The Accuracy of Confocal Laser Endomicroscopy in Diagnosing Bladder Cancer: A Systematic Review and Meta-Analyses

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ARTICLE INFO

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ABSTRACT

Background: Multiple advancements of endoscopic technology were designed to enhance the sensitivity and specificity of the diagnostic tools of bladder cancer; thus, we perform a meta-analysis to compare diagnostic performance between confocal laser endomicroscopy (CLE) and biopsy for detecting bladder cancer.

Methods: We compared CLE's accuracy in diagnosing bladder cancer reported by studies obtained from the electronic database MEDLINE, CENTRAL, and CINAHL, from May to June 2020. The pooled effect estimate was calculated employing the DerSimonian and Laird random-effects model. We only included moderate to high-quality studies, which had been assessed by the QUADAS-2 tool.

Results: Eight studies were included in this review; five of those were good-quality studies. A total of 519 samples from 345 patients were included in the pooled effect estimate calculation. Pooled sensitivity and specificity of CLE in diagnosing bladder cancer were 90.2% (0.86, 0.93) and 78.1% (0.71, 0.85), respectively. The use of white-light cystoscopy (WLC) before CLE increased its specificity (56.8% versus 84.6%). Pooled sensitivity and specificity of CLE in predicting low-grade lesion were 73% (0.66, 0.80) dan 83% (0.78, 0.87), respectively. Meanwhile, pooled sensitivity and specificity of CLE in predicting high-grade lesion were 73% (0.66, 0.78) and 79% (0.73, 0.83), respectively.

Conclusions: CLE has good accuracy in distinguishing malignant and benign tumors. Grading tumors with this modality is also accurate. The use of probe CLE (pCLE), coupled with WLC, will increase its specificity.

INTRODUCTION

Bladder cancer is one of the most malignant cancers globally, placed as the sixth most common malignancy [1] The five-year relative survival rates of patients with breast, prostate, and colon cancer have increased by over 15%, while the trend was elevated only merely by 6% for bladder cancer [2]. In addition, the incidence of bladder cancer has been shown to keep increasing remarkably in the developed nation, which can be associated with high productivity and bladder cancer risk factors, including alcohol, red meat consumption, smoking, and obesity. Bladder cancer incidence rate was also found to be the highest in Southern and Western Europe and North America. Meanwhile, the highest mortality rates were in Western Asia and Northern Africa [3].

There are three main types of bladder cancer, which are named after the type of cells. They are transitional cell carcinoma or sometimes called urothelial carcinoma (UCC), squamous cell carcinoma (SCC), and adenocarcinoma (ADC). UCC is derived from cells at the innermost tissue of the bladder tissue that functions to stretch when the bladder is full. It is the most common type of bladder cancer that accounts for almost 90% of bladder cancer [4]. SCC is emanated from the cell that lines the bladder, while ADC is originated from glandular cells underneath the lining of the bladder. Moreover, the survival rate of bladder cancer is higher when the cancer is still localized

(69%) than when cancer has spread to distant organs (5%) [2]. Unfortunately, bladder cancer has a notorious characteristic, it is a high tendency to relapse and its imminent progression risk [5,6]. This trend increases the frequency of follow-up schedules, making bladder cancer expensive cancer to treat [6]. Furthermore, the cancer was found to be invasive in around 10–15% of relapse cases [5]. Therefore, early yet accurate diagnosis and prompt treatment play an essential role in recognizing early relapse and minimizing the risk of tumor progression.

For diagnosing bladder cancer, cystoscopy/biopsy and urinary cytology remain the current gold standard [7]. White light cystoscopy (WLC) is initially used to determine the gross structure, location, size, and number of the tumor. WLC can also be employed as a guide for transurethral resection of bladder tumors (TURBT) [8]. However, WLC has very low sensitivity and specificity in detecting bladder cancer (68.3% and 82.9%, respectively) [9]. Several factors, including limited WLC visualization in distinguishing the borders of the tumor and margins of the submucosal tumor, contribute to the poor diagnosis [10]. It will lead to incomplete tumor resection, especially when multifocal lesions are presented [11]. In addition, a conventional biopsy cannot be performed accurately and should be replaced with a more specific tool, such as a real-time in vivo optical biopsy.

