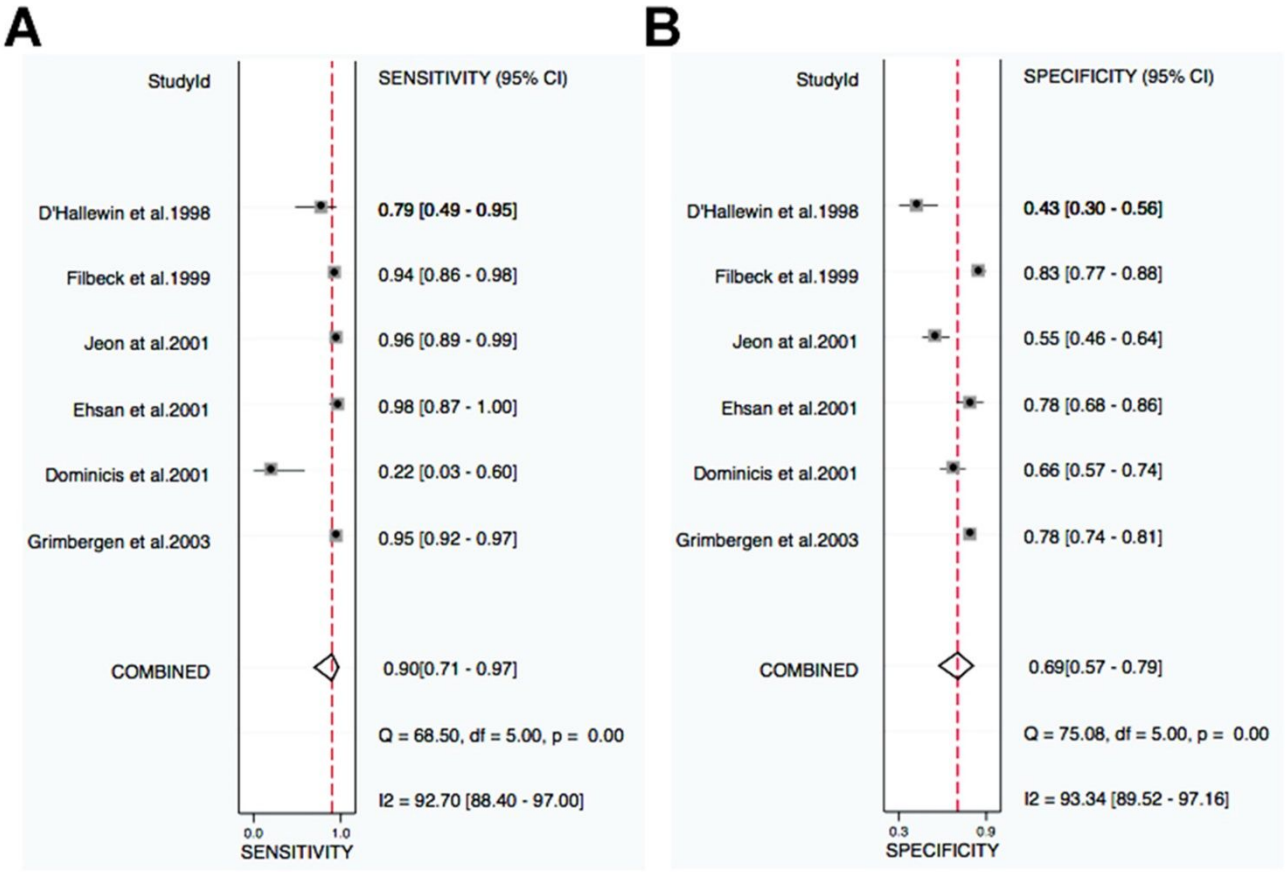


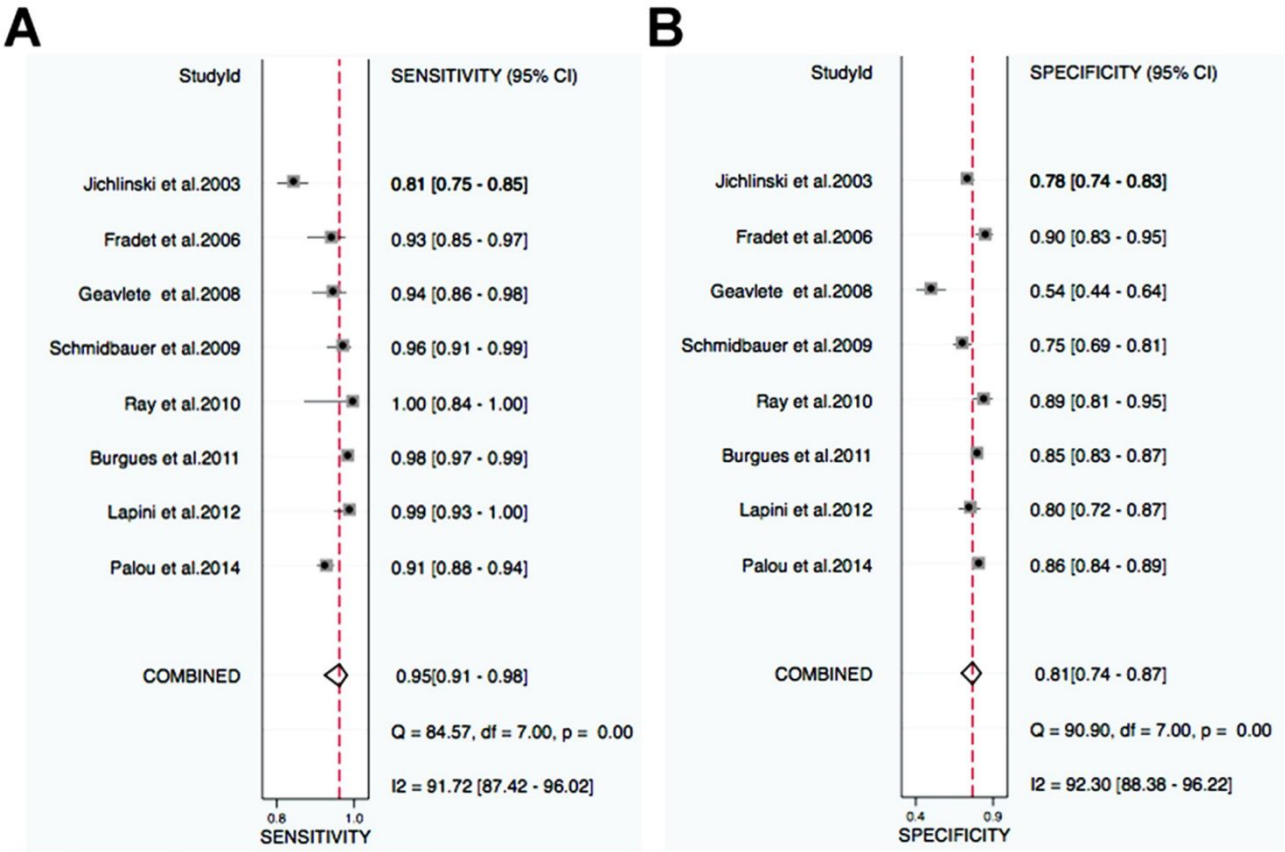
Figure 4. Deeks' funnel plot with asymmetry test for NBI (A), HAL (B) and 5-ALA (C) in lesion level.

177x147mm (300 x 300 DPI)

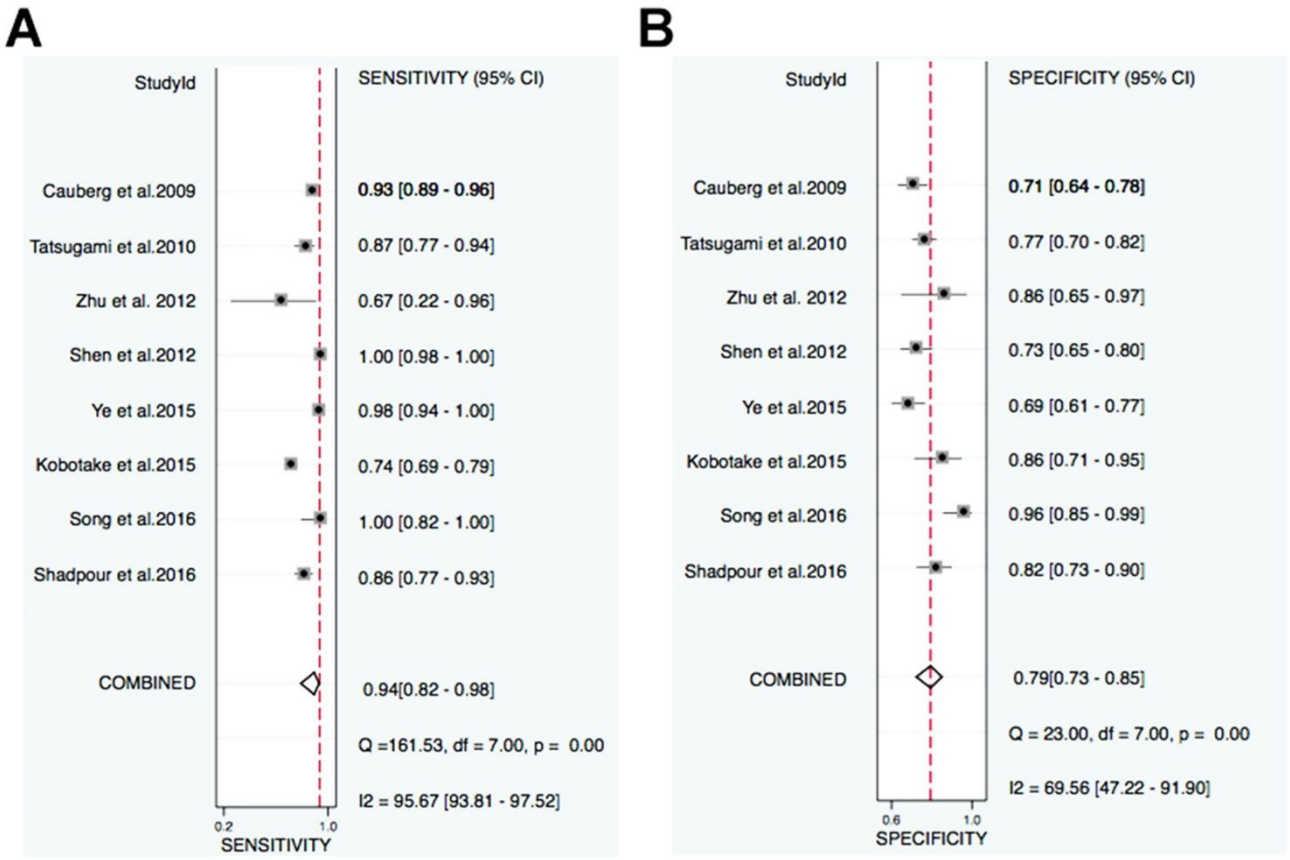
Supplementary Information



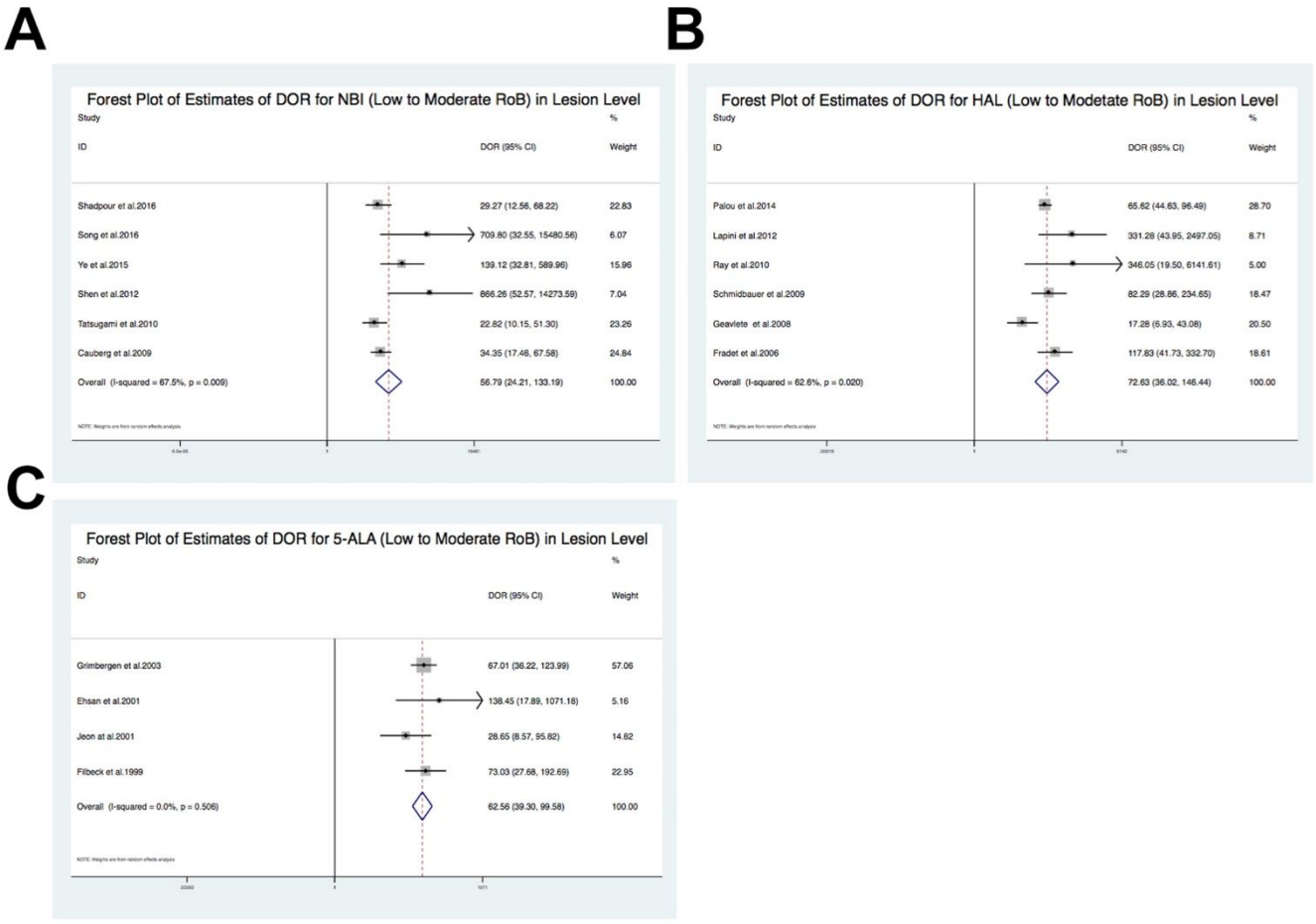
Supplementary Figure 1. The Forest Plot of study specific and pooled sensitivity (A) and specificity (B) for NBI in lesion level.



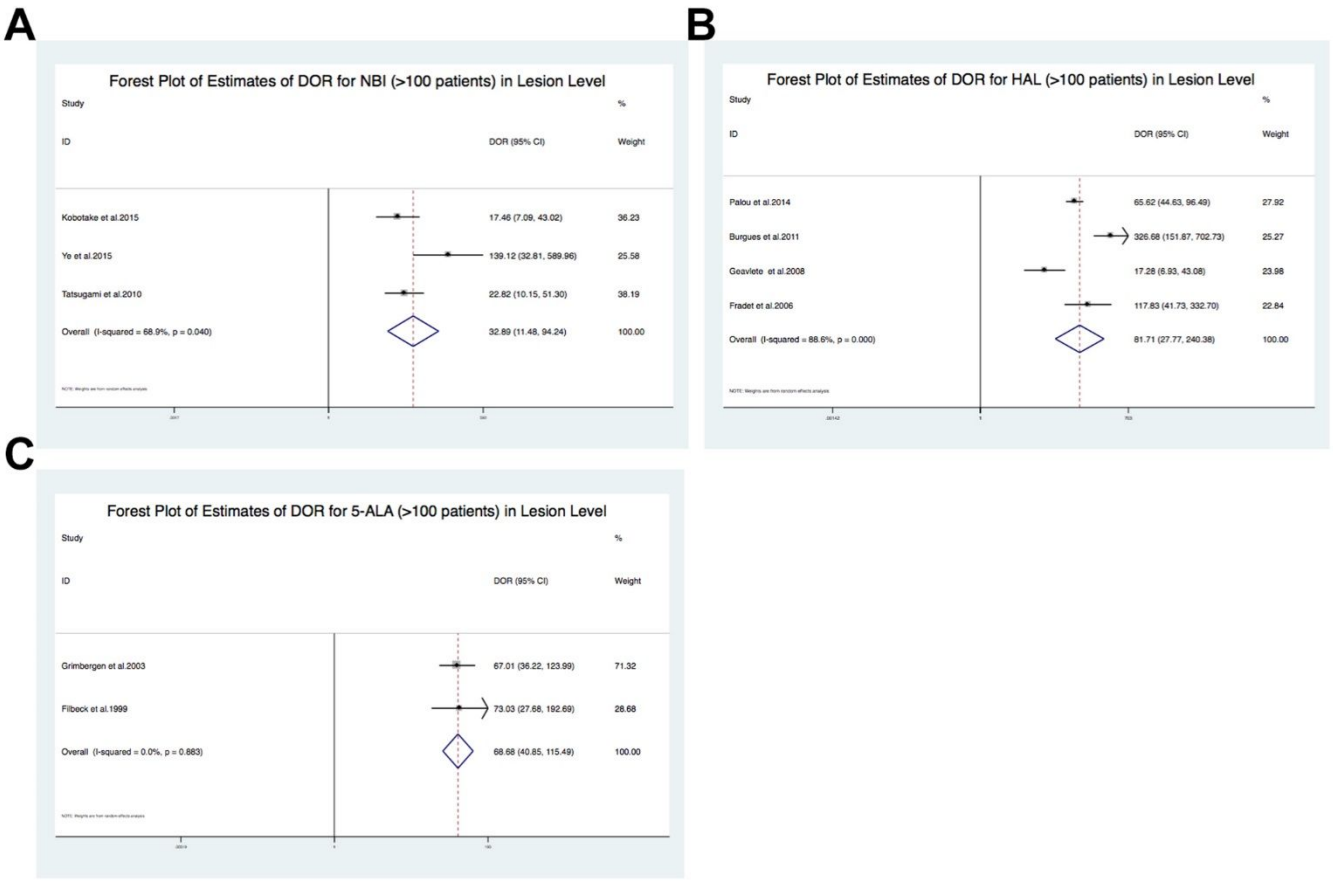
Supplementary Figure 2. The Forest Plot of study specific and pooled sensitivity (A) and specificity (B) for HAL in lesion level.



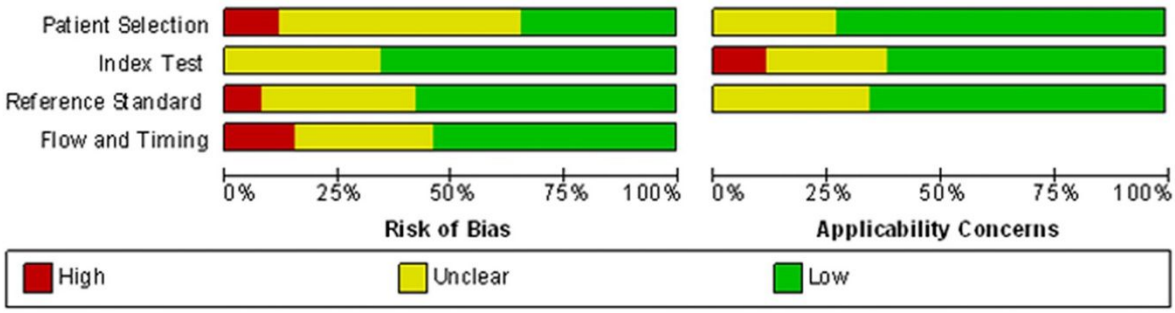
Supplementary Figure 3. The Forest Plot of study specific and pooled sensitivity (A) and specificity (B) for 5-ALA in lesion level.



Supplementary Figure 4. The Forest Plot of estimates of DOR for NBI (A), HAL (B) and 5-ALA (C) with low to moderate RoB in lesion level.



Supplementary Figure 5. The Forest Plot of estimates of DOR for NBI (A), HAL (B) and 5-ALA (C) with at least 100 patients in lesion level.



Supplementary Figure 6. Quality assessment of included studies. The distribution plot for risk of bias using QUADAS-2 tool. Studies are deemed to be at high, low or unclear risk of bias for each domain.

Supplementary Table1. Diagnostic performance results of individual studies for Meta-analysis

Study ID	Patient-level analysis							Lesion-level analysis						
	Patient No.	SSY	SPY	FPR	FNR	PPV	NPV	Lesion No.	SSY	SPY	FPR	FNR	PPV	NPV
NBI vs WLC														
Shadpour et al.2016[1]	50	NR	NR	NR	NR	NR	NR	175	69/80	70/85	15/85	11/80	69/84	74/75
Song et al.2016[2]	63	16/16	46/47	1/47	0/16	16/17	23/23	66	19/19	45/47	2/47	0/19	19/21	7/7
Kobotake et al.2015[3]	135	NR	NR	NR	NR	NR	NR	379	78/84	227/263	36/263	6/84	78/114	203/203
Ye et al.2015[4]	103	56/56	16/45	29/46	0/56	56/85	8/8	300	124/126	92/133	41/133	2/126	124/165	83/85
Shen et al.2012[5]	78	47/47	9/22	13/22	0/47	47/47	7/7	309	160/160	98/134	36/134	0/160	160/196	72/72
Zhu et al. 2012[6]	12	NR	NR	NR	NR	NR	NR	31	4/6	19/22	3/22	2/6	4/7	20/20
Tatsugami et al.2010[7]	104	NR	NR	NR	NR	NR	NR	313	55/63	156/203	47/203	8/63	55/102	144/144
Cauberg et al.2009[8]	95	NR	NR	NR	NR	NR	NR	389	167/179	116/163	47/163	12/179	167/214	47/51
Herr et al.2008[9]	427	90/90	311/324	13/324	0/90	90/103	265/265	NR	NR	NR	NR	NR	NR	NR
HAL vs WLC														
Palou et al.2014[10]	283	NR	NR	NR	NR	NR	NR	1492	379/416	820/948	128/948	37/416	379/507	699/702
Lapini et al.2012[11]	96	NR	NR	NR	NR	NR	NR	234	82/83	101/126	25/126	1/83	82/107	80/81
Burgues et al.2011[12]	305	NR	NR	NR	NR	NR	NR	1659	404/441	900/1059	159/1059	7/441	404/563	863/863

Ray et al.2010[13]	27	NR	NR	NR	NR	NR	NR	120	21/21	84/94	10/94	0/21	21/31	35/35
Schmidbauer et al.2009[14]	66	52/52	2/8	6/8	0/52	52/58	3/3	364	109/113	151/201	50/201	4/113	109/159	158/158
Geavlete et al.2008[15]	128	NR	NR	NR	NR	NR	NR	243	87/93	56/103	47/103	6/93	87/134	76/82
Fradet et al.2006[16]	196	40/48	128/138	10/138	8/48	40/50	106/113	206	77/83	101/112	11/112	6/83	77/88	63/71
Jichlinski et al.2003[17]	52	33/33	7/17	10/17	0/33	33/43	3/3	143	205/254	269/343	74/343	49/254	205/279	306/314
5-ALA vs WLC														
Grimbergen et al.2003[18]	160	NR	NR	NR	NR	NR	NR	889	232/244	409/527	118/527	12/244	232/350	248/257
Filbeck et al.2002[19]	279	168/168	93/102	9/102	0/168	168/177	81/81	NR	NR	NR	NR	NR	NR	NR
Dominicis et al.2001[20]	49	NR	NR	NR	NR	NR	NR	179	2/9	84/127	43/127	7/9	2/45	80/80
Ehsan et al.2001[21]	30	NR	NR	NR	NR	NR	NR	151	39/40	71/91	20/91	1/40	39/59	59/59
Jeon at al.2001[22]	62	NR	NR	NR	NR	NR	NR	257	71/74	69/126	57/126	3/74	71/128	54/54
Zaak et al.2001[23]	605	288/363	271/460	189/460	75/363	288/477	55/108	NR	NR	NR	NR	NR	NR	NR
Filbeck et	123	NR	NR	NR	NR	NR	NR	341	75/80	185/223	38/223	5/80	75/113	78/78

al.1999[24]														
Riedl et al.1999[25]	52	26/26	10/18	8/18	0/26	26/34	6/6	NR	NR	NR	NR	NR	NR	NR
D'Hallewin et al.1998[26]	16	NR	NR	NR	NR	NR	NR	113	11/14	27/63	36/63	3/14	11/47	34/34

NMIBC: non-muscle-invasive bladder cancer; WLC: white light cystoscopy; 5-ALA: 5-aminolaevulinic acid; HAL: hexylaminolevulinate; NBI: narrow band imaging; NT: new technology; SSY: sensitivity; SPY: specificity; FPR: false positive rate; FNR: false negative rate; PPV: positive predictive value; NPV: negative predictive value; NR: not reported.

Supplementary Table2. Diagnostic performance results for sensitivity analysis of studies with low to moderate RoB and at least 100 patients at lesion level.

	Low to moderate RoB			At least 100 patients		
	Median	**Lower Quartile**	**Upper Quartile**	**Median**	**Lower Quartile**	**Upper Quartile**
NBI vs WLC (n=6)				**NBI vs WLC (n=3)**		
Sensitivity	95.85	88.80	99.60	92.86	90.08	95.63
Specificity	74.99	71.66	80.98	76.85	73.01	81.58
Positive predictive value	79.84	75.87	82.02	68.42	61.17	71.79
Negative predictive value	99.33	97.90	100	100	98.82	100
False positive rate	25.01	19.02	28.34	23.15	18.42	26.99
False negative rate	4.15	0.40	11.20	7.14	4.37	9.92
HAL vs WLC (n=6)				**HAL vs WLC (n=4)**		
Sensitivity	95.00	92.97	98.21	92.19	91.48	92.97
Specificity	83.33	76.38	88.65	85.74	77.33	87.42
Positive predictive value	71.65	67.94	76.16	73.26	70.05	77.94
Negative predictive value	99.17	94.20	99.89	96.13	91.70	99.68
False positive rate	16.67	11.35	23.62	14.26	12.58	22.67
False negative rate	5.00	1.79	7.03	6.84	5.24	7.65
5-ALA vs WLC (n=4)				**5-ALA vs WLC (n=2)**		
Sensitivity	95.51	94.75	96.33	94.42	-	-
Specificity	77.82	71.90	79.26	80.28	-	-
Positive predictive value	66.19	63.44	66.31	66.33	-	-
Negative predictive value	100	99.12	100	98.25	-	-
False positive rate	22.18	20.74	28.10	19.72	-	-
False negative rate	4.49	3.67	5.25	5.58	-	-

NMIBC: non-muscle-invasive bladder cancer; WLC: white light cystoscopy; 5-ALA: 5-aminolaevulinic acid; HAL: hexylaminolevulinate; NBI: narrow band imaging; NR: not reported.

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title page
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	None
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7-8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Figure1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8-9
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	9-10

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	10
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	11
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	11
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Supplementary Figure 6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Supplementary Table 1
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	11-12
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	13
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	12
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14-15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15-16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	17-18

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doi:10.1371/journal.pmed1000097

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Diagnostic Performance of Image Technique Based Transurethral Resection for Non-muscle Invasive Bladder Cancer: Systematic Review and Diagnostic Meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-028173.R1
Article Type:	Original research
Date Submitted by the Author:	06-Aug-2019
Complete List of Authors:	Chen, Changhao; Sun Yat-Sen Memorial Hospital, Department of Urology Huang, Hao; Sun Yat-Sen Memorial Hospital, Department of Urology Zhao, Yue; the First Affiliated Hospital of Sun Yat-Sen University, Department of Gastroenterology Liu, Hao; Chengdu Fifth People's Hospital, Department of Urology Sylvester, Richard; EAU Guidelines Office, Brussels Lin, Tianxin; Sun Yat-Sen Memorial Hospital, Department of Urology Huang, Jian; Sun Yat-Sen Memorial Hospital, Department of Urology
Primary Subject Heading:	Urology
Secondary Subject Heading:	Diagnostics
Keywords:	bladder cancer, diagnostic performance, Narrow band imaging, photodynamic diagnosis, white light-guided cystoscopy

Diagnostic Performance of Image Technique Based Transurethral Resection for Non-muscle Invasive Bladder Cancer: Systematic Review and Diagnostic Meta-analysis

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Abstract

Objective To explore diagnostic performance of image technique based transurethral resection for bladder cancer, with white light-guided cystoscopy (WLC) as reference standard.

Design Systematic review and meta-analysis.

Data sources PubMed/MEDLINE, Web of Science, the Cochrane Library, Central Register of Controlled Trials and Embase from inception through 31st March 2018.

Methods We included studies reporting diagnostic performance of PDD with 5-ALA, PDD with HAL, or NBI, with WLC as reference standard in patient or lesion level. Study risk of bias was assessed using the Quality Assessment of Diagnostic Studies-2 (QUADAS-2). We pooled data using random-effect diagnostic meta-analysis and relevant subgroup analyses were undertaken.

Results: 26 studies recruiting a total of 3979 patients were enrolled in this diagnostic meta-analysis. Pooled sensitivity (SSY), specificity (SPY), diagnostic odds ratio (DOR) and area under the receiver operating characteristic curve (AUROC) values were calculated per groups of NBI, HAL and 5-ALA in lesions or patient level. NBI showed significant diagnostic superiority compared with WLC in lesion level (SSY 0.94, 95% CI, 0.82-0.98; SPY 0.79, 95% CI, 0.73-0.85; DOR 40.09, 95% CI, 20.08-80.01; AUROC 0.88, 95% CI, 0.85-0.91). NBI presented highest DOR (358.71, 95% CI, 44.50-2891.71) in patient level. Subgroup analyses were performed on studies with low to moderate RoB and at least 100 patients at lesion level. These results showed consistency with those obtained in our overall analysis.

Conclusions Pooled data indicates image technique based transurethral resection (NBI, HAL and 5-ALA) show diagnostic superiority than WLC. Moreover, NBI could potentially be the most promising diagnostic intervention with best diagnostic performance outcomes. It is still needed to evaluate diagnostic and prognostic outcome of novel imaging technologies and WLC.

Key words: bladder cancer, diagnostic performance, Narrow band imaging, photodynamic diagnosis, white light-guided cystoscopy

Strengths and limitations of this study

- This is the first systematic review and diagnostic meta-analysis exploring diagnostic accuracy of image technique based transurethral resection compared with WLC.
- Our study includes the stringent methodology used to synthesize the evidence obtained, such as adhering to PRISMA guidelines, using standardized definitions of diagnostic performance analysis and applying QUADAS-2 tool for RoB assessment.
- The majority of studies had a low or moderate risk of bias. All studies clearly reported methodology for the index test and reference standard, and were not considered a significant source of potential bias.
- The further subgroup analysis was based on relatively few studies, but we used random-effect models to compensate for clinical and methodological diversity among studies.
- The lack of data on important clinical variables, such as grade and stage of disease, primary vs recurrent disease and intravesical instillation settings, may introduce clinical heterogeneity and prevent further subgroup analyses. We attempted to minimize biases by standardizing data extraction and performing several subgroup analyses.

Introduction

Bladder cancer is a prevalent malignancy with an estimated 80,470 newly diagnosed cases and 17,670 deaths in USA in 2019, among which about 75% of patients present with non-muscle invasive bladder cancer (NMIBC) [1-3]. Today, white light cystoscopy (WLC) is the gold-standard technique for detection of bladder cancer. However, the accuracy of WLC in detecting disease is unsatisfactory. The detection reliability of smaller tumors or carcinoma in situ (CIS) may be missed, which leads to that recurrence is remarkably common with up to 30% of patients having tumor identified at the first-check cystoscopy at 3 months and 50% of patients developing tumors within 12 months [4 5]. Thus, different optical imaging techniques have emerged as an adjunct to WLC to improve visualization of tumors by means of contrast enhancement.

Photodynamic diagnosis (PDD) is performed using blue-violet (380-440nm) light with intravesical instillation of 5-aminolevulinic acid (5-ALA) or hexaminolevulinic acid (HAL). The effect of 5-ALA induced fluorescence on tumor detection in the urinary bladder has been identified to be an efficient method of mapping the entire mucosa to detect urothelial tumors and flat CIS lesions [6-8]. HAL is the lipophilic hexylester of 5-ALA and has been commercially available since 2006, which has been established as the preferred intravesical agent for detection of NMIBC. However, intravesical inflammation leads to decreased specificity and pre-operative procedure contributed technical complexity and cost.

Narrow band imaging (NBI) is a new image-processing modality filtering white light down to two narrow band widths of 415 and 540 nm with advantage of avoiding the need for intravesical contrast administration [9]. Hemoglobin absorbs these wavelengths preferentially, which results in dark neovascularized bladder cancer strongly different from light background of normal mucosa. The superior diagnostic performance of NBI compared with WLC has been confirmed in several studies [10-12]. Overall, NBI yield a 9.9% increased detection rate on patient level and a 19.2% increase on lesion level in a recent meta-analysis, while subgroup

analysis showed NBI was associated with 53% reduction in recurrence rate at 3 months and 19% at 12months compared with WLC[13]. Noticeably, NBI may be associated with increased false-positives, especially for patients with prior intravesical instillations [14].

Although several studies demonstrated the diagnostic superiority of novel image technique-assisted transurethral resection. It is still uncertain which technique could better improve diagnosis accuracy of bladder cancer detection. In this study, the specific objective was to perform a systematic review and diagnosis meta-analysis assessing the diagnostic performance of PDD using 5-ALA, PDD using HAL, and NBI against the reference standard of WLC for NMIBC.

Methods

The diagnostic meta-analysis was conducted based on the Meta-analysis of Observational Studies in Epidemiology statement[15]. All included studies were observational studies. When an included primary study did not match the Standards for Reporting of Diagnostic Accuracy statement, we gathered the information by the authors[16].

Literature search

All studies reporting the diagnostic performance of PDD with 5-ALA, PDD with HAL, or NBI, with WLC as reference standard, were retrieved from multiple databases including PubMed/MEDLINE, Web of Science, the Cochrane Library, Central Register of Controlled Trials and Embase up to 31st March 2018. The following MeSH free and combined terms which were adjusted for the different databases terms were used: “photodynamic diagnosis, PDD, hexaminolevulinate, HAL, 5-aminolevulinate acid, 5-ALA, narrow imaging, NBI, white light cystoscopy, urothelial cell carcinoma of bladder, transitional cell carcinoma, bladder cancer, bladder tumor and BCa”. The full search strategy was showed in Appendix (supplementary material). The review was performed according to Preferred Reporting Items for Systematic Reviews

(PRISMA)[17] and Standards for Reporting Diagnostic Accuracy Studies (STARD)[18]. The search was restricted to English-language publications. At least two reviewers (CHC and HH) screened all abstracts and full-text articles independently. Disagreement was resolved by consultation with an independent arbiter (JH).

Inclusion and exclusion criteria

Inclusion criteria included the following elements: 1) Population: Patients diagnosed with primary NMIBC, or patients previously diagnosed with NMIBC (recurrent tumors); 2) Reference standard: WLC must be provided as the reference standard for all patients, and the diagnosis of NMIBC was confirmed by histopathological examination; 3) studies reported data of intra-patient comparison. 4) Only the updated data was included in this study, when two or more studies provided data from the same institution during an overlapping time period.

Articles were excluded if the full-text article was not written in English. Abstracts, conference articles, historical overviews, case studies, reviews, and meta-analysis were not considered. Studies that failed to report on sensitivity and/or specificity data as compared with WLC were excluded. For missing or unclear data, we contacted the authors to get more information.

Patient and Public Involvement

Patients and public were not involved in this research.

Study Quality

The Quality Assessment of Diagnostic Studies-2 (QUADAS-2) [19] and the Strength Of Recommendation Taxonomy (SORT) numerical scale were applied on included studies[20]. Both checklists were performed independently by two authors (YZ and CHC); disagreement was resolved by consultation with an independent arbiter (JH). The “low RoB” was defined as at least 3 domains with “low” in both categories and without any domains evaluated “high” in either category; the “moderate RoB” was defined as

at least 2 domains with "low" in both categories and without any domain scoring "high" in either category; in addition to this was defined as "high" RoB.

Data Extraction

The following data were extracted from the selected studies: 1) study characteristics (first author, study design, number of patients, follow-up); 2) intervention characteristics (index tests, duration of follow-up, schedule and nature of WLC); 3) patient characteristics (age, sex, NMIBC patients, tumor lesions); 4) diagnostic performance measure (sensitivity: SSY; specificity: SPY; negative predictive value: NPV; positive predictive value: PPV; false positive rate: FPR; false negative rate: FNR). Data was extracted from each study at lesion or patient level to assess 5-ALA, HAL and NBI as the index test using WLC as the reference standard, with positive or negative disease as determined by histopathological examination.

The Primary outcomes of SSY, SPY, NPV, PPV, FPR and FNR for individual studies were calculated with the following standard definitions. SSY was defined as the proportion of positive patients or lesions with index test in all cases of WLC-positive findings. SPY was defined as the proportion of negative patients or lesions with index test in all cases of WLC-negative findings. NPV was defined as the proportion of true negatives findings (both negative in index test and WLC) in all index test-negative cases or lesions; PPV was defined as the proportion of true positives findings (both positive in index test and WLC) in all index test-positive cases or lesions. FNR was defined as the proportion of index test-negative findings in all cases of WLC-positive cases or lesions; FPR was defined as the proportion of index test-positive findings in all cases of WLC-negative cases or lesions.

Statistical analysis

Separate meta-analyses were performed for the currently new technology-assisted cystoscopy in NMIBC patients to best summarize the totality of the available evidence. The diagnostic meta-analysis was performed using Stata 13.0 (StataCorp, College Station, TX, USA) with metan and midas commands. A two-sided p

value of less than 0.05 was considered significant. In this study, a random-effect model was applied to quantify the pooled sensitivity, specificity, diagnostic odds ratio (DOR) and AUROC, with 95% confidence intervals (CIs) of the compared end points. DOR reflects the ability of a test to detect, a DOR of 1 indicates that the test has no discriminative power, the higher the DOR, the better the diagnostic ability of the new imaging technique. The AUROC is an overall summary measure index of the diagnostic accuracy. A perfect test will have an AUROC close to 1 and a poor test has AUROC close to 0.5[21], which were plotted on Summary Receiver Operating Curve (SROC) using RevMan 5.2 software. We also formulated forest plots of the summary measures of accuracy and examined the heterogeneity of the summary measures of sensitivity and specificity. The publication bias was assessed using Deeks' funnel plot, and statistical significance was determined with Deeks' asymmetry test[22 23]. To explore the effect of heterogeneity on the results, subgroup analyses were planned based on disease grade (low grade vs high grade), stage (pTa vs pT1), setting (primary vs recurrent tumours), number of participants (studies with n>100 patients only), and on studies with low to moderate RoB.

Results

Search and Study Selection

The flow diagram summarizing the literature screening and inclusion process is presented in Figure 1. Of the 652 potentially relevant articles identified in the database search, 271 studies were excluded for duplication. We excluded 278 studies when screening titles and abstracts: 32 editorials or letters, 24 reviews or meeting abstracts, 85 non-comparative studies and 137 papers on an obviously different topic. During the screening of 103 full-text articles, 36 studies were excluded for not being relevant to this review and another 41 studies were excluded for not having within-patient comparisons. Finally, 26 studies[12 24-48] were included in the diagnostic meta-analysis.