For this reason, multiple advancements of endoscopic technology were designed to enhance the sensitivity and specificity of the diagnostic tools. Several endoscopies have been designed to be able to accurately pinpoint the tumor location through fluorescent, enhanced visualization of the vasculature or near-infrared light. For instance, photodynamic diagnosis (PDD) and narrow-band imaging (NBI) were utilized for macroscopic imaging, whereas confocal laser endomicroscopy (CLE) and optical coherence tomography (OCT) were used as microscopic imaging [12]. In addition, each endoscopic technology possesses its advantages and disadvantages. For instance, PDD and NBI are beneficial for observing suspicious lesions, while OCT and CLE are useful for tumor staging and grading [10].

CLE is an optical biopsy equipped with a high microscopic resolution with images comparable with a traditional histopathology biopsy sample. CLE is, by far, one of the optical biopsy technologies that can differentiate between low and high-grade bladder cancer [10]. Therefore, the purpose of this study is to perform a meta-analysis to compare CLE and biopsy diagnostic performance for detecting bladder cancer.

METHODS

Description of condition and intervention

This study aims to find the accuracy of the CLE modality in diagnosing bladder cancer. Therefore, this systematic review included studies comparing biopsy methods (golden standard) with CLE (index test) in diagnosing patients with suspected bladder cancer. We excluded studies describing the use of CLE in the detection or grading of urological cancer or pre-malignant disease processes without any restriction of CLE specification. CLE assessment employed CLE criteria as described by Chang et al. [13], which comprised papillary configuration, cell organization, the cohesiveness of cells, cellular morphology, the definition of cell borders, vasculature, and polarity.

Database searching and literature screening

A literature search was conducted in five electronic databases (MEDLINE, CENTRAL, CINAHL, Scopus, and ProQuest). We utilized PICOS to make it easier to track studies and identify the suitability of studies we found. We conducted this literature search from May to June 2020. We used specific keywords adjusted according to each database (**Table 1**). We also looked for references from other systematic reviews analyzing similar things. We also restricted studies written in Indonesian/English to be included in this systematic review.

Study selection

This systematic review's writing was based on preferred reporting items for systematic reviews and meta-analysis (PRISMA) statements and Standards for Reporting Diagnostic Accuracy Studies (STARD). The inclusion criteria for this study included: 1) Clinical studies according to PICOS; 2) English/Indonesian articles; 3) Full-text articles were available; 5) Published in the last ten years. This study's exclusion criteria consisted of studies in the form of systematic or meta-analysis, literature review, case reports, case series, editorial letters, studies on animals, and/or studies in the process of peer review (not yet published). Each author independently assessed the study eligibility by looking at the title and abstract and analyzing full-text for the remaining articles. Any discrepancies among authors were resolved by discussion.

Data extraction and outcome of interest

Each writer extracted data independently onto a pre-defined extraction sheet. We extracted data from study characteristics, including patient characteristics, study design, sample size, and diagnosis modalities. However, we did not restrict the type of CLE modality performed on patients. The biopsy method was also not restricted. Any disagreement was resolved by discussion.

Moreover, this systematic review aims to assess the accuracy of the bladder cancer diagnosis method using CLE. The primary outcome of interest was the sensitivity and specificity of CLE compared to biopsy. The secondary outcomes studied were feasibility, cost, and standard operative equipment. We used a 2x2 contingency table to assess the accuracy of the CLE examination results for each study. The accuracy reported by each study

was then calculated employing the forest plot. We also utilized the Meta-Disc 1.4 application to compile these outcomes and create ROC curves, using the DerSimonian and Laird random-effects model.

Assessment of methodologic quality

This systematic review included diagnostic studies with both experimental and observational designs. We assessed the risk of bias in all studies using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool [14]. We only included studies of at least moderate quality in meta-analysis.

RESULTS

Literature search

A search with specific keywords in five electronic databases found 459 articles, with 31 articles found in more than one database. We screened titles and abstracts in the remaining articles and found 20 studies that we thought were following our PICOS systematic review. However, after we analyzed the article's full text, only eight studies were in accordance with this PICO systematic review. PRISMA flow chart describing the process for identifying included articles can be seen in **Figure 1**.

Study characteristics

Eight studies were included in this systematic review. Among these eight studies, only two studies were published before 2015. Seven studies analyzed CLE's ability in tumors grading (high/low-grade), and six studies investigated CLE's ability to differentiate malignant from benign tumors. Based on each study's

population, this systematic review involved 345 patients and 519 tissue samples. These studies spread across three continents, America, Asia, and Europe, most of which were conducted in Europe (**Table 2**).

This systematic review also tried to analyze the accuracy of a measuring instrument in diagnosing a condition; therefore, diagnostic studies were included in this review. To assess the quality of these diagnostic studies, we utilized the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool. In general, the studies we included were of moderate to good quality. Only three studies had moderate quality. The results of the risk assessment bias can be found in **Figure 2**.

CLE accuracy in differentiating malignant and benign tumors

Most studies reported that CLE had high sensitivity in differentiating malignant tumors from benign tumors. Five experiments in four studies reported a sensitivity of more than 90%. Only the study of Marien et al. [21] reported sensitivity below 80%. We conducted a pooling effect estimate using Mosses-Litenberg's Bivariate Model and found a pooled sensitivity of 90.2% (0.86, 0.93). The result is shown in **Table 3**.

CLE's specificity in determining malignant lesions is not as excellent as its sensitivity. 4 out of 7 experiments reported specificity at> 70%. However, the other 3 showed very low results. After we conducted a meta-analysis with the random effect model, we found a pooled specificity of 78.1% (0.71, 0.85). The area under the Curve was recorded at 0.9033 (0.0279), which indicates that CLE has high sensitivity and a low false-positive rate. The results of the pooling effect estimate are in **Figure 3**.

Table 1. Literature finding's result

| Database	Keywords	Hit	Selected	Comments