Study Demographics

The characteristics of the 26 studies included in this meta-analysis are summarized in Table 1. The studies were published from 1994 to 2016 with sample size ranged from 12 to 605 patients. The mean or median age and he male/female ratio in the studies showed no differences. In 9 studies, the NBI diagnostic intervention was applied, while 5-ALA-based PDD was conducted in 9 studies, and HAL-based PDD in 8 studies. Most enrolled patients in included studies were NMIBC.

Lesion level analysis

All studies used non-standardized definitions to calculate their diagnostic outcomes, in which case the results of included studies were recalculated using standard definitions with the raw data provided (Supplementary Table 1). The diagnostic meta-analysis results were presented in lesion-level and patient-level analyses. Based on lesion level, the forest plot of estimates of DOR for NBI, HAL and 5-ALA compared with WLC were showed in Figure 2, the pooled DOR for NBI, HAL and 5-ALA were 40.09 (95% CI, 20.08-80.01, Figure 2A), 78.14 (95% CI, 31.42-194.28, Figure 2B) and 18.14 (95% CI, 4.28-76.87, Figure 2C). The SROC curves for NBI, HAL and 5-ALA were showed in Figure 3A, the AUROC of NBI, HAL and 5-ALA were 0.88 (95% CI, 0.85-0.91), 0.94 (95% CI, 0.92-0.96) and 0.82 (95% CI, 0.79-0.85). Importantly, the results of the SSY and SPY for each intervention are shown in Supplementary Figures 1-3. The pooled estimates for the SSY data for NBI, HAL and 5-ALA were 0.94 (95% CI, 0.82-0.98, Supplementary Figure 1A), 0.95 (95% CI, 0.91-0.98, Supplementary Figure 2A) and 0.90 (95% CI, 0.71-0.97, Supplementary Figure 3A), whereas the SPY data for NBI, HAL and 5-ALA were 0.79 (95% CI, 0.73-0.85, Supplementary Figure 1B), 0.81 (95% CI, 0.74-0.87, Supplementary Figure 2B) and 0.69 (95% CI, 0.57-0.79, Supplementary Figure 3B), presenting superiority compared with WLC. The DOR value and AUROC of NBI, HAL and 5-ALA presented excellent diagnostic performance.

Patient level analysis

As for patient level analysis, the AUROC, SSY and SPY could not be calculated as few studies included. Figure 2 showed the forest plots of DOR for NBI, HAL and 5-ALA. For NBI, the highest DOR were reached. The DOR for NBI and HAL were 358.71 (95% CI, 44.50-2891.71, Figure 2D) and 59.95 (95% CI, 24.30-147.92, Figure 2E), present better performance compared with WLC. The SROC curves for NBI, HAL and 5-ALA were showed in Figure 3B. However, the DOR for 5-ALA was 79.52 (95% CI, 0.94-6759.92, Figure 2F), without statistic difference.

Subgroup Analysis

Subgroup analyses were performed on studies with low to moderate RoB and at least 100 patients at lesion level. The diagnostic performance results for studies with low to moderate RoB and at least 100 patients were demonstrated at Supplementary Table 2. The forest plot of estimates of pooled DOR for NBI, HAL and 5-ALA with low to moderate RoB were showed in Supplementary Figure 4; while forest plot of estimates of pooled DOR for NBI, HAL and 5-ALA with at least 100 patients were showed in Supplementary Figure 5. These results showed consistency with those obtained in our overall analysis.

RoB of included studies

The comparison-adjusted funnel plots of the diagnostic meta-analysis were not suggestive of any publication bias, showed in Figure 4. QUADAS-2 tool was applied for RoB assessment of included studies in our meta-analysis (Supplementary Figure 6). Overall, all studies reported methodology for the index test and reference standard clearly without significant source of potential bias. 69% (18/26) of the studies were presented as low or unclear RoB across most domains. The risk of bias in the patient selection in 3 studies were deemed high due to the absence of consecutive inclusion of patients；4 studies were at high RoBs for the flow and timing.

Discussion

Our systematic review indicated that pooled diagnostic performance of NBI, HAL or 5-ALA showed excellent efficacy compared with WLC. NBI could potentially be the most promising diagnostic intervention for NMIBC patients with advantages in terms of simplicity, cost and reliability. In this study, we have summarized the diagnostic performance of new technique-assisted cystoscopy strategies for NMIBC. Our diagnostic meta-analysis was further undertaken to estimate diagnostic performance of NBI, HAL and 5-ALA compared with WLC. Since virtually all of the techniques assessed in this review based on the reference standard of WLC, new technique-assisted cystoscopy showed diagnostic superiority than conventional WLC. In this context, adoption of these strategies in bladder cancer diagnosis practice is essential. The present results do strongly suggest that new imaging-based technologies, in particular NBI, are promising diagnostic intervention for bladder cancer detection in clinical practice.

Due to latent disadvantage of WLC, PDD and NBI have been recently developed to improve the visualization of bladder tumors. Diagnostic superiority of PDD or NBI over WLC have been demonstrated in several studies [12 49 50] for tumor detection. Further meta-analysis comparing PDD and WLC found a 21% increase in tumor detection with PDD in the pooled estimates for both patients and biopsies[51]. NBI, another optical enhancement technology, improve diagnostic accuracy by increasing contrast of superficial vasculature between normal mucosa and tumor tissue. Previous studies reported significant detection improvement in bladder tumors with NBI cystoscopy compared with standard WLC [12 14]. Our former meta-analysis indicated that NBI provides an additional 17% of patients and an additional 24% of tumors compared with WLC [52]. However, these studies did not use standardized diagnostic accuracy definitions. Our diagnostic meta-analysis applied standard diagnostic accuracy definitions and further pooled estimates demonstrated new technique assisted cystoscopy showed significant diagnostic superiority than conventional WLC, demonstrating the sub-optimal performance of WLC in diagnosing NMIBC.

Study performed by Burger [53] showed that PDD using HAL significantly reduced recurrence rate at 9–12

months compared with WLC-assisted TUR alone. Also, Lee et al performed a meta-analysis[54] evaluating oncologic outcomes for WLC, PDD- and NBI-assisted TUR, which showed both PDD and NBI reduced recurrence rate compared with WLC. However, therapeutic effectiveness of new technique assisted TUR such as recurrence and progression could not be demonstrated in this review. Future therapeutic efficacy analysis was needed to identify promising intervention.

The strengths of our study include the stringent methodology used to rigorous search and study inclusion procedure, standard definition of diagnostic performance and data extraction, strict diagnostic meta-analysis, specific QUADAS-2 tool for RoB assessment. Moreover, the strict diagnostic meta-analysis and further subgroup analysis was applied to synthesize diagnostic accuracy for reliable result. However, potential study limitations should be acknowledged. The lack of data on important clinical variables, such as grade and stage of disease, primary vs recurrent disease and intravesical instillation settings, may introduce clinical heterogeneity and prevent further subgroup analyses. And predictive performance of recurrence or progression was not demonstrated in our study, which may decrease the reliability of diagnostic performance. We have attempted to minimize biases throughout the whole procedure, with rigorous search and selection criteria, standard data extraction and re-calculation, subgroup analysis application, to evaluate the robustness of our findings.

In summary, this meta-analysis provides pooled diagnostic accuracy for NBI, HAL and 5-ALA techniques for NMIBC patients compared with WLC as a reference standard. The results demonstrate that diagnostic performance of NBI, HAL and 5-ALA all show superiority than WLC at lesion level in diagnostic meta-analysis. The findings demonstrate the superior diagnostic performance of new imaging technique in bladder detection compared with conventional WLC. New imaging technique are promising diagnostic intervention improving clinical procedure in bladder cancer detection in the future.

Abbreviations CI: Confidence intervals; CIS: carcinoma in situ; DOR: Diagnostic odds ratios; DTA: Diagnostic test accuracy; FNR: False negative rate; FPR: False positive rate; IQR: Interquartile range; HAL: hexylaminolevulinate; NBI: and narrow band imaging; NMIBC: Non-muscle-invasive bladder cancer; NPV: Negative predictive value; PDD: Photodynamic diagnosis; PPV: Positive predictive value; SPY: Specificity; SSY: Sensitivity; SROC: Summary receiver operating curve; AUROC: Area under the receiver operating characteristic curve; TURBT: Transurethral resection of bladder tumors; WLC: White light cystoscopy; 5-ALA: 5-aminolaevulinic acid.

Acknowledgements We would like to thank Prof. J.X. Zhang, Department of Medical Statistics and Epidemiology, School of Public Health, Sun Yat-Sen University, Guangzhou, China, for statistical advice and research comments.

Contributors CHC conceptualized and designed the study, drafted the initial and final manuscript, provided funding support. HH contributed to data collection and extraction, data analysis and interpretation, drafted initial and final manuscript. YZ contributed to article screening, data collection and extraction, assessment of risk of bias and drafting manuscript: HL contributed to article screening, data collection and extraction and assessment of risk of bias. RJ Sylvester led and supervised statistical analysis, provided administrative support. TXL and JH contributed to study conceptualization and design, supervised study implementation, and critically reviewed the manuscript.

Funding This study was funded by the National Natural Science Foundation of China (Grant No. 81572514,81472384, 81472381, 81402106, 81772719, 81772728, 91740119, 91529301); Guangdong Medical Research Fund (A2018330); Science and Technology Program of Guangzhou (Grant No. 201604020156, 201604020177, 201707010116, 201803010098); National Natural Science Foundation

of Guangdong (Grant No. 2018A030313564, 2018B030311009, 2018A030310250,2016A030313321, 2015A030311011, 2015A030310122). Yixian Youth project of Sun Yat-sen Memorial Hospital (YXQH201812).

Competing interests None declared.

Patient consent Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement All data relevant to the study are included in the article or uploaded as supplementary information.

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Figure legend

Figure 1. The PRISMA flow chart of included studies in DTA analysis.

Figure 2. The Forest Plot of estimates of DOR for NBI (A), HAL (B), 5-ALA (C) in lesion level and estimates of DOR for NBI (D), HAL (E), 5-ALA (F) in patient level.

Figure 3. The SROC curve for NBI, HAL and 5-ALA diagnosing NMIBC in lesion level (A) and patient level (B).

Figure 4. Deeks' funnel plot with asymmetry test for NBI (A), HAL (B) and 5-ALA (C) in lesion level.

Table 1 Summary of the characteristics of the included studies

Study	Institution No.	patients	Index test	period	Age, mean (range)	Male (%)	NMIBC (%)	Tumor lesions (n)
NBI vs WLC								
Shadpour et al.2016[29]	Unicentre, Observational	50	NBI	2012-2013	63.86 ± 10.05	34(68.0)	100	95
Song et al.2016[27]	Unicentre, Observational	63	NBI	2012-2013	66(56-76)	39(61.9)	94.1	21
Kobotake et Al.2015[35]	Unicentre, Observational	135	NBI	2010-2014	75	110(81.5)	100	120
Ye et al.2015[12]	Multicentre, Observational	384	NBI	NR	61(21-79)	267(69.5)	100	167
Shen et al.2012[28]	Unicentre, Observational	78	NBI	2009-2010	68 (33–75)	62(79.5)	100	211
Zhu et al. 2012[24]	Unicentre, Observational	12	NBI	2009-2010	57(28-73)	9(75.0)	100	9
Tatsugami et Al.2010[26]	Unicentre, Observational	104	NBI	2007-2009	70.6 (38-90)	88(84.6)	NR	110
Cauberg et Al.2009[47]	Multicentre, Observational	95	NBI	2007-2009	70.6 (38.1-90.2)	70(73.7)	NR	226
Herr et Al.2008[38]	Unicentre, Observational	427	NBI	2007	65 (26-90)	316(74.0)	100	NR
HAL vs WLC								
Palou et Al.2014[33]	Multicentre, Observational	283	HAL	2008-2009	67.5(42-95)	242(85.5)	94.1	621
Lapini et Al.2012[34]	Multicentre, Observational	96	HAL	2010-2011	NR	80(83.3)	NR	108
Burgues et Al.2011[55]	Multicentre, Observational	305	HAL	2006-2009	66.9(39-93)	270(88.5)	100	600
Ray et al.2010[32]	Unicentre, Observational	27	HAL	2005-2006	70(49-82)	21(77.8)	100	NR
Schmidbauer et al.2009[30]	Unicentre, Observational	66	HAL	NR	63(38-84)	49(74.2)	93.1	NR
Geavlete et Al.2008[40]	Unicentre, Observational	128	HAL	2007-2008	65(36-81)	NR	92.2	NR
Fradet et Al.2006[41]	Multicentre, Observational	298	HAL	NR	67±11	223(74.8)	100	113
Jichlinski et Al.2003[36]	Multicentre, Observational	52	HAL	2000-2001	72±12	38(73.1)	100	143
5-ALA vs WLC								
Grimbergen et Al.2003[6]	Unicentre, Observational	160	5-ALA	1998-2002	67(30-91)	NR	90.0%	390
Filbeck et Al.2002[43]	Unicentre, Observational	279	5-ALA	1997-2000	34-89	NR	90.3%	336
Dominicis et	Unicentre,	49	5-ALA	NR	60(31-77)	42(85.7)	100	52

Al.2001[45]	Observational							
Ehsan et	Unicentre,	30	5-ALA	NR	55-89	19(63.3)	NR	NR
Al.2001[44]	Observational							
Jeon at	Unicentre,	62	5-ALA	1997-1999	61.9(32-80)	57(91.1)	NR	148
Al.2001[37]	Observational							
Zaak et	Unicentre,	605	5-ALA	NR	65.6(16-99)	472(78.0)	NR	552
Al.2001[25]	Observational							
Filbeck et	Unicentre,	123	5-ALA	1997	64.5(28-86)	NR	91.9	124
Al.1999[42]	Observational							
Riedl et	Unicentre,	52	5-ALA	NR	44-79	NR	100	123
Al.1999[31]	Observational							
D'hallewin et	Unicentre,	16	5-ALA	NR	NR	NR	100	50
Al.1998[46]	Observational							

WLC: white light cystoscopy; NT: new technology; 5-ALA: 5-aminolaevulinic acid; HAL: hexylaminolevulinate; NBI: narrow band imaging; NR: not reported.

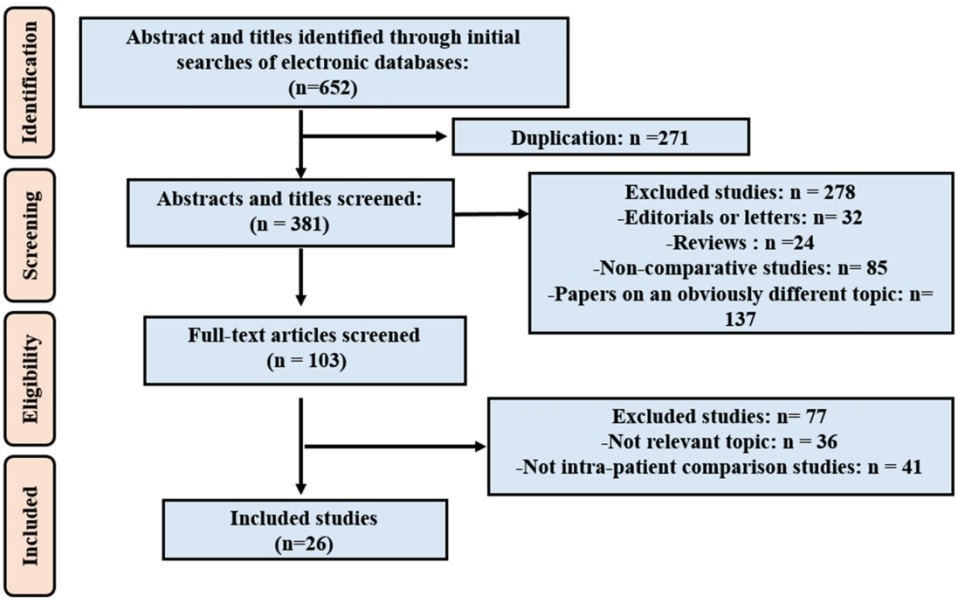


Figure 1. The PRISMA flow chart of included studies in DTA analysis.

177x108mm (300 x 300 DPI)

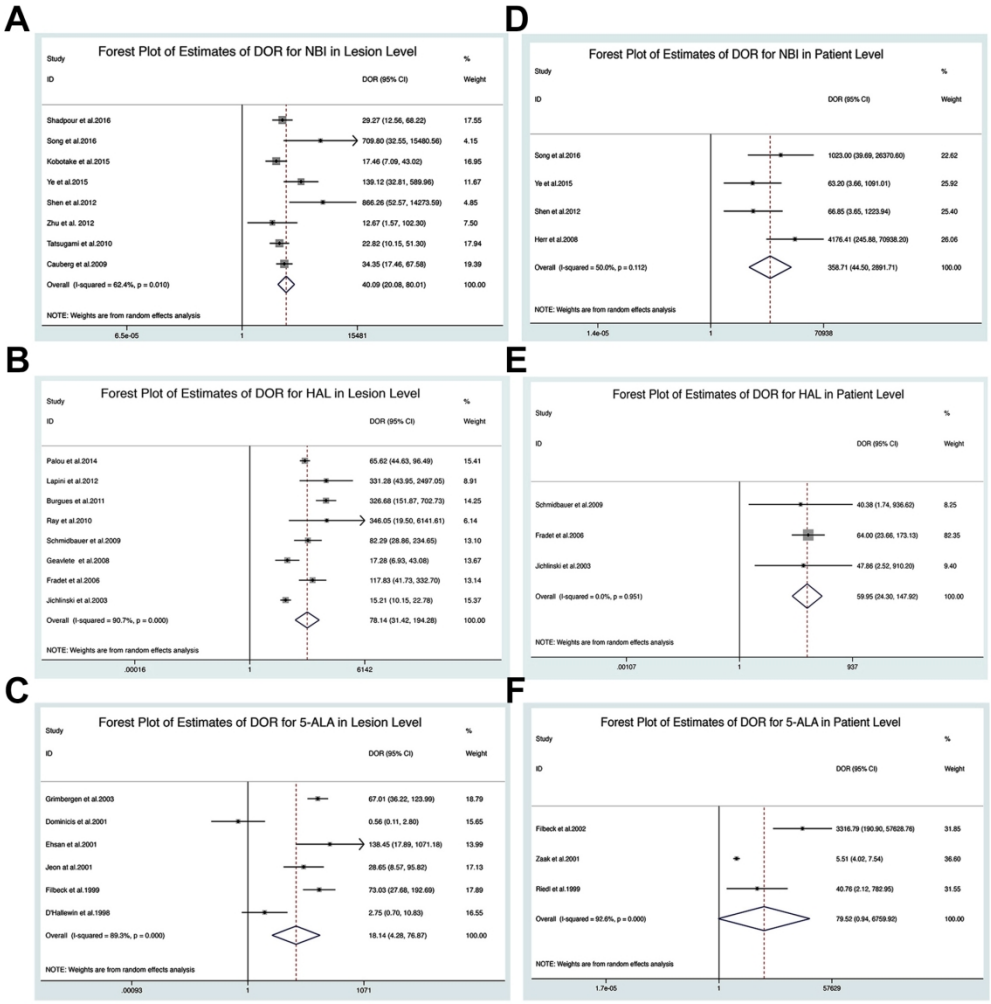


Figure 2. The Forest Plot of estimates of DOR for NBI (A), HAL (B), 5-ALA (C) in lesion level and estimates of DOR for NBI (D), HAL (E), 5-ALA (F) in patient level.

177x180mm (300 x 300 DPI)

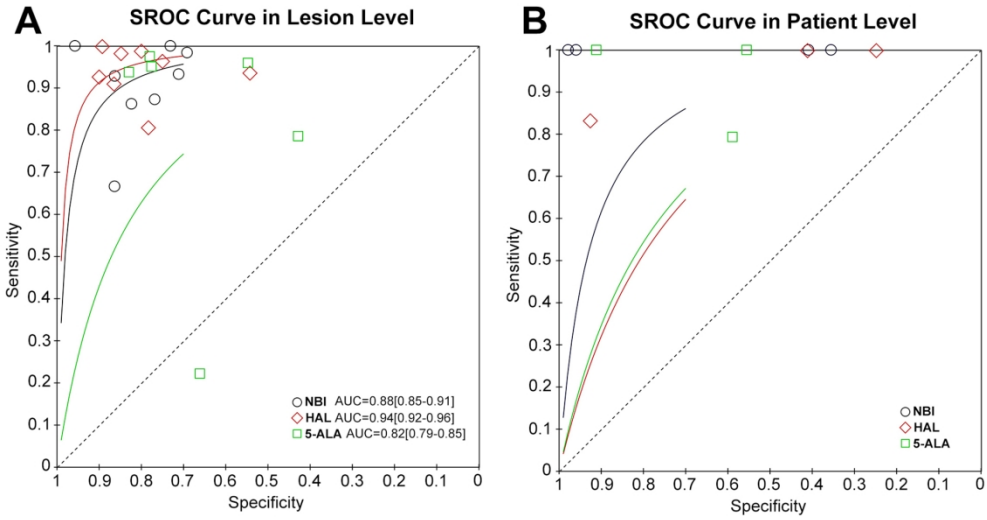


Figure 3. The SROC curve for NBI, HAL and 5-ALA diagnosing NMIBC in lesion level (A) and patient level (B).

177x94mm (300 x 300 DPI)

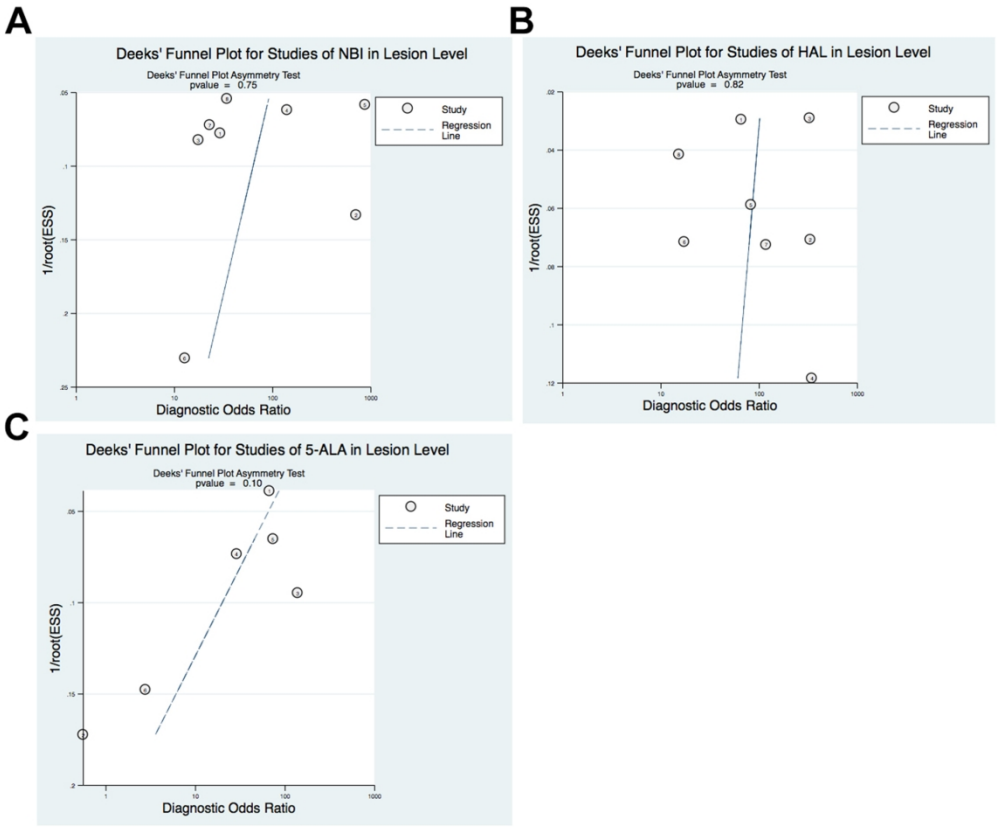
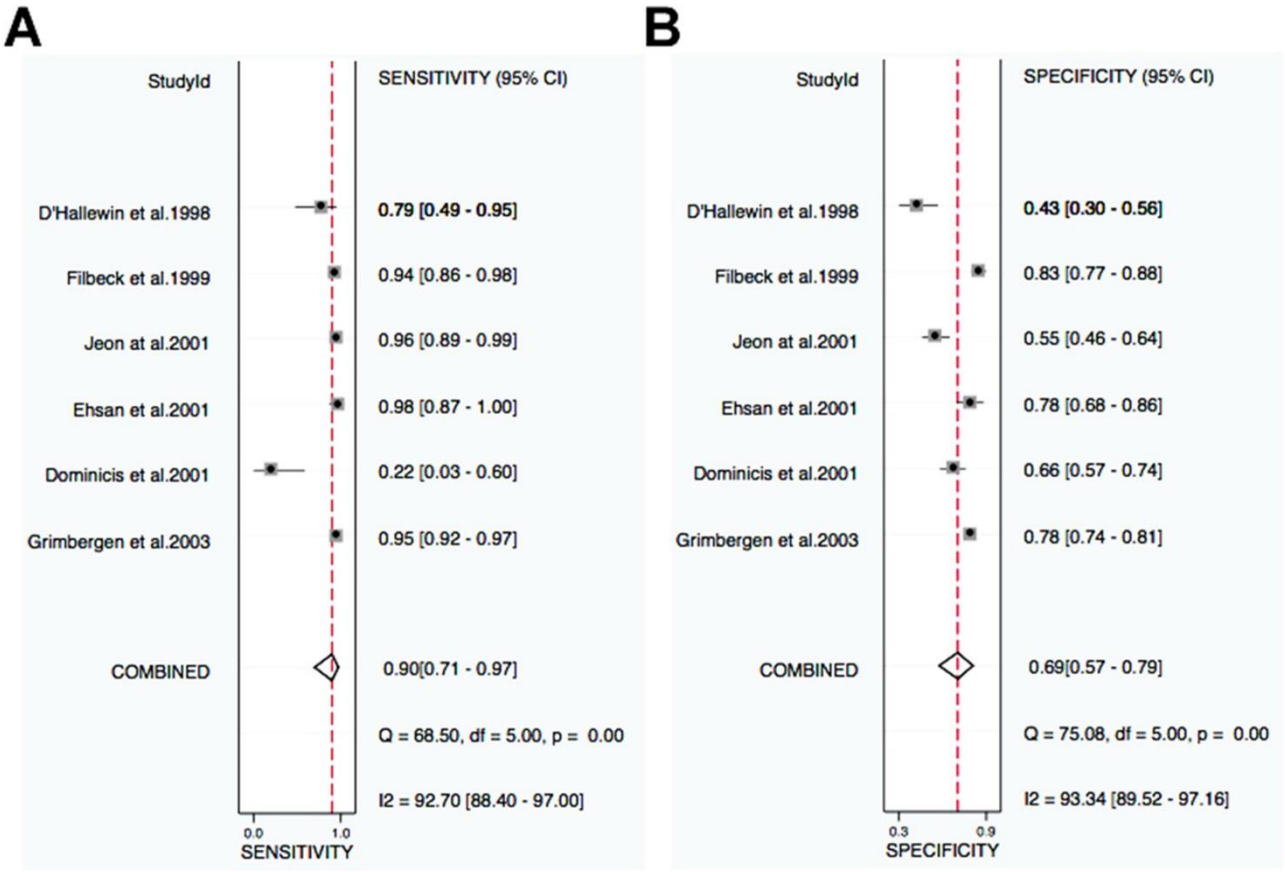


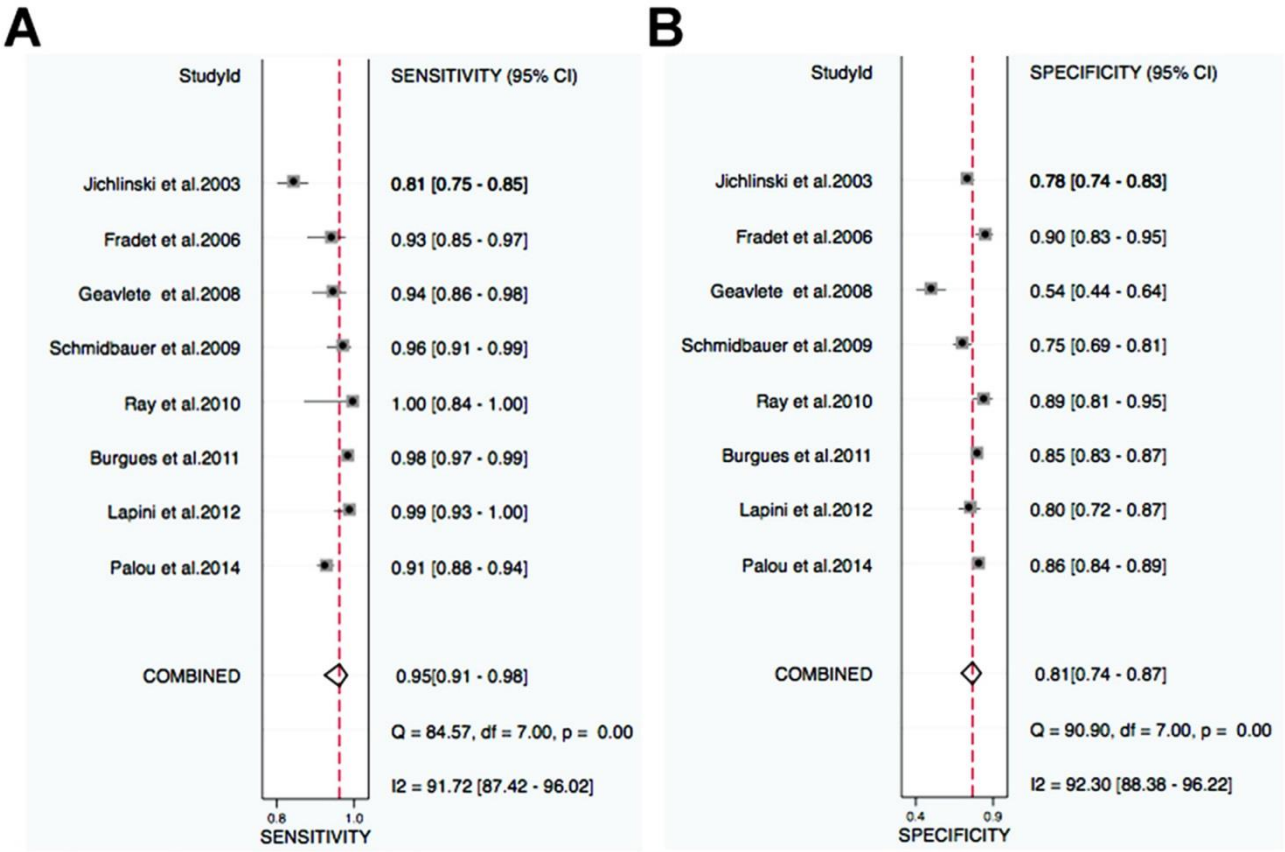
Figure 4. Deeks' funnel plot with asymmetry test for NBI (A), HAL (B) and 5-ALA (C) in lesion level.

177x147mm (300 x 300 DPI)

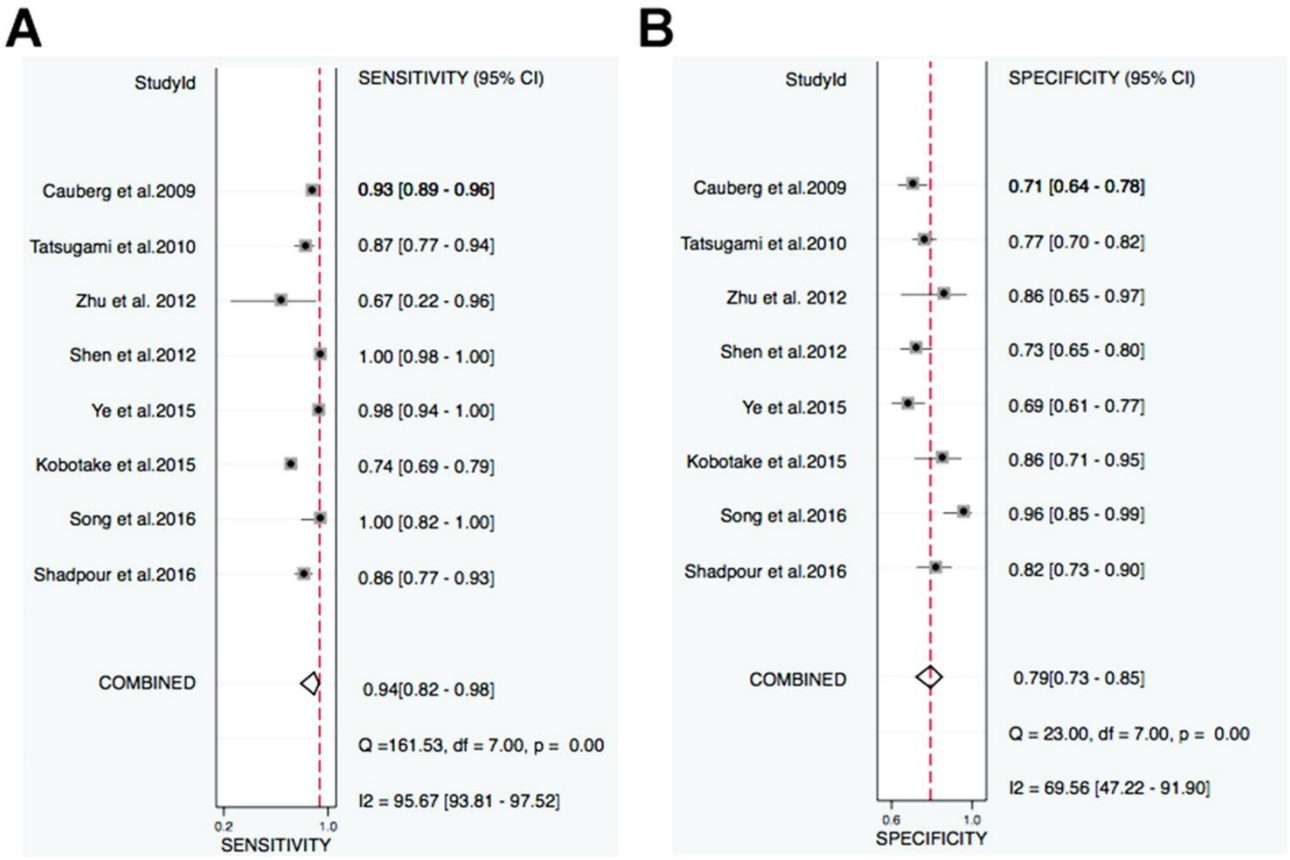
Supplementary Information



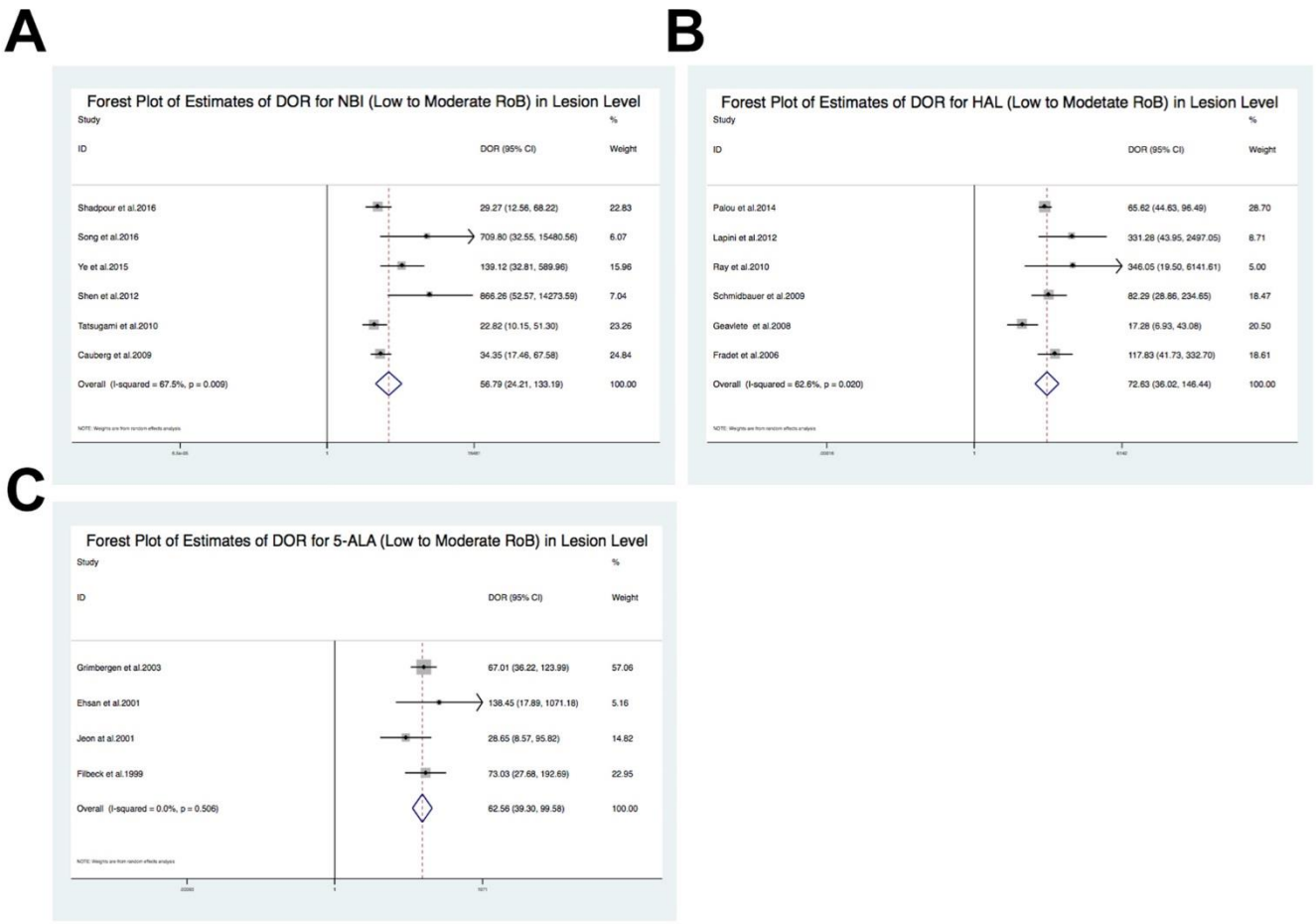
Supplementary Figure 1. The Forest Plot of study specific and pooled sensitivity (A) and specificity (B) for NBI in lesion level.