MEDLINE	((((bladder cancer[MeSH Terms]) OR (bladder tumor[MeSH Terms])) OR (bladder tumors[MeSH Terms])) OR (urothelial carcinoma)) AND ((confocal laser scanning microscopy[MeSH Terms]) OR (confocal laser endomicroscopy)) Limit to: clinical trial	3	1	1 not match PICOS 1 excluded after full-text analysis as no outcome measure estimated
CENTRAL	"confocal laser endomicroscopy" in All Text AND "bladder cancer" OR "bladder tumor" OR "bladder tumors" OR "urothelial cell carcinoma" in All Text AND "sensitivity" OR "specificity" OR "accuracy" in All Text - (Word variations have been searched)	0	0	-
CINAHL	TX "confocal laser endomicroscopy" AND TX ("bladder cancer" OR "bladder tumor" OR "bladder tumors" OR "urothelial cell carcinoma") AND TX ("sensitivity" OR "specificity" OR "accuracy")	74	4	54 not match PICOS 16 article review
Scopus	ALL("confocal laser endomicroscopy") AND ALL("bladder cancer" OR "bladder tumor" OR "bladder tumors" OR "urothelial cell carcinoma") AND ALL("sensitivity" OR "specificity" OR "accuracy")	168	4	121 not match PICOS 40 article review 3 pilot study
ProQuest	(confocal laser endomicroscopy) AND ("bladder cancer" OR "bladder tumor" OR "bladder tumors" OR "urothelial cell carcinoma") AND ("sensitivity" OR "specificity" OR "accuracy")	205	3	155 not match PICO 43 article review 4 pilot study
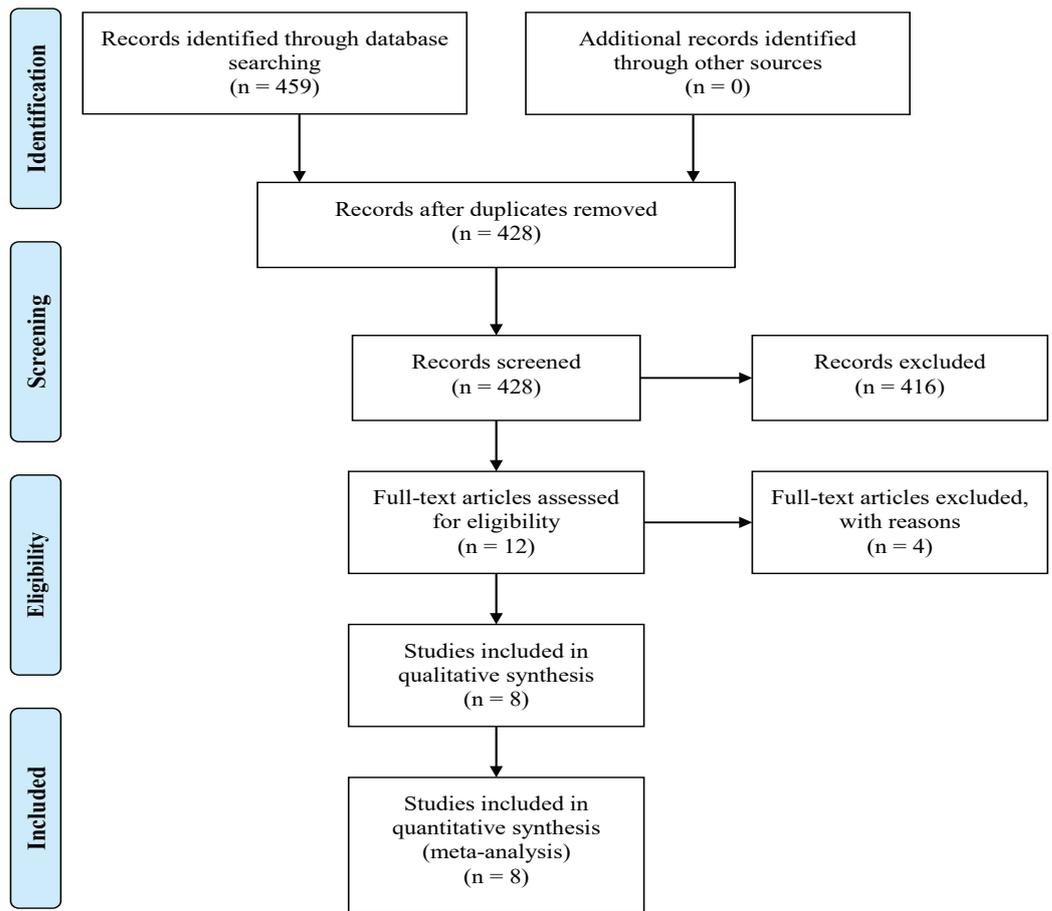
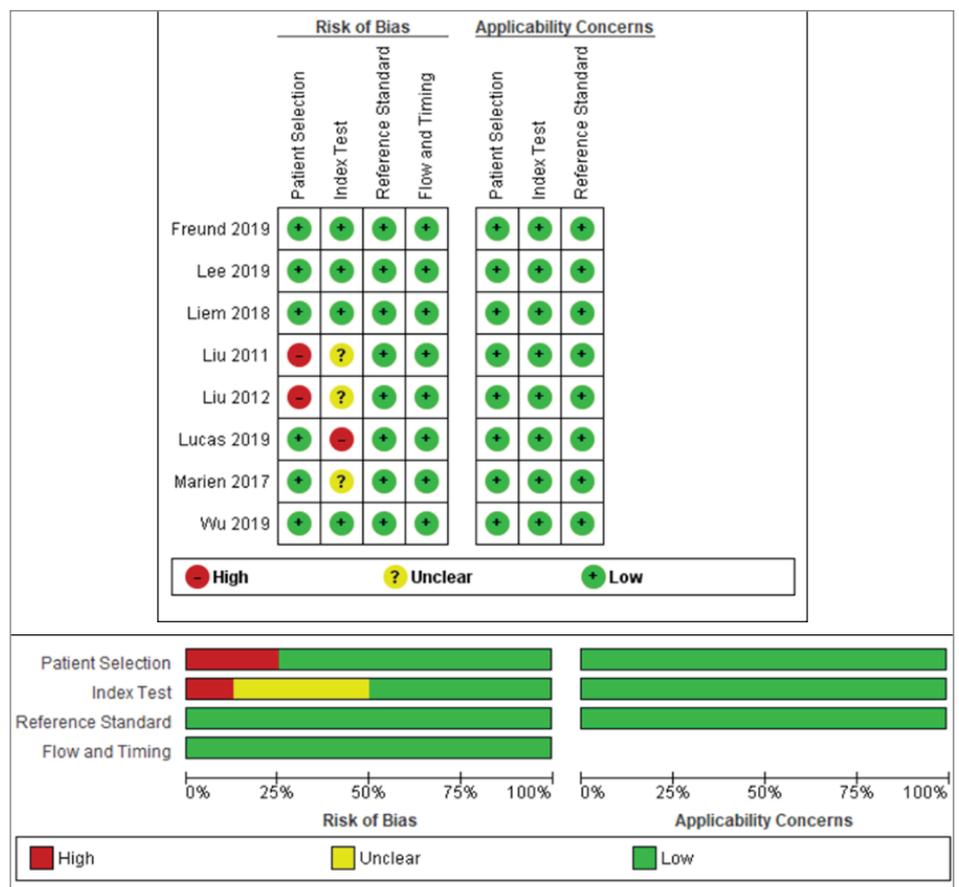**Figure 1.** PRISMA flow chart describing the process for identifying included articles

Figure 2. Risk of bias assessment of RCTs using Cochrane Risk of Bias Assessment.