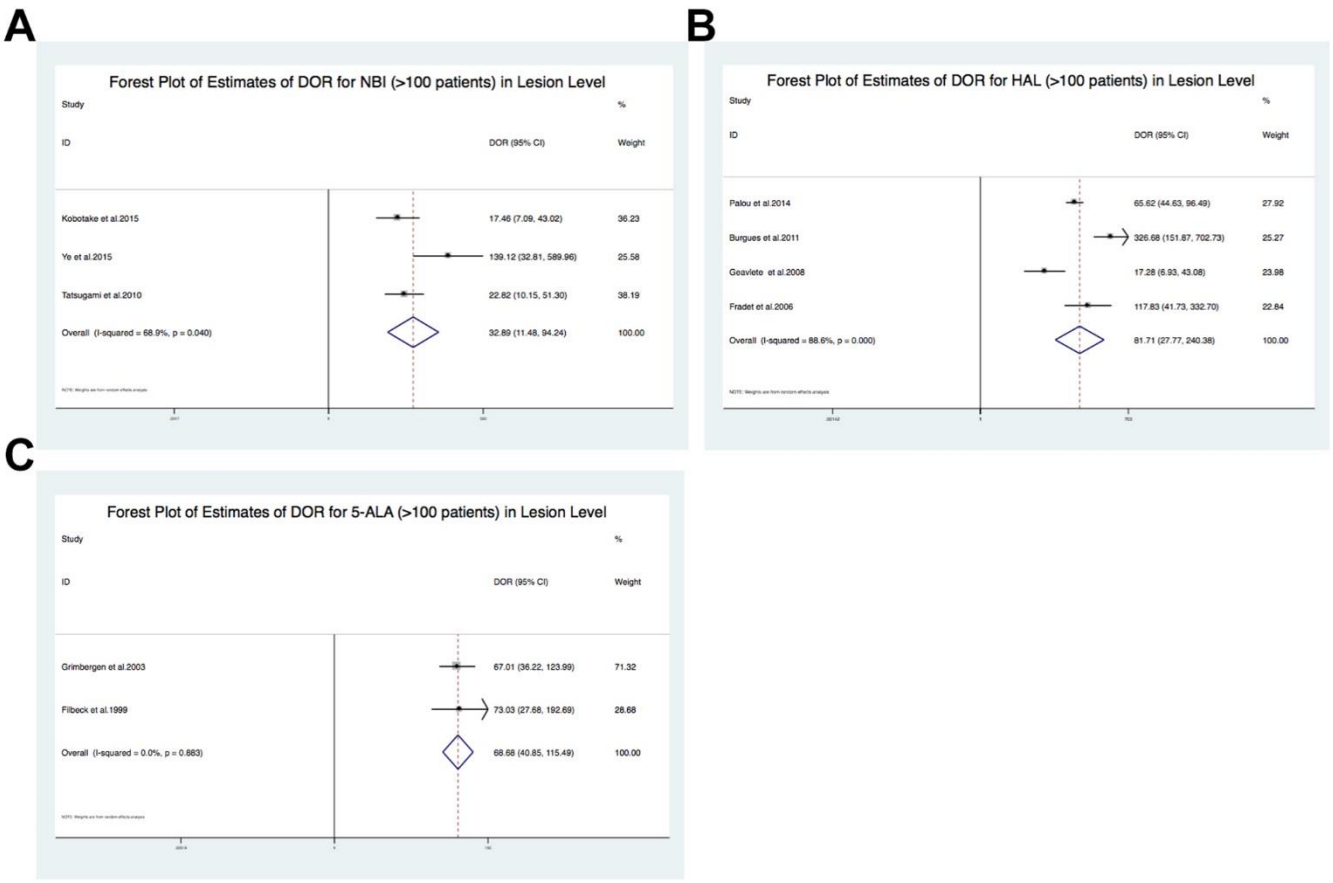
Supplementary Figure 2. The Forest Plot of study specific and pooled sensitivity (A) and specificity (B) for HAL in lesion level.



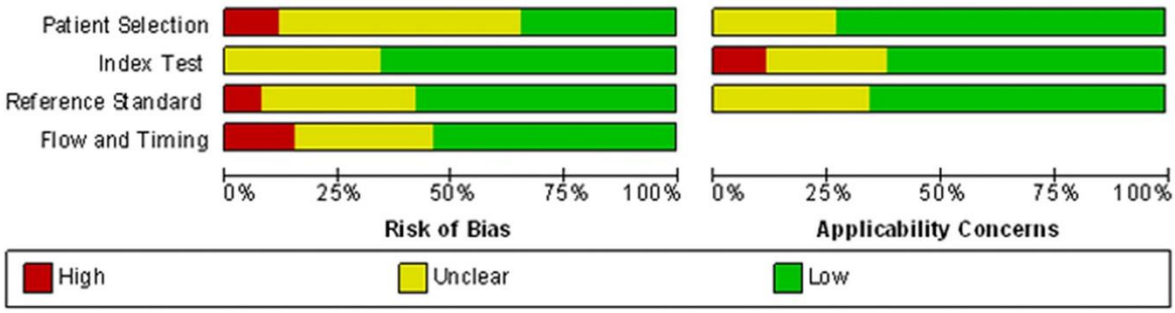
Supplementary Figure 3. The Forest Plot of study specific and pooled sensitivity (A) and specificity (B) for 5-ALA in lesion level.



Supplementary Figure 4. The Forest Plot of estimates of DOR for NBI (A), HAL (B) and 5-ALA (C) with low to moderate RoB in lesion level.



Supplementary Figure 5. The Forest Plot of estimates of DOR for NBI (A), HAL (B) and 5-ALA (C) with at least 100 patients in lesion level.



Supplementary Figure 6. Quality assessment of included studies. The distribution plot for risk of bias using QUADAS-2 tool. Studies are deemed to be at high, low or unclear risk of bias for each domain.

Supplementary Table1. Diagnostic performance results of individual studies for Meta-analysis

Study ID	Patient-level analysis							Lesion-level analysis						
	Patient No.	SSY	SPY	FPR	FNR	PPV	NPV	Lesion No.	SSY	SPY	FPR	FNR	PPV	NPV
NBI vs WLC														
Shadpour et al.2016[1]	50	NR	NR	NR	NR	NR	NR	175	69/80	70/85	15/85	11/80	69/84	74/75
Song et al.2016[2]	63	16/16	46/47	1/47	0/16	16/17	23/23	66	19/19	45/47	2/47	0/19	19/21	7/7
Kobotake et al.2015[3]	135	NR	NR	NR	NR	NR	NR	379	78/84	227/263	36/263	6/84	78/114	203/203
Ye et al.2015[4]	103	56/56	16/45	29/46	0/56	56/85	8/8	300	124/126	92/133	41/133	2/126	124/165	83/85
Shen et al.2012[5]	78	47/47	9/22	13/22	0/47	47/47	7/7	309	160/160	98/134	36/134	0/160	160/196	72/72
Zhu et al. 2012[6]	12	NR	NR	NR	NR	NR	NR	31	4/6	19/22	3/22	2/6	4/7	20/20
Tatsugami et al.2010[7]	104	NR	NR	NR	NR	NR	NR	313	55/63	156/203	47/203	8/63	55/102	144/144
Cauberg et al.2009[8]	95	NR	NR	NR	NR	NR	NR	389	167/179	116/163	47/163	12/179	167/214	47/51
Herr et al.2008[9]	427	90/90	311/324	13/324	0/90	90/103	265/265	NR	NR	NR	NR	NR	NR	NR
HAL vs WLC														
Palou et al.2014[10]	283	NR	NR	NR	NR	NR	NR	1492	379/416	820/948	128/948	37/416	379/507	699/702
Lapini et al.2012[11]	96	NR	NR	NR	NR	NR	NR	234	82/83	101/126	25/126	1/83	82/107	80/81
Burgues et al.2011[12]	305	NR	NR	NR	NR	NR	NR	1659	404/441	900/1059	159/1059	7/441	404/563	863/863

Ray et al.2010[13]	27	NR	NR	NR	NR	NR	NR	120	21/21	84/94	10/94	0/21	21/31	35/35
Schmidbauer et al.2009[14]	66	52/52	2/8	6/8	0/52	52/58	3/3	364	109/113	151/201	50/201	4/113	109/159	158/158
Geavlete et al.2008[15]	128	NR	NR	NR	NR	NR	NR	243	87/93	56/103	47/103	6/93	87/134	76/82
Fradet et al.2006[16]	196	40/48	128/138	10/138	8/48	40/50	106/113	206	77/83	101/112	11/112	6/83	77/88	63/71
Jichlinski et al.2003[17]	52	33/33	7/17	10/17	0/33	33/43	3/3	143	205/254	269/343	74/343	49/254	205/279	306/314
5-ALA vs WLC														
Grimbergen et al.2003[18]	160	NR	NR	NR	NR	NR	NR	889	232/244	409/527	118/527	12/244	232/350	248/257
Filbeck et al.2002[19]	279	168/168	93/102	9/102	0/168	168/177	81/81	NR	NR	NR	NR	NR	NR	NR
Dominicis et al.2001[20]	49	NR	NR	NR	NR	NR	NR	179	2/9	84/127	43/127	7/9	2/45	80/80
Ehsan et al.2001[21]	30	NR	NR	NR	NR	NR	NR	151	39/40	71/91	20/91	1/40	39/59	59/59
Jeon at al.2001[22]	62	NR	NR	NR	NR	NR	NR	257	71/74	69/126	57/126	3/74	71/128	54/54
Zaak et al.2001[23]	605	288/363	271/460	189/460	75/363	288/477	55/108	NR	NR	NR	NR	NR	NR	NR
Filbeck et	123	NR	NR	NR	NR	NR	NR	341	75/80	185/223	38/223	5/80	75/113	78/78

al.1999[24]														
Riedl et al.1999[25]	52	26/26	10/18	8/18	0/26	26/34	6/6	NR	NR	NR	NR	NR	NR	NR
D'Hallewin et al.1998[26]	16	NR	NR	NR	NR	NR	NR	113	11/14	27/63	36/63	3/14	11/47	34/34

NMIBC: non-muscle-invasive bladder cancer; WLC: white light cystoscopy; 5-ALA: 5-aminolaevulinic acid; HAL: hexylaminolevulinate; NBI: narrow band imaging; NT: new technology; SSY: sensitivity; SPY: specificity; FPR: false positive rate; FNR: false negative rate; PPV: positive predictive value; NPV: negative predictive value; NR: not reported.

Supplementary Table2. Diagnostic performance results for sensitivity analysis of studies with low to moderate RoB and at least 100 patients at lesion level.

	Low to moderate RoB			At least 100 patients		
	Median	**Lower Quartile**	**Upper Quartile**	**Median**	**Lower Quartile**	**Upper Quartile**
NBI vs WLC (n=6)				**NBI vs WLC (n=3)**		
Sensitivity	95.85	88.80	99.60	92.86	90.08	95.63
Specificity	74.99	71.66	80.98	76.85	73.01	81.58
Positive predictive value	79.84	75.87	82.02	68.42	61.17	71.79
Negative predictive value	99.33	97.90	100	100	98.82	100
False positive rate	25.01	19.02	28.34	23.15	18.42	26.99
False negative rate	4.15	0.40	11.20	7.14	4.37	9.92
HAL vs WLC (n=6)				**HAL vs WLC (n=4)**		
Sensitivity	95.00	92.97	98.21	92.19	91.48	92.97
Specificity	83.33	76.38	88.65	85.74	77.33	87.42
Positive predictive value	71.65	67.94	76.16	73.26	70.05	77.94
Negative predictive value	99.17	94.20	99.89	96.13	91.70	99.68
False positive rate	16.67	11.35	23.62	14.26	12.58	22.67
False negative rate	5.00	1.79	7.03	6.84	5.24	7.65
5-ALA vs WLC (n=4)				**5-ALA vs WLC (n=2)**		
Sensitivity	95.51	94.75	96.33	94.42	-	-
Specificity	77.82	71.90	79.26	80.28	-	-
Positive predictive value	66.19	63.44	66.31	66.33	-	-
Negative predictive value	100	99.12	100	98.25	-	-
False positive rate	22.18	20.74	28.10	19.72	-	-
False negative rate	4.49	3.67	5.25	5.58	-	-

NMIBC: non-muscle-invasive bladder cancer; WLC: white light cystoscopy; 5-ALA: 5-aminolaevulinic acid; HAL: hexylaminolevulinate; NBI: narrow band imaging; NR: not reported.

Appendix: Full search strategy

1. Searching in MEDLINE, Embase and CENTRAL

All databases were searched using both controlled vocabulary (namely MeSH in MEDLINE and EMTREE in Embase) and a wide range of free-text terms

Search code for MEDLINE (accessed via PubMed) and CENTRAL

Patients		
Bladder cancer	#1	bladder neoplasms [MeSH] OR carcinoma OR tumor, urothelial cell [MeSH] OR transitional cell carcinoma*[tiab] OR bladder neoplasm*[tiab] OR bladder cancer[tiab] OR BCa[tiab]
Index test		
Photodynamic diagnosis	#2	"photodynamic diagnosis" [MeSH] OR "PDD" [tiab] OR "photodynamic" [tiab] OR hexaminolevulinate [tiab] OR HAL[tiab] OR "5-aminolevulinate acid"[tiab] OR 5-ALA[tiab] OR cystoscopic[tiab] OR cystoscopy
Narrow band imaging	#3	"narrow band imaging" [MeSH] OR NBI [tiab] OR cystoscopic[tiab] OR cystoscopy[tiab]
Cochrane Highly Sensitive Search Strategy	#4	(observational trial[Publication Type] OR diagnostic[Publication Type] OR detection[tiab] OR observational[tiab] OR trial[tiab] OR groups[tiab]) NOT (animals[mh] NOT humans[mh])
Search algorithm		#1 AND (#2 OR #3) AND #4

2.Searching other resources

Previous systematic reviews in the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effectiveness and the PROSPERO international prespective register of systematic reviews for completed or published systematic reviews

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title page
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	None
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5-6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Figure1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6-7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6-7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8

PRISMA 2009 Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7-8

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6-7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8-9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Supplementary Figure 6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Supplementary Table 1
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	9-10
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	10
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10-12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12
FUNDING			

PRISMA 2009 Checklist

Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	13-14

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

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BMJ Open

Diagnostic Performance of Image Technique-Based Transurethral Resection for Non-muscle Invasive Bladder Cancer: Systematic Review and Diagnostic Meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-028173.R2
Article Type:	Original research
Date Submitted by the Author:	20-Sep-2019
Complete List of Authors:	Chen, Changhao; Sun Yat-Sen Memorial Hospital, Department of Urology Huang, Hao; Sun Yat-Sen Memorial Hospital, Department of Urology Zhao, Yue; the First Affiliated Hospital of Sun Yat-Sen University, Department of Gastroenterology Liu, Hao; Chengdu Fifth People's Hospital, Department of Urology Sylvester, Richard; EAU Guidelines Office, Brussels Lin, Tianxin; Sun Yat-Sen Memorial Hospital, Department of Urology Huang, Jian; Sun Yat-Sen Memorial Hospital, Department of Urology
Primary Subject Heading:	Oncology
Secondary Subject Heading:	Diagnostics, Urology
Keywords:	bladder cancer, diagnostic performance, Narrow band imaging, photodynamic diagnosis, white light-guided cystoscopy

Diagnostic Performance of Image Technique-Based Transurethral Resection for Non-muscle Invasive Bladder Cancer: Systematic Review and Diagnostic Meta-analysis

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ABSTRACT

Objective To explore the diagnostic performance of image technique-based transurethral resection for bladder cancer, with white light-guided cystoscopy (WLC) as the reference standard.

Design Systematic review and meta-analysis.

Data sources PubMed/MEDLINE, Web of Science, the Cochrane Library, Central Register of Controlled Trials, and Embase from inception to 31st March 2018.

Methods Included studies reported the diagnostic performance of photodynamic diagnosis (PDD) with 5-aminolevulinic acid (5-ALA), PDD with hexaminolevulinic acid (HAL), or narrow band imaging (NBI), with WLC as the reference standard at the patient or lesion level. The studies' risk of bias (RoB) was assessed using Quality Assessment of Diagnostic Studies-2 (QUADAS-2). Data were pooled using a random-effect diagnostic meta-analysis and subgroup analyses were performed.

Results: Twenty-six studies comprising a total of 3979 patients were included in this diagnostic meta-analysis. Pooled sensitivity (SSY), specificity (SPY), diagnostic odds ratio (DOR), and area under the receiver operating characteristic curve (AUROC) values were calculated per group for NBI, HAL, and 5-ALA at the lesion or patient level. NBI showed significant diagnostic superiority compared with WLC at the lesion level (SSY 0.94, 95% confidence interval (CI), 0.82–0.98; SPY 0.79, 95% CI, 0.73–0.85; DOR 40.09, 95% CI, 20.08–80.01; AUROC 0.88, 95% CI, 0.85–0.91). NBI presented the highest DOR (358.71, 95% CI, 44.50–2891.71) in the patient level. Subgroup analyses were performed on studies with low to moderate RoB and at least 100 patients at the lesion level. These results were

consistent with those of the overall analysis.

Conclusions Pooled data indicated that image technique-based transurethral resection (NBI, HAL, and 5-ALA) showed diagnostic superiority compared with WLC. Moreover, NBI is potentially the most promising diagnostic intervention, showing the best diagnostic performance outcomes. Further prognostic outcomes of novel imaging technologies compared with those WLC should be explored in addition to current diagnostic performance analysis.

Key words: bladder cancer, diagnostic performance, Narrow band imaging, photodynamic diagnosis, white light-guided cystoscopy

Strengths and limitations of this study

- This is the first systematic review and diagnostic meta-analysis exploring diagnostic accuracy of image technique based transurethral resection compared with WLC.
- Our study includes the stringent methodology used to synthesize the evidence obtained, such as adhering to PRISMA guidelines, using standardized definitions of diagnostic performance analysis and applying QUADAS-2 tool for RoB assessment.
- Most included studies had a low or moderate risk of bias. All studies clearly reported methodology for the index test and reference standard, and were not considered a significant source of potential bias.
- The further sensitivity analysis was based on relatively few studies, but we used random-effect models to compensate for clinical and methodological diversity among studies.
- The lack of data on important clinical variables, such as grade and stage of disease, primary vs recurrent disease and intravesical instillation settings, may introduce clinical heterogeneity and prevent further sensitivity analyses. We attempted to minimize biases by standardizing data extraction and performing several sensitivity analyses.

INTRODUCTION

Bladder cancer is a widespread malignancy with an estimated 80,470 newly diagnosed cases and 17,670 deaths in USA in 2019, among which about 75% of patients presented with non-muscle invasive bladder cancer (NMIBC)[1 2] . Currently, white light cystoscopy (WLC) is the gold-standard technique to detect bladder cancer, despite having an unsatisfactory accuracy to detect disease. The detection reliability for smaller tumors or carcinoma *in situ* (CIS) is poor, leading to markedly high recurrence, with up to 30% of patients having a tumor identified at the first-check cystoscopy at 3 months and 50% of patients developing tumors within 12 months[3 4]. Thus, different optical imaging techniques have emerged as an adjunct to WLC to improve the visualization of tumors via contrast enhancement.

Photodynamic diagnosis (PDD) is performed using blue-violet (380–440 nm) light with intravesical instillation of 5-aminolevulinic acid (5-ALA) or hexaminolevulinic acid (HAL). The effect of 5-ALA-induced fluorescence on tumor detection in the urinary bladder has identified it as an efficient method to map the entire mucosa to detect urothelial tumors and flat CIS lesions[5-7]. HAL, the lipophilic hexylester of 5-ALA, has been commercially available since 2006, and has been established as the preferred intravesical agent to detect NMIBC. However, intravesical inflammation leads to decreased specificity and pre-operative procedures are technically complex and costly.

Narrow band imaging (NBI) is a new image-processing modality that filters white light down to two narrow band widths of 415 and 540 nm, with advantage of avoiding the need for intravesical contrast administration[8]. Hemoglobin absorbs these wavelengths preferentially, resulting in dark neovascularized bladder cancer appearing very different from the light

background of the normal mucosa. The superior diagnostic performance of NBI compared with WLC has been confirmed in several studies[9-11]. Overall, NBI led to a 9.9% increase in the detection rate at the patient level and a 19.2% increase in lesion detection in a recent meta-analysis, while subgroup analysis showed that NBI was associated with a 53% reduction in the recurrence rate at 3 months and 19% at 12 months compared with those of WLC[12]. Noticeably, NBI might be associated with increased false-positives, especially for patients with prior intravesical instillations[13].

As a standard procedure, cystoscopy is performed using white light. However, the use of white light can lead to lesions that are present but not visible being missed. New imaging techniques could improve cancer detection compared with WLC; however, some studies showed that new imaging techniques might produce higher false positive rates than WLC[13-15]. In addition, their complex procedures and costs restrict their wider application[16]. Therefore, it is still uncertain which technique could better improve the diagnostic accuracy of bladder cancer detection. The present study aimed to perform a systematic review and meta-analysis to assess the diagnostic performance of PDD using 5-ALA, PDD using HAL, and NBI against the current reference standard of WLC for NMIBC.