Table 2. Characteristics of the study included in this systematic review

Author	Country	N	Age	Lesions (n)	% male	Outcome	Design
Freund, et al. (2019).[15]	Netherland	36	70 ± 11	53	69	Grading high/low grade tumor	Prospective clinical trial
Lee, et al. (2019).[16]	South Korea	75	68.32 ± 9.45	119	86.7	Differentiating benign/ malignant lesion, grading high/ low-grade malignant tumor	Prospective clinical trial
Liem, et al. (2018).[17]	Netherland	53	70 ± 12	66	74	Differentiating benign/ malignant lesion, grading high/ low-grade malignant tumor	Prospective clinical trial
Liu, et al. (2012).[18]	USA	57	NR	78	NR	Grading high/low-grade tumor	Prospective clinical trial
Liu, et al. (2011).[19]	USA	29	71 (28–90)	89	NR	Differentiating benign/ malignant lesion	Prospective clinical trial
Lucas, et al. (2019).[20]	Netherland	53	NR	72	NR	Differentiating benign/ malignant lesion, grading high/ low-grade malignant tumor	Prospective clinical trial
Marien, et al. (2017).[21]	France	21	68 (51–82)	21	NR	Differentiating benign/ malignant lesion, grading high/ low-grade malignant tumor	Prospective clinical trial
Wu, et al. (2019).[22]	People's Republic of China	21	61 (32–81)	21	81	Differentiating benign/ malignant lesion, grading high/ low-grade malignant tumor	Prospective clinical trial

NR, not reported; Age, presented either in mean ± SD or mean (range)

Table 3. Systematic review table of CLE's performance on diagnosing bladder cancer

Author	CLE specification	Pattern	Malignancy differentiating accuracy		Low-grade tumor differentiating accuracy		High-grade tumor differentiating accuracy		Quality
			Sens	Spec	Sens	Spec	Sens	Spec	
Freund, et al. 2019.[15]	2.7 Fr probe UroFlex	pCLE	NR	NR	76.47%†	63.16%†	63.16%†	76.47%†	Good
Lee, et al. 2019.[16]	2.5-mm probe GastrFlex	pCLE	91.67%	73.91%	66.67%†	94.55%†	94.55%†	66.67%†	Good
Liem, et al. (A) 2018.[17]	2.6-mm probe Cystoflex	pCLE	96.15%	28.57%	76.00%	75.61%	70.37%	69.23%	Good
Liem, et al. (B) 2018.[17]	2.6-mm probe Cystoflex	pCLE + WLC	92.31%	50.00%	80.00%	78.05%	66.67%	79.49%	Good
Liu, et al. (A) 2012.[18]	1.4-mm probe AlveoFlex	pCLE	NR	NR	58.82%	81.97%	54.55%	82.22%	Fair
Liu, et al. (B) 2012.[18]	1.4-mm probe AlveoFlex	pCLE + WLC	NR	NR	64.71%	80.33%	66.67%	80.00%	Fair
Liu, et al. 2011.[19]	1.4-mm probe AlveoFlex	pCLE + WLC	93.10%	96.67%	NR	NR	NR	NR	Fair
Lucas, et al. 2019.[20]	2.6-mm probe Cystoflex	pCLE + WLC	81.58%	78.57%	79.17%†	85.71%†	85.71%†	79.17%†	Fair
Marien, et al. 2017.[21]	Single-band 2.5-mm probe GastroFlex and dual-band Ultra Mini O-Probe (prototype)	pCLE + HAL	53.33%	100.00%	71.43%	100.00%	37.50%	100.00%	Good
Wu, et al. 2019.[22]	2.6-mm probe Cystoflex	pCLE + WLC	100.00%	50.00%	85.71%	85.71%	80.00%	90.91%	Good

NR, not reported; †, differentiating low-grade and high-grade neoplasm only; pCLE, probe confocal laser endomicroscopy; WLC, white-light cystoscopy; HAL, Hexylaminolevulinate blue light cystoscopy; FLUO, fluorescein; Sens, sensitivity; Spec, specificity
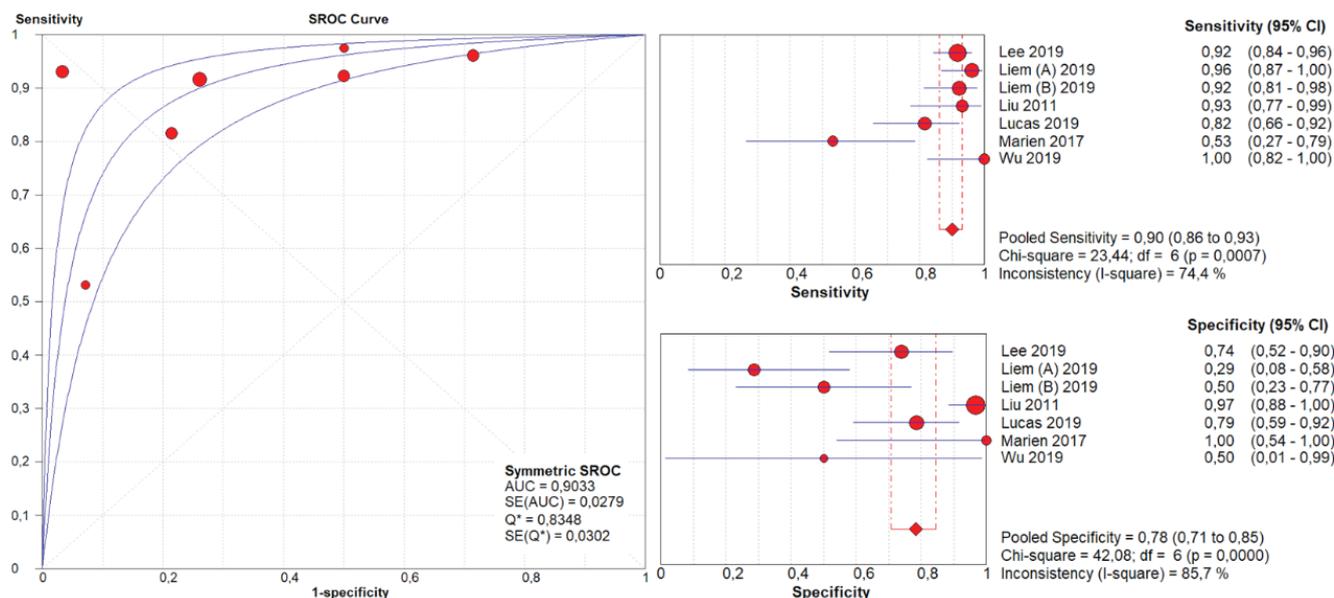
Figure 3. ROC curve and forest plot of malignant lesion differentiating performance

Table 4. Subgroup analysis for several pCLE patterns on diagnosing bladder cancer

Pattern	N	Sensitivity	Specificity	AUC
pCLE	2	0.932 (0.879, 0.967)	0.568 (0.395, 0.729)	N/A
pCLE + WLC	4	0.906 (0.844, 0.949)	0.846 (0.762, 0.909)	0.9483 (0.037)
pCLE + HAL	1	0.533 (0.266, 0.787)	1.000 (0.824, 1.000)	N/A