METHODS

The diagnostic meta-analysis was conducted based on the Meta-analysis of Observational Studies in Epidemiology statement[17]. All included studies were observational studies. When an included primary study did not match the Standards for Reporting of Diagnostic Accuracy statement, we gathered the information by contacting the authors[18].

Literature search

Studies reporting the diagnostic performance of PDD with 5-ALA, PDD with HAL, or NBI, with WLC as reference standard, were retrieved from multiple databases including PubMed/MEDLINE, Web of Science, the Cochrane Library, Central Register of Controlled Trials and Embase up to 31st March 2018. The following MeSH free and combined terms, which were adjusted for the different databases terms, were used: "photodynamic diagnosis, PDD, hexaminolevulinate, HAL, 5-aminolevulinate acid, 5-ALA, narrow imaging, NBI, white light cystoscopy, urothelial cell carcinoma of bladder, transitional cell carcinoma, bladder cancer, bladder tumor, and BCa". The full search strategy is shown in the Appendix (supplementary material). The review was performed according to Preferred Reporting Items for Systematic Reviews (PRISMA)[19] and Standards for Reporting Diagnostic Accuracy Studies (STARD)[20]. The search was restricted to English-language publications. At least two reviewers (CHC and HH) screened all the abstracts and full-text articles independently. Disagreement was resolved by consultation with an independent arbiter (JH).

Inclusion and exclusion criteria

The inclusion criteria were as follows: 1) Population: Patients diagnosed with primary NMIBC, or patients previously diagnosed with NMIBC (recurrent tumors); 2) Reference

standard: WLC must be provided as the reference standard for all patients, and the diagnosis of NMIBC was confirmed by histopathological examination; 3) studies reported data of intra-patient comparison; 4) when two or more studies provided data from the same institution during an overlapping time period, only the updated data was included in this study.

Articles were excluded if the full-text article was not written in English. Abstracts, conference articles, historical overviews, case studies, reviews, and meta-analyses were not considered. Studies that failed to report on sensitivity and specificity data or both in comparison with WLC were excluded. For missing or unclear data, we contacted the authors to obtain more information.

Patient and Public Involvement

Patients and the public were not involved in this research.

Study Quality

The Quality Assessment of Diagnostic Studies-2 (QUADAS-2) [21] and the Strength Of Recommendation Taxonomy (SORT) numerical scale were applied to the included studies[22]. Both checklists were performed independently by two authors (YZ and CHC); disagreement was resolved by consultation with an independent arbiter (JH). The "low risk of bias (RoB)" was defined as at least three domains with "low" in both categories and without any domains evaluated as "high" in either category; "moderate RoB" was defined as at least two domains with "low" in both categories and without any domain scoring "high" in either category; in addition to this was defined as "high" RoB.

Data Extraction

The following data were extracted from the selected studies: 1) Study characteristics (first author, study design, number of patients, and follow-up); 2) intervention characteristics (index tests, duration of follow-up, schedule, and nature of WLC); 3) patient characteristics (age, sex, NMIBC patients, and tumor lesions); 4) diagnostic performance measures (sensitivity (SSY), specificity (SPY), negative predictive value (NPV), positive predictive value (PPV), false positive rate (FPR), and false negative rate (FNR)). Data were extracted from each study at the lesion or patient level to assess 5-ALA, HAL, and NBI as the index test using WLC as the reference standard, with positive or negative disease being determined using histopathological examination.

The primary outcomes of SSY, SPY, NPV, PPV, FPR, and FNR for individual studies were calculated using the following standard definitions. SSY was defined as the proportion of positive patients or lesions with index tests in all cases of WLC-positive findings. SPY was defined as the proportion of negative patients or lesions with index tests in all cases of WLC-negative findings. NPV was defined as the proportion of true negatives findings (both negative in index tests and WLC) in all index test-negative cases or lesions. PPV was defined as the proportion of true positives findings (both positive in index tests and WLC) in all index test-positive cases or lesions. FNR was defined as the proportion of index test-negative findings in all cases of WLC-positive cases or lesions. FPR was defined as the proportion of index test-positive findings in all cases of WLC-negative cases or lesions.

Statistical analysis

Separate meta-analyses were performed for the currently new technology-assisted cystoscopy in patients with NMIBC to best summarize the totality of the available evidence.

The diagnostic meta-analysis was performed using Stata 13.0 (StataCorp, College Station, TX, USA) with the metan and midas commands. A two-sided p value of less than 0.05 was considered significant. In this study, a random-effect model was applied to quantify the pooled sensitivity, specificity, diagnostic odds ratio (DOR), and area under the receiver operating characteristic curve (AUROC), with 95% confidence intervals (CIs) of the compared end points. DOR reflects the diagnostic performance of a new imaging technique to detect lesions. A DOR value of 1 indicates that the test has no discriminative power; the higher the DOR value, the better the diagnostic performance of the new imaging technique. The AUROC is an overall summary measure index of the diagnostic accuracy. A perfect test will have an AUROC close to 1 and a poor test will have an AUROC close to 0.5[23]. We will plot the sensitivities and specificities in the Summary Receiver Operating Curve (SROC) space, using different symbols for different imaging techniques, and used RevMan 5.2 software to build hierarchical SROC curves for each imaging technique. We also formulated forest plots of the summary measures of accuracy and examined the heterogeneity of the summary measures of sensitivity and specificity. The publication bias was assessed using Deeks' funnel plot, and statistical significance was determined using Deeks' asymmetry test[24 25]. To explore the effect of heterogeneity on the results, subgroup analyses were planned based on disease grade (low grade *vs*. high grade), stage (pTa *vs*. pT1), setting (primary *vs*. recurrent tumors), number of participants (studies with n >100 patients only), and on studies with low to moderate RoB.

RESULTS

Search and Study Selection

The flow diagram summarizing the literature screening and inclusion process is presented in Figure 1. Of the 652 potentially relevant articles identified in the database search, 271 studies were excluded as duplicates. We excluded 278 studies when screening the titles and abstracts: 32 were editorials or letters, 24 were reviews or meeting abstracts, 85 were non-comparative studies, and 137 papers concerned an obviously different topic. During the screening of 103 full-text articles, 36 studies were excluded for not being relevant to this review and another 41 studies were excluded for not having within-patient comparisons. Finally, 26 studies[11 15 26-49] were included in the diagnostic meta-analysis.

Study Demographics

The characteristics of the 26 studies included in this meta-analysis are summarized in Table 1. The studies were published from 1994 to 2016 with sample sizes ranging from 12 to 605 patients. The mean or median age and male/female ratio showed no significant differences among included studies. In nine studies, the NBI diagnostic intervention was applied, while 5-ALA-based PDD was conducted in nine studies, and HAL-based PDD in eight studies. Most of the enrolled patients in the included studies suffered from NMIBC.

Lesion level analysis

All studies used non-standardized definitions to calculate their diagnostic outcomes, in which case the results of the included studies were recalculated using standard definitions from the raw data provided (Supplementary Table 1). The diagnostic meta-analysis results are presented using lesion-level and patient-level analyses. Based on the lesion level, the

Forest plot of estimates of the DOR for NBI, HAL, and 5-ALA compared with WLC are shown in Figure 2. The pooled DOR values for NBI, HAL, and 5-ALA were 40.09 (95% CI, 20.08–80.01, Figure 2A), 78.14 (95% CI, 31.42–194.28, Figure 2B), and 18.14 (95% CI, 4.28–76.87, Figure 2C), respectively. The SROC curves for NBI, HAL, and 5-ALA are shown in Figure 3A. The AUROC values of NBI, HAL, and 5-ALA were 0.88 (95% CI, 0.85–0.91), 0.94 (95% CI, 0.92–0.96), and 0.82 (95% CI, 0.79-0.85), respectively. Importantly, the results of the SSY and SPY for each intervention are shown in Supplementary Figures 1–3. The pooled estimates for the SSY data for NBI, HAL, and 5-ALA were 0.94 (95% CI, 0.82–0.98, Supplementary Figure 1A), 0.95 (95% CI, 0.91–0.98, Supplementary Figure 2A), and 0.90 (95% CI, 0.71–0.97, Supplementary Figure 3A), respectively, whereas the SPY values for NBI, HAL, and 5-ALA were 0.79 (95% CI, 0.73–0.85, Supplementary Figure 1B), 0.81 (95% CI, 0.74–0.87, Supplementary Figure 2B), and 0.69 (95% CI, 0.57–0.79, Supplementary Figure 3B), respectively, presenting superiority compared with WLC. The DOR and AUROC values of NBI, HAL, and 5-ALA indicated excellent diagnostic performance.

Patient level analysis

For the patient level analysis, the AUROC, SSY, and SPY could not be calculated because few studies included these data. Figure 2 shows the Forest plots of DOR for NBI, HAL, and 5-ALA. NBI showed the highest DOR. The DOR values for NBI and HAL were 358.71 (95% CI, 44.50–2891.71, Figure 2D) and 59.95 (95% CI, 24.30–147.92, Figure 2E), respectively, presenting a better performance compared with that of WLC. The SROC curves for NBI, HAL, and 5-ALA are shown in Figure 3B. However, the DOR value for 5-ALA was 79.52

(95% CI, 0.94–6759.92, Figure 2F), and did not show a statistical difference.

Subgroup Analysis

Subgroup analyses were performed on studies with low to moderate RoB and at least 100 patients at the lesion level. The diagnostic performance results for studies with low to moderate RoB and at least 100 patients are shown in Supplementary Table 2. The Forest plot of the estimates of the pooled DOR for NBI, HAL, and 5-ALA with low to moderate RoB are shown in Supplementary Figure 4; while the Forest plot of the estimates of the pooled DOR for NBI, HAL, and 5-ALA with at least 100 patients are shown in Supplementary Figure 5. These results were consistent with those obtained in the overall analysis.

RoB of the included studies

The comparison-adjusted funnel plots of the diagnostic meta-analysis were not suggestive of any publication bias, as shown in Figure 4. The QUADAS-2 tool was applied for RoB assessment of the included studies in our meta-analysis (Supplementary Figure 6). Overall, all studies reported methodology for the index test and reference standard clearly, without a significant source of potential bias. Among them 69% (18/26) of the studies were presented as low or unclear RoB across most domains. The risk of bias in the patient selection in three studies was deemed high because of the absence of the consecutive inclusion of patients; four studies were deemed to have a high RoB for flow and timing.

DISCUSSION

Our systematic review indicated that the pooled diagnostic performance of NBI, HAL, or 5-ALA showed excellent efficacy compared with WLC. NBI could potentially be the most promising diagnostic intervention for patients with NMIBC, with advantages in terms of simplicity, cost, and reliability. In the present study, we have summarized the diagnostic performance of new technique-assisted cystoscopy strategies for NMIBC. A diagnostic meta-analysis was further undertaken to estimate the diagnostic performance of NBI, HAL, and 5-ALA compared with that of WLC. WLC has been the standard method to detect urothelial cell carcinoma of the bladder. However, the sensitivity of WLC is unsatisfactory and it can miss small 'satellite' tumors or carcinoma *in situ*. Thus, new imaging techniques (photodynamic diagnosis, narrow band imaging) have been introduced to enhance bladder cancer visualization to improve diagnostic accuracy and the thoroughness of resection. Several studies have demonstrated that the new imaging techniques showed superior diagnostic performance compared with WLC[11 50]. However, the application of these new imaging techniques has been limited by their increased false positives caused by intravesical instillation or inflammation, their technical complexity and increased cost[13-16]. It remains uncertain which technique could better improve the diagnostic accuracy of bladder cancer detection beyond the standard WLC. Virtually all the techniques assessed in this review were based on the reference standard of WLC, and new technique-assisted cystoscopy showed diagnostic superiority compared with conventional WLC. In this context, adoption of these strategies for practical bladder cancer diagnosis is essential. The results of the present study strongly suggested that new imaging-based technologies, in particular NBI,

would be promising diagnostic interventions for bladder cancer detection in clinical practice.

In response to the latent disadvantages of WLC, PDD, and NBI have been developed recently to improve the visualization of bladder tumors. The diagnostic superiority of PDD or NBI over WLC for tumor detection has been demonstrated in several studies [11 51 52]. A meta-analysis comparing PDD with WLC found a 21% increase in tumor detection with PDD in the pooled estimates for both patients and biopsies[53]. NBI, another optical enhancement technology, improves diagnostic accuracy by increasing the contrast of the superficial vasculature between the normal mucosa and tumor tissue. Previous studies reported significant improvement in the detection of bladder tumors using NBI cystoscopy compared with standard WLC [11 13]. Our previous meta-analysis indicated that NBI identifies an additional 17% of patients and an additional 24% of tumors compared with WLC [54]. However, these studies did not use standardized diagnostic accuracy definitions. Our diagnostic meta-analysis applied standard diagnostic accuracy definitions and furthermore, the pooled estimates demonstrated that new technique assisted-cystoscopy had significant diagnostic superiority compared with conventional WLC, demonstrating the sub-optimal performance of WLC in diagnosing NMIBC.

A study performed by Burger[55] showed that HAL assisted transurethral resection (TUR) significantly reduced the recurrence rate at 9-12 months compared with WLC-assisted TUR alone. In addition, Lee et al. performed a meta-analysis[56] evaluating oncological outcomes for WLC, PDD, and NBI-assisted TUR, which showed that both PDD and NBI reduced the recurrence rate compared with WLC. However, the therapeutic effectiveness of new

technique-assisted TUR, in terms of recurrence and progression, could not be demonstrated in the present review. Further therapeutic efficacy analysis is needed to identify promising interventions.

The strengths of our study include the stringent methodology used for searching and the study inclusion procedure, the standard definition of diagnostic performance and data extraction, the use of the strict diagnostic meta-analysis, and the specific QUADAS-2 tool for RoB assessment. Moreover, the strict diagnostic meta-analysis and further subgroup analysis was applied to synthesize the diagnostic accuracy to obtain a reliable result. However, potential study limitations should be acknowledged. The lack of data on important clinical variables, such as grade and stage of disease, primary *vs*. recurrent disease, and intravesical instillation settings, might have introduced clinical heterogeneity and prevented further subgroup analyses. The predictive performance of recurrence or progression was not demonstrated in our study, which might decrease the reliability of diagnostic performance. We have attempted to minimize bias throughout the whole procedure, with rigorous search and selection criteria, standard data extraction, and re-calculation, and subgroup analysis application, to evaluate the robustness of our findings.

In summary, this meta-analysis provided pooled diagnostic accuracy for NBI, HAL, and 5-ALA techniques for patients with NMIBC in comparison with WLC as the reference standard. The results demonstrated that the diagnostic performances of NBI, HAL, and 5-ALA were superior to that of WLC at the lesion level in diagnostic meta-analysis. The findings demonstrate the superior diagnostic performance of new imaging techniques in bladder detection compared with conventional WLC. These new imaging techniques are

promising diagnostic interventions to improve clinical procedures in bladder cancer detection.

Abbreviations

CI: Confidence intervals; CIS: carcinoma in situ; DOR: Diagnostic odds ratios; DTA: Diagnostic test accuracy; FNR: False negative rate; FPR: False positive rate; IQR: Interquartile range; HAL: hexylaminolevulinate; NBI: and narrow band imaging; NMIBC: Non-muscle-invasive bladder cancer; NPV: Negative predictive value; PDD: Photodynamic diagnosis; PPV: Positive predictive value; SPY: Specificity; SSY: Sensitivity; SROC: Summary receiver operating curve; AUROC: Area under the receiver operating characteristic curve; TURBT: Transurethral resection of bladder tumors; WLC: White light cystoscopy; 5-ALA: 5-aminolaevulinic acid.

Acknowledgements

We would like to thank Prof. J.X. Zhang, Department of Medical Statistics and Epidemiology, School of Public Health, Sun Yat-Sen University, Guangzhou, China, for statistical advice and research comments.

Contributors

CHC conceptualized and designed the study, drafted the initial and final manuscript, provided funding support. HH contributed to data collection and extraction, data analysis and interpretation, drafted initial and final manuscript. YZ contributed to article screening, data

collection and extraction, assessment of risk of bias and drafting manuscript: HL contributed to article screening, data collection and extraction and assessment of risk of bias. RJ Sylvester led and supervised statistical analysis, provided administrative support. TXL and JH contributed to study conceptualization and design, supervised study implementation, and critically reviewed the manuscript.

Funding

This study was funded by the National Natural Science Foundation of China (Grant No. 81572514,81472384, 81472381, 81402106, 81772719, 81772728, 91740119, 91529301); Guangdong Medical Research Fund (A2018330); Science and Technology Program of Guangzhou (Grant No. 201604020156, 201604020177, 201707010116, 201803010098); National Natural Science Foundation of Guangdong (Grant No. 2018A030313564, 2018B030311009, 2018A030310250,2016A030313321, 2015A030311011, 2015A030310122). Yixian Youth project of Sun Yat-sen Memorial Hospital (YXQH201812).

Competing interests

None declared.

Patient consent

Not required.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data sharing statement

There are no additional data available.

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Figure legends

Figure 1. The PRISMA flow chart of included studies in DTA analysis.

Figure 2. The Forest Plot of estimates of DOR for NBI (A), HAL (C), 5-ALA (E) in lesion level and estimates of DOR for NBI (B), HAL (D), 5-ALA (F) in patient level.

Figure 3. The SROC curve for NBI, HAL and 5-ALA diagnosing NMIBC in lesion level (A) and patient level (B).

Figure 4. Deeks' funnel plot with asymmetry test for NBI (A), HAL (B) and 5-ALA (C) in lesion level.

Table 1 Summary of the characteristics of the included studies

Study	Institution No.	patients	Index test	period	Age, mean (range)	Male (%)	NMIBC (%)	Tumor lesions (n)
Shadpour et al.2016[31]	Unicentre	50	NBI	2012-2013	63.86 ± 10.05	34(68.0)	100	95
Song et al.2016[29]	Unicentre	63	NBI	2012-2013	66(56-76)	39(61.9)	94.1	21
Kobotake et Al.2015[36]	Unicentre	135	NBI	2010-2014	75	110(81.5)	100	120
Ye et al.2015[11]	Multicentre	384	NBI	NR	61(21-79)	267(69.5)	100	167
Shen et al.2012[30]	Unicentre	78	NBI	2009-2010	68 (33–75)	62(79.5)	100	211
Zhu et al. 2012[26]	Unicentre	12	NBI	2009-2010	57(28-73)	9(75.0)	100	9
Tatsugami et Al.2010[28]	Unicentre	104	NBI	2007-2009	70.6 (38-90)	88(84.6)	NR	110
Cauberg et Al.2009[48]	Multicentre	95	NBI	2007-2009	70.6 (38.1-90.2)	70(73.7)	NR	226
Herr et Al.2008[39]	Unicentre	427	NBI	2007	65 (26-90)	316(74.0)	100	NR
Palou et Al.2014[34]	Multicentre	283	HAL	2008-2009	67.5(42-95)	242(85.5)	94.1	621
Lapini et Al.2012[35]	Multicentre	96	HAL	2010-2011	NR	80(83.3)	NR	108
Burgues et Al.2011[49]	Multicentre	305	HAL	2006-2009	66.9(39-93)	270(88.5)	100	600
Ray et al.2010[15]	Unicentre	27	HAL	2005-2006	70(49-82)	21(77.8)	100	NR
Schmidbauer et al.2009[32]	Unicentre	66	HAL	NR	63(38-84)	49(74.2)	93.1	NR
Geavlete et Al.2008[41]	Unicentre	128	HAL	2007-2008	65(36-81)	NR	92.2	NR
Fradet et Al.2006[42]	Multicentre	298	HAL	NR	67±11	223(74.8)	100	113
Jichlinski et Al.2003[37]	Multicentre	52	HAL	2000-2001	72±12	38(73.1)	100	143
Grimbergen et Al.2003[5]	Unicentre	160	5-ALA	1998-2002	67(30-91)	NR	90.0%	390

Filbeck et Al.2002[44]	Unicentre	279	5-ALA	1997-2000	34-89	NR	90.3%	336
Dominicis et Al.2001[46]	Unicentre	49	5-ALA	NR	60(31-77)	42(85.7)	100	52
Ehsan et Al.2001[45]	Unicentre	30	5-ALA	NR	55-89	19(63.3)	NR	NR
Jeon at Al.2001[38]	Unicentre	62	5-ALA	1997-1999	61.9(32-80)	57(91.1)	NR	148
Zaak et Al.2001[27]	Unicentre	605	5-ALA	NR	65.6(16-99)	472(78.0)	NR	552
Filbeck et Al.1999[43]	Unicentre	123	5-ALA	1997	64.5(28-86)	NR	91.9	124
Riedl et Al.1999[33]	Unicentre	52	5-ALA	NR	44-79	NR	100	123
D'hallewin et Al.1998[47]	Unicentre	16	5-ALA	NR	NR	NR	100	50

WLC: white light cystoscopy; NT: new technology; 5-ALA: 5-aminolaevulinic acid; HAL: hexylaminolevulinate; NBI: narrow band imaging; NR: not reported.

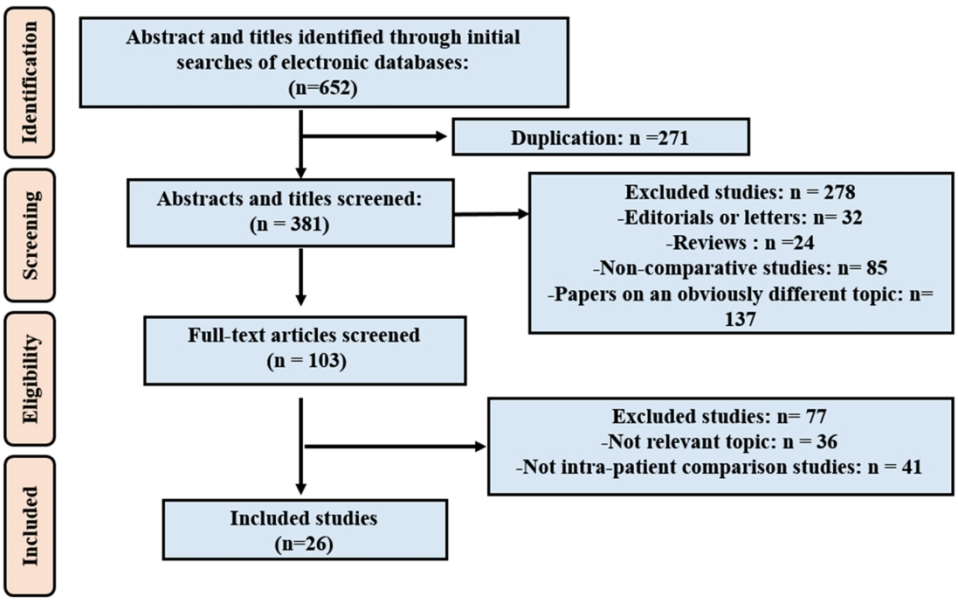

Figure 1. The PRISMA flow chart of included studies in DTA analysis.

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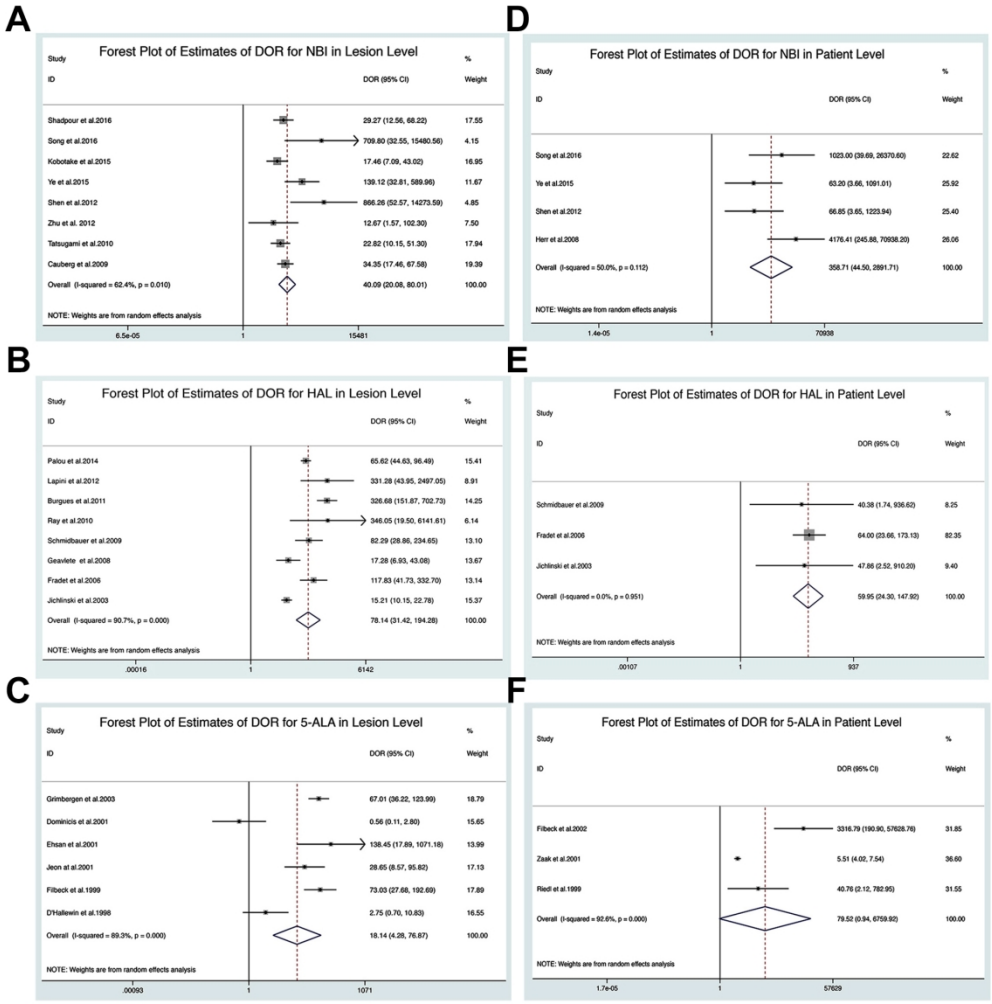


Figure 2. The Forest Plot of estimates of DOR for NBI (A), HAL (B), 5-ALA (C) in lesion level and estimates of DOR for NBI (D), HAL (E), 5-ALA (F) in patient level.

177x180mm (300 x 300 DPI)

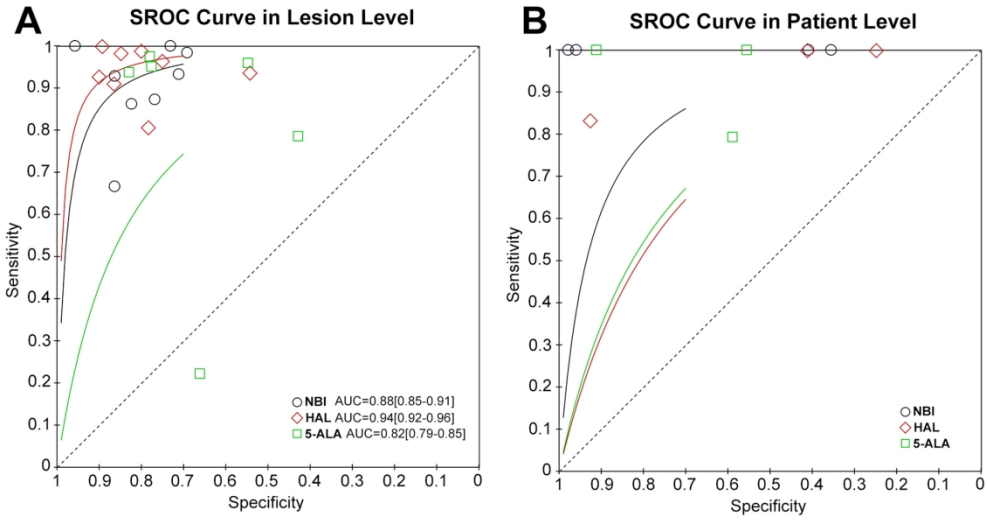


Figure 3. The SROC curve for NBI, HAL and 5-ALA diagnosing NMIBC in lesion level (A) and patient level (B).

177x94mm (300 x 300 DPI)

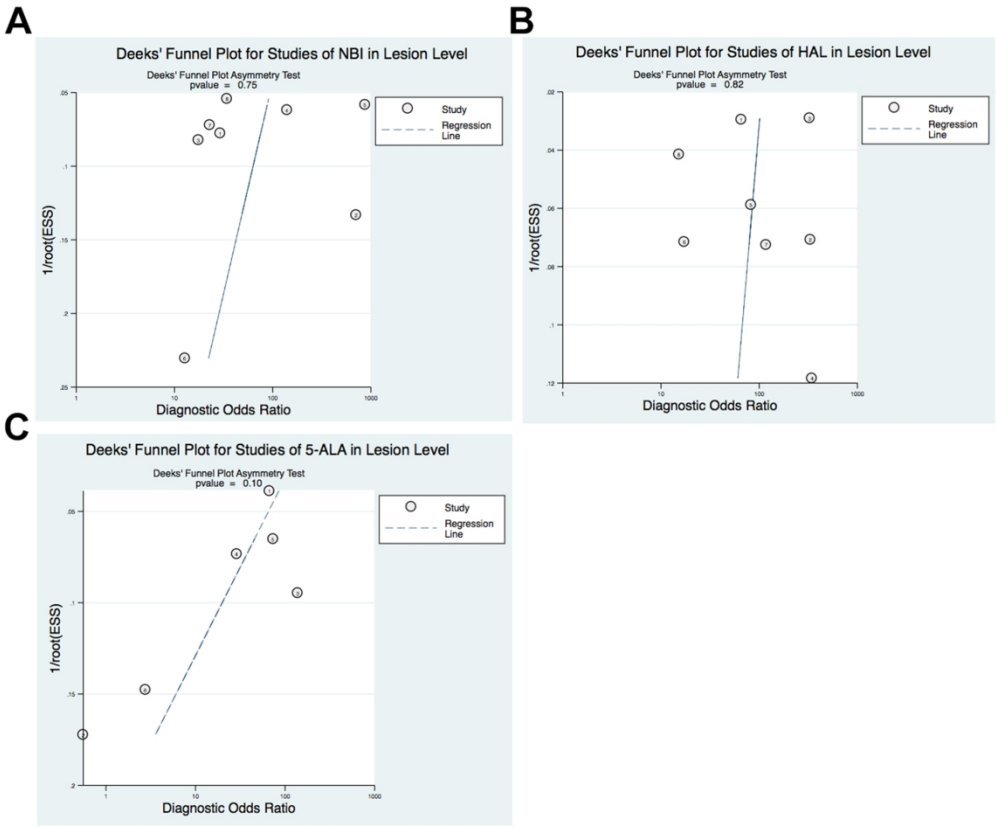
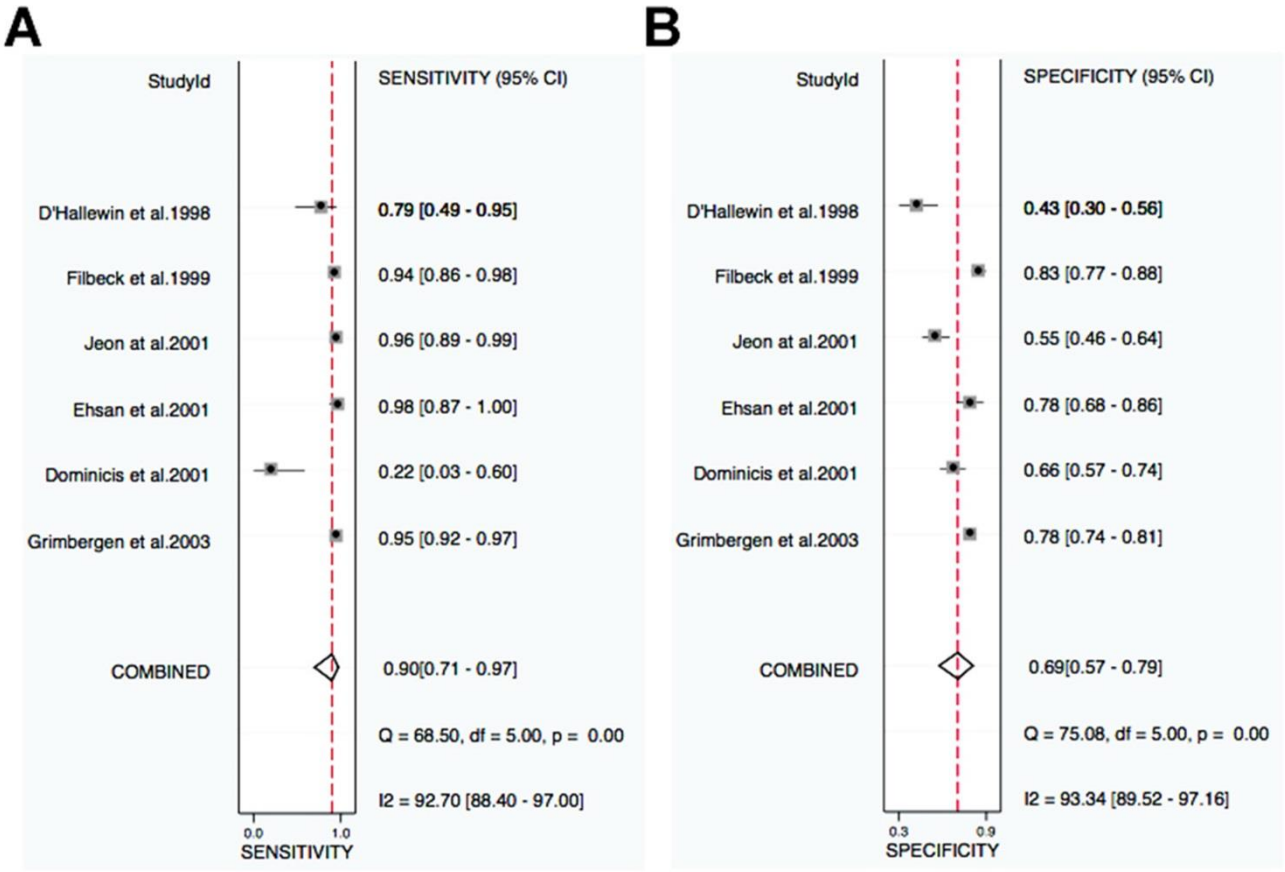


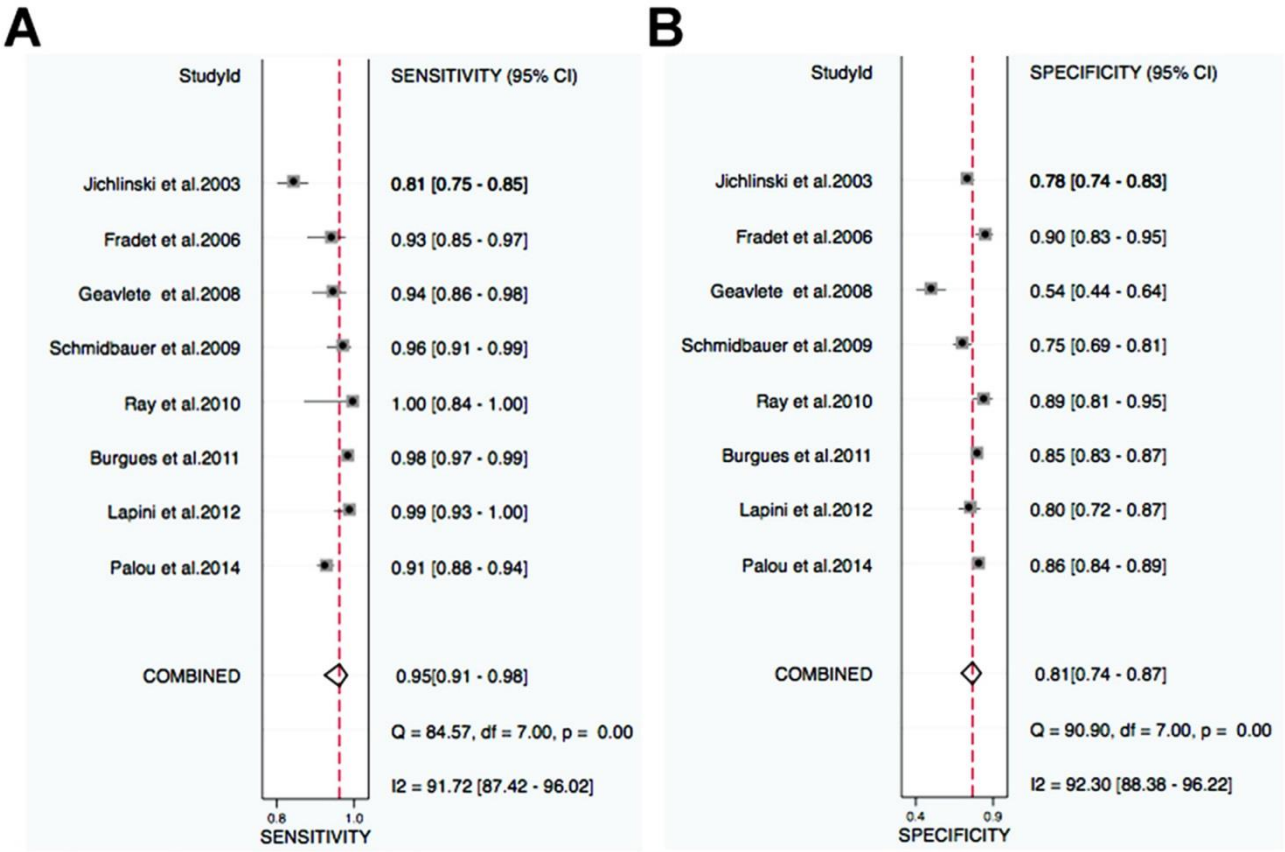
Figure 4. Deeks' funnel plot with asymmetry test for NBI (A), HAL (B) and 5-ALA (C) in lesion level.