N, number of experiments; AUC, area under curve; N/A, not available, the number of studies involved is less than three; pCLE, probe confocal laser endomicroscopy; WLC, white-light cystoscopy; HAL, Hexylaminolevulinate blue light cystoscopy
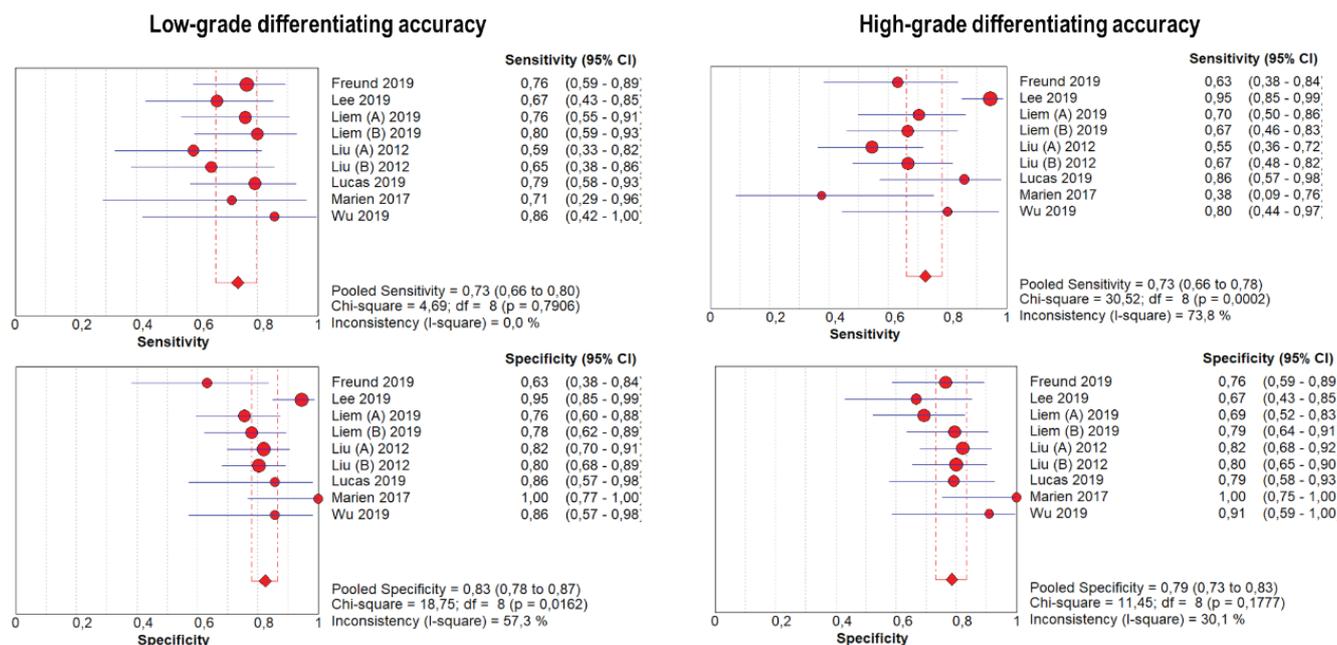

Figure 4. Forest plot of CLE's neoplasm grading performance

CLE's specificity in determining malignant lesions is not as excellent as its sensitivity. Four out of 7 experiments reported specificity at > 70%. However, the other 3 showed very low results. After we conducted a meta-analysis with the random effect model, we found a pooled specificity of 78.1% (0.71, 0.85). The area under the Curve was recorded at 0.9033 (0.0279), which indicates that CLE has high sensitivity and a low false-positive rate. The results of the pooling effect estimate are in **Figure 3**.

Subgroup analyzes were performed to assess the performance of each pCLE technique pattern. pCLE alone has high sensitivity and low specificity. Combining pCLE with WLC increased pCLE specificity while maintaining pCLE sensitivity above 90%. When pCLE was combined with Hexylaminolevulinate blue light cystoscopy (HAL), the specificity was perfect, but the sensitivity decreased dramatically to 53% (**Table 4**).

CLE accuracy in grading tumor

The CLE technique was designed not only to determine malignant or benign lesions but also to help diagnose the neoplasm degree. Our meta-analysis found that CLE performance determined the neoplasm degree not as good as CLE performance in determining benign or malignant lesions. We also found CLE's sensitivity and specificity in determining low-grade tumors of 73% (0.66, 0.80) and 83% (0.78, 0.87), respectively. The Area Under Curve (AUC) was recorded at 0.8377.

We also obtained the same thing in CLE performance in determining high-grade tumors. The sensitivity of CLE to determine high-grade tumors was only 73% (0.66, 0.78), while the specificity was 79% (0.73, 0.83). AUC was recorded at 0.8110. In addition, all results were heterogeneous, except for the sensitivity of CLE in diagnosing benign tumors (**Figure 4**).

DISCUSSION

Bladder cancer is one of the most malignant cancers globally, placed as the sixth most common malignancy [1]. Multiple advancements in endoscopic technology have been designed to enhance the sensitivity and specificity of the diagnostic tools. Confocal laser endomicroscopy (CLE) and optical coherence tomography (OCT) are used as microscopic imaging and are useful for tumor staging and grading [12]. CLE is an optical biopsy equipped with a high microscopic resolution with images comparable with a traditional histopathology biopsy sample. CLE is by far one of the optical biopsy technologies that can differentiate between the low and high grades of bladder cancer [10].

A systematic review was conducted by Brunckhorst et al. [23]. However, the systematic review was superficial in reviewing CLE's performance in diagnosing bladder cancer, as only one study was included, which

reported a proper effect estimate of diagnostic study in the form of sensitivity and specificity [23]. On this basis, the current study attempts to re-explore the performance of CLE in diagnosing bladder cancer, which has never been comprehensively reported before. Our meta-analysis found that CLE had an excellent overall performance in diagnosing bladder cancer, with sensitivity and specificity of 90.2% (0.86, 0.93) and 78.1% (0.71, 0.85). Compared to WLC, CLE has a better sensitivity performance in diagnosing bladder cancer, while the specificity is not much different. Subgroup analysis also uncovered that combining the pCLE technique with WLC would increase CLE's specificity (56.8% versus 84.6%) and maintaining its sensitivity above 90% (93.2% versus 90.6%).

Moreover, CLE is a sophisticated high-resolution imaging modality that makes it possible to carry out probe-based optical in vivo tissue examinations during endoscopy. Initially, this method was used to improve the accuracy of the WLC examination through improved visualization of flat lesions, differentiation of benign and malignant tumors, and determination of tumor boundaries [24]. WLC is a standard imaging modality for bladder cancer; however, this technique has a false negative rate that is high enough so that sensitivity is relatively low. In clinical settings, WLC is involved as an initial survey and is used to guide CLE to the intended area; thus, the use of CLE and WLC is highly recommended and has essential clinical relevance [13].

It is in line with what we encountered in this meta-analysis in subgroup analysis. The use of pCLE alone had a pooled sensitivity of 93.2% (0.879, 0.967). The merging of pCLE with WLC reduced its sensitivity but remained above 90% [90.6% (0.844, 0.949)]. On the other hand, the specificity of pCLE alone was 56.8% (0.395, 0.729). The pooled specificity of experiments using pCLE with WLC was recorded at 84.6% (0.395, 0.729).

CLE is also designed to grade neoplasms, as CLE can visualize the tissue microarchitecture. Our meta-analysis found that the accuracy of CLE in grading neoplastic tissue was not as excellent as its accuracy in excluding benign lesions. CLE's sensitivity in distinguishing low-grade tumors from high-grade or non-neoplastic tissue was only 73% (0.66, 0.80). Conversely, the sensitivity of CLE in distinguishing high-grade tumors from low-grade or non-neoplastic tissue was 73% (0.66, 0.78). Specificity for each of these abilities was only 83% (0.78, 0.87) and 79% (0.73, 0.83), respectively. However, the determination of the lesion grade was done through an interobserver agreement, so the low sensitivity and specificity could occur due to an imperfect agreement in determining the lesion degree.

By far, so many imaging modalities have been developed to assist urologists in determining the malignancy of bladder lesions. However, no clinical studies compared the accuracy of each modality comprehensively

and reliably. In vivo studies in animals have been reported by Ren et al. [25], who used transgenic mice with bladder carcinoma in situ. The sensitivity and specificity of WLC, OCT, NBI, and fluorescence cystoscopy (PDD) were 3% and 78%, 93% and 94%, 90% and 28%, 45% and 100%, respectively. However, the experiment's results on animals might be different in humans. Therefore, with considerable ethical challenges, further investigation is needed to be carried out on humans.

Although this meta-analysis could explain CLE's performance in the diagnosis of bladder cancer, several important points are needed to be reviewed further. First, not all studies carried out CLE according to general clinical settings, which are real-time and in vivo. Second, no studies reported the applicability of this modality in terms of costs and benefits. Third, the ultimate criteria for CLE diagnosis and lesion/tumor grading should have been established and tested for validity and reliability.

However, several factors might confound the interpretation of this review. First, we compiled all studies with CLE diagnostic accuracy outcomes without regard to diagnostic patterns/techniques due to limited studies. Heterogeneity of inter-study techniques was thought to confound the interpretation of the meta-analysis results. Second, we found reasonably high heterogeneity in each analysis. After we conducted the subgroup analysis, we have not been able to address the high heterogeneity problem. Third, we included studies with various CLE specifications. Even though it is unlikely, we thought this would confound the reports of each study.

CONCLUSIONS

CLE has good accuracy in distinguishing malignant and benign tumors. Grading tumors with this modality is also accurate. The use of pCLE coupled with WLC will also increase its specificity.

DECLARATIONS

Competing of Interest
The authors declare no competing interest in this study.

Acknowledgment

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