177x147mm (300 x 300 DPI)

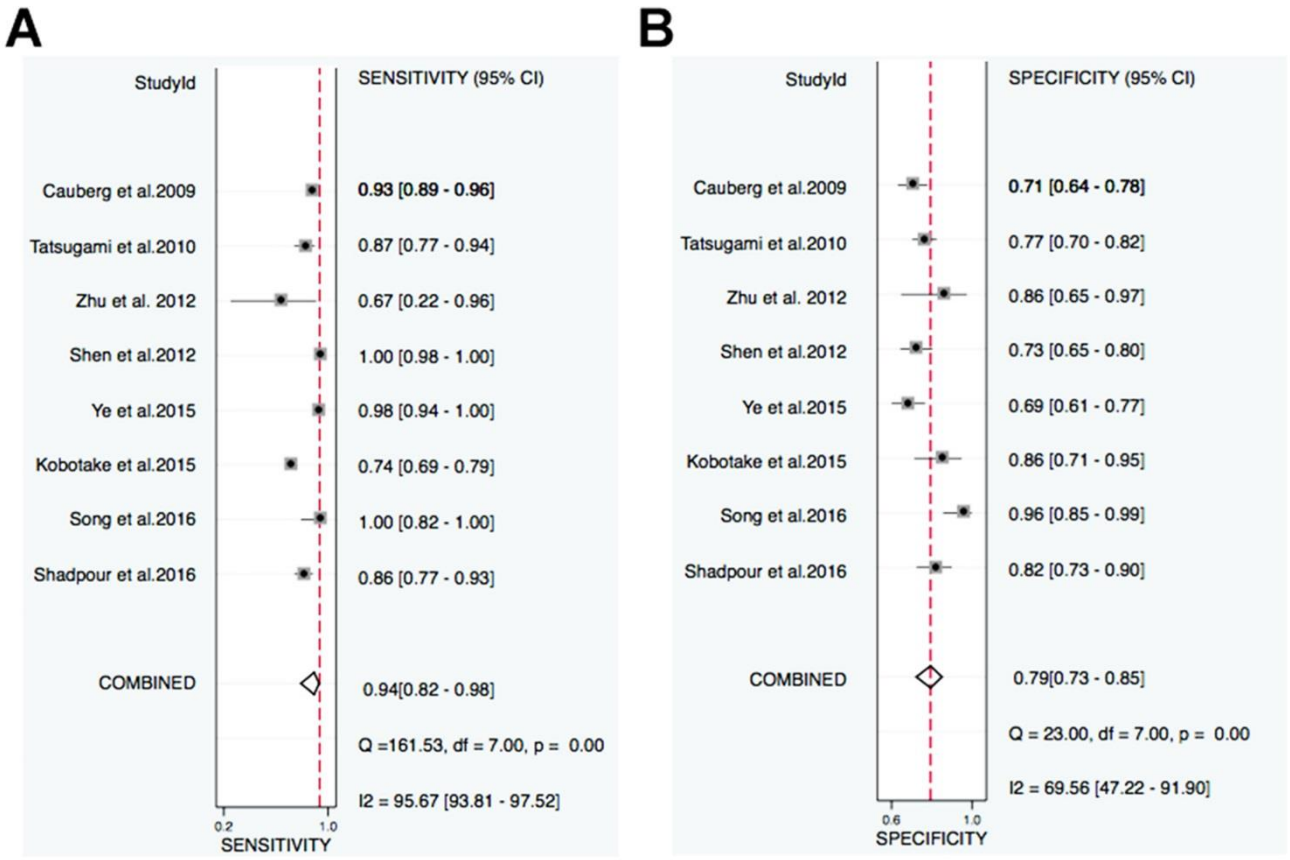
Supplementary Information



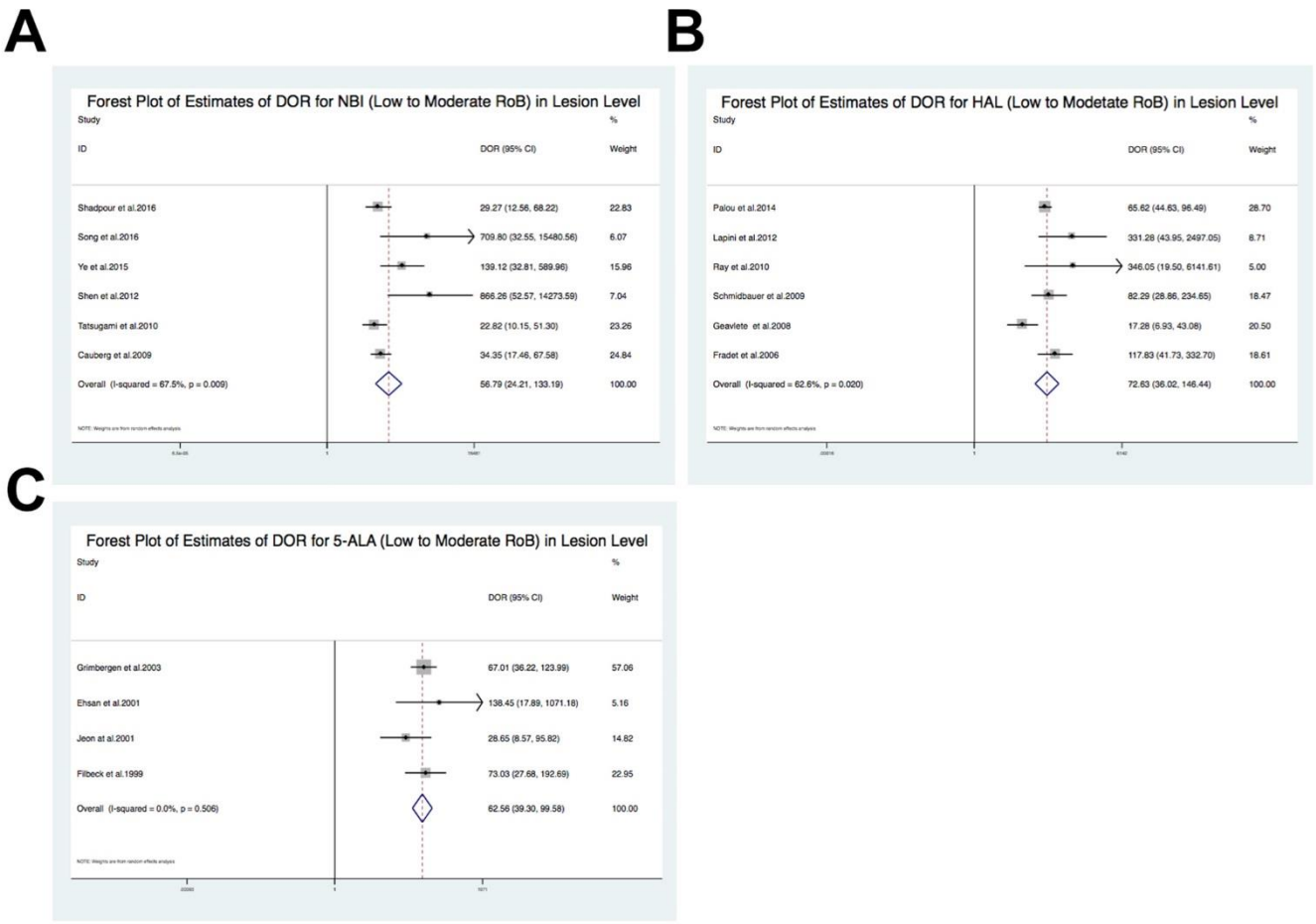
Supplementary Figure 1. The Forest Plot of study specific and pooled sensitivity (A) and specificity (B) for NBI in lesion level.



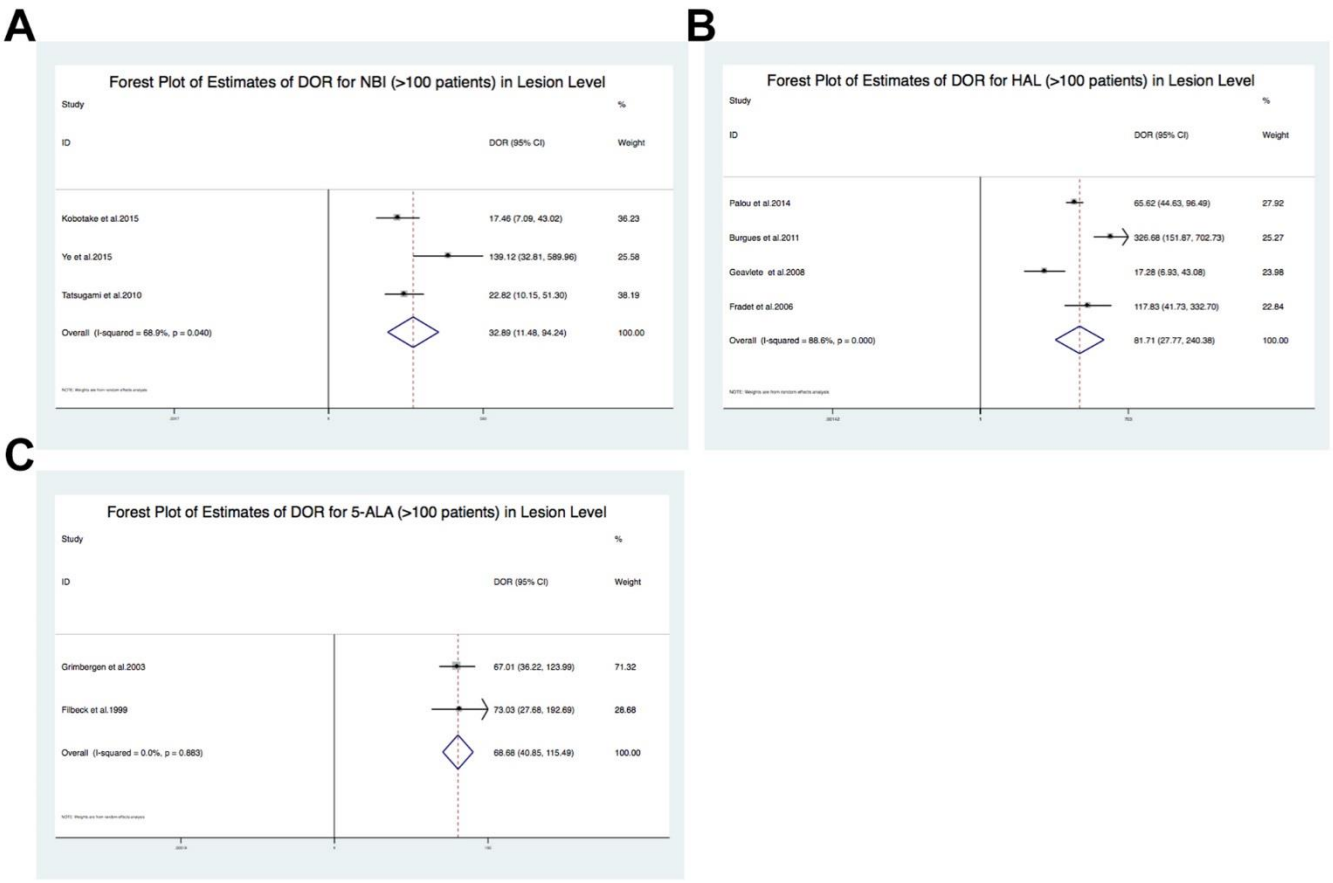
Supplementary Figure 2. The Forest Plot of study specific and pooled sensitivity (A) and specificity (B) for HAL in lesion level.



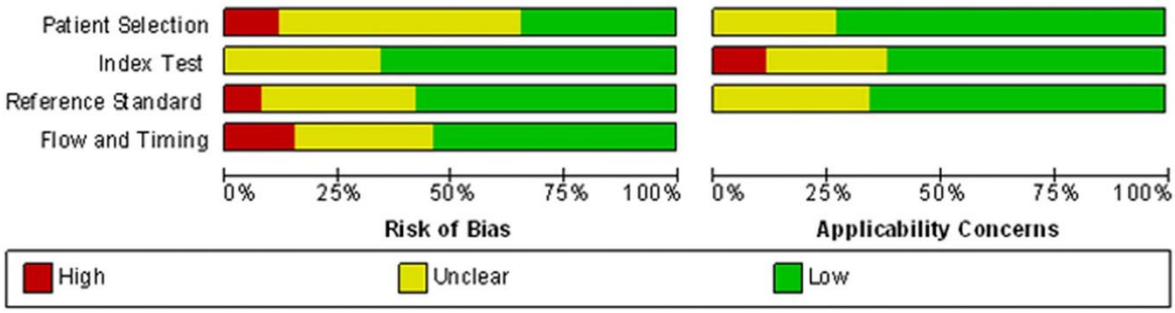
Supplementary Figure 3. The Forest Plot of study specific and pooled sensitivity (A) and specificity (B) for 5-ALA in lesion level.



Supplementary Figure 4. The Forest Plot of estimates of DOR for NBI (A), HAL (B) and 5-ALA (C) with low to moderate RoB in lesion level.



Supplementary Figure 5. The Forest Plot of estimates of DOR for NBI (A), HAL (B) and 5-ALA (C) with at least 100 patients in lesion level.



Supplementary Figure 6. Quality assessment of included studies. The distribution plot for risk of bias using QUADAS-2 tool. Studies are deemed to be at high, low or unclear risk of bias for each domain.

Supplementary Table1. Diagnostic performance results of individual studies for Meta-analysis

Study ID	Patient-level analysis							Lesion-level analysis						
	Patient No.	SSY	SPY	FPR	FNR	PPV	NPV	Lesion No.	SSY	SPY	FPR	FNR	PPV	NPV
NBI vs WLC														
Shadpour et al.2016[1]	50	NR	NR	NR	NR	NR	NR	175	69/80	70/85	15/85	11/80	69/84	74/75
Song et al.2016[2]	63	16/16	46/47	1/47	0/16	16/17	23/23	66	19/19	45/47	2/47	0/19	19/21	7/7
Kobotake et al.2015[3]	135	NR	NR	NR	NR	NR	NR	379	78/84	227/263	36/263	6/84	78/114	203/203
Ye et al.2015[4]	103	56/56	16/45	29/46	0/56	56/85	8/8	300	124/126	92/133	41/133	2/126	124/165	83/85
Shen et al.2012[5]	78	47/47	9/22	13/22	0/47	47/47	7/7	309	160/160	98/134	36/134	0/160	160/196	72/72
Zhu et al. 2012[6]	12	NR	NR	NR	NR	NR	NR	31	4/6	19/22	3/22	2/6	4/7	20/20
Tatsugami et al.2010[7]	104	NR	NR	NR	NR	NR	NR	313	55/63	156/203	47/203	8/63	55/102	144/144
Cauberg et al.2009[8]	95	NR	NR	NR	NR	NR	NR	389	167/179	116/163	47/163	12/179	167/214	47/51
Herr et al.2008[9]	427	90/90	311/324	13/324	0/90	90/103	265/265	NR	NR	NR	NR	NR	NR	NR
HAL vs WLC														
Palou et al.2014[10]	283	NR	NR	NR	NR	NR	NR	1492	379/416	820/948	128/948	37/416	379/507	699/702
Lapini et al.2012[11]	96	NR	NR	NR	NR	NR	NR	234	82/83	101/126	25/126	1/83	82/107	80/81
Burgues et al.2011[12]	305	NR	NR	NR	NR	NR	NR	1659	404/441	900/1059	159/1059	7/441	404/563	863/863

Ray et al.2010[13]	27	NR	NR	NR	NR	NR	NR	120	21/21	84/94	10/94	0/21	21/31	35/35
Schmidbauer et al.2009[14]	66	52/52	2/8	6/8	0/52	52/58	3/3	364	109/113	151/201	50/201	4/113	109/159	158/158
Geavlete et al.2008[15]	128	NR	NR	NR	NR	NR	NR	243	87/93	56/103	47/103	6/93	87/134	76/82
Fradet et al.2006[16]	196	40/48	128/138	10/138	8/48	40/50	106/113	206	77/83	101/112	11/112	6/83	77/88	63/71
Jichlinski et al.2003[17]	52	33/33	7/17	10/17	0/33	33/43	3/3	143	205/254	269/343	74/343	49/254	205/279	306/314
5-ALA vs WLC														
Grimbergen et al.2003[18]	160	NR	NR	NR	NR	NR	NR	889	232/244	409/527	118/527	12/244	232/350	248/257
Filbeck et al.2002[19]	279	168/168	93/102	9/102	0/168	168/177	81/81	NR	NR	NR	NR	NR	NR	NR
Dominicis et al.2001[20]	49	NR	NR	NR	NR	NR	NR	179	2/9	84/127	43/127	7/9	2/45	80/80
Ehsan et al.2001[21]	30	NR	NR	NR	NR	NR	NR	151	39/40	71/91	20/91	1/40	39/59	59/59
Jeon at al.2001[22]	62	NR	NR	NR	NR	NR	NR	257	71/74	69/126	57/126	3/74	71/128	54/54
Zaak et al.2001[23]	605	288/363	271/460	189/460	75/363	288/477	55/108	NR	NR	NR	NR	NR	NR	NR
Filbeck et	123	NR	NR	NR	NR	NR	NR	341	75/80	185/223	38/223	5/80	75/113	78/78

al.1999[24]														
Riedl et al.1999[25]	52	26/26	10/18	8/18	0/26	26/34	6/6	NR	NR	NR	NR	NR	NR	NR
D'Hallewin et al.1998[26]	16	NR	NR	NR	NR	NR	NR	113	11/14	27/63	36/63	3/14	11/47	34/34

NMIBC: non-muscle-invasive bladder cancer; WLC: white light cystoscopy; 5-ALA: 5-aminolaevulinic acid; HAL: hexylaminolevulinate; NBI: narrow band imaging; NT: new technology; SSY: sensitivity; SPY: specificity; FPR: false positive rate; FNR: false negative rate; PPV: positive predictive value; NPV: negative predictive value; NR: not reported.

Supplementary Table2. Diagnostic performance results for sensitivity analysis of studies with low to moderate RoB and at least 100 patients at lesion level.

	Low to moderate RoB			At least 100 patients		
	Median	**Lower Quartile**	**Upper Quartile**	**Median**	**Lower Quartile**	**Upper Quartile**
NBI vs WLC (n=6)				**NBI vs WLC (n=3)**		
Sensitivity	95.85	88.80	99.60	92.86	90.08	95.63
Specificity	74.99	71.66	80.98	76.85	73.01	81.58
Positive predictive value	79.84	75.87	82.02	68.42	61.17	71.79
Negative predictive value	99.33	97.90	100	100	98.82	100
False positive rate	25.01	19.02	28.34	23.15	18.42	26.99
False negative rate	4.15	0.40	11.20	7.14	4.37	9.92
HAL vs WLC (n=6)				**HAL vs WLC (n=4)**		
Sensitivity	95.00	92.97	98.21	92.19	91.48	92.97
Specificity	83.33	76.38	88.65	85.74	77.33	87.42
Positive predictive value	71.65	67.94	76.16	73.26	70.05	77.94
Negative predictive value	99.17	94.20	99.89	96.13	91.70	99.68
False positive rate	16.67	11.35	23.62	14.26	12.58	22.67
False negative rate	5.00	1.79	7.03	6.84	5.24	7.65
5-ALA vs WLC (n=4)				**5-ALA vs WLC (n=2)**		
Sensitivity	95.51	94.75	96.33	94.42	-	-
Specificity	77.82	71.90	79.26	80.28	-	-
Positive predictive value	66.19	63.44	66.31	66.33	-	-
Negative predictive value	100	99.12	100	98.25	-	-
False positive rate	22.18	20.74	28.10	19.72	-	-
False negative rate	4.49	3.67	5.25	5.58	-	-

NMIBC: non-muscle-invasive bladder cancer; WLC: white light cystoscopy; 5-ALA: 5-aminolaevulinic acid; HAL: hexylaminolevulinate; NBI: narrow band imaging; NR: not reported.

Appendix: Full search strategy

1. Searching in MEDLINE, Embase and CENTRAL

All databases were searched using both controlled vocabulary (namely MeSH in MEDLINE and EMTREE in Embase) and a wide range of free-text terms

Search code for MEDLINE (accessed via PubMed) and CENTRAL

Patients		
Bladder cancer	#1	bladder neoplasms [MeSH] OR carcinoma OR tumor, urothelial cell [MeSH] OR transitional cell carcinoma*[tiab] OR bladder neoplasm*[tiab] OR bladder cancer[tiab] OR BCa[tiab]
Index test		
Photodynamic diagnosis	#2	"photodynamic diagnosis" [MeSH] OR "PDD" [tiab] OR "photodynamic" [tiab] OR hexaminolevulinate [tiab] OR HAL[tiab] OR "5-aminolevulinate acid"[tiab] OR 5-ALA[tiab] OR cystoscopic[tiab] OR cystoscopy
Narrow band imaging	#3	"narrow band imaging" [MeSH] OR NBI [tiab] OR cystoscopic[tiab] OR cystoscopy[tiab]
Cochrane Highly Sensitive Search Strategy	#4	(observational trial[Publication Type] OR diagnostic[Publication Type] OR detection[tiab] OR observational[tiab] OR trial[tiab] OR groups[tiab]) NOT (animals[mh] NOT humans[mh])
Search algorithm		#1 AND (#2 OR #3) AND #4

2.Searching other resources

Previous systematic reviews in the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effectiveness and the PROSPERO international prespective register of systematic reviews for completed or published systematic reviews

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Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title page
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	None
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5-6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Figure1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6-7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6-7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8

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Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7-8

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6-7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8-9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Supplementary Figure 6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Supplementary Table 1
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	9-10
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	10
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10-12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12
FUNDING			

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Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	13-14

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

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