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The diagnostic performance of probe-based confocal laser endomicroscopy in the detection of gastric cancer: a systematic review and meta-analysis

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Abstract

Background Gastric cancer (GC) represents a significant global health burden with high morbidity and mortality, especially when diagnosed at advanced stages. Therefore, early detection of GC is critical. Probe-based confocal laser endomicroscopy (pCLE) is a new evolving technology that uses real-time, high-resolution imaging to inspect the mucosa at the cellular and microvascular level, using a confocal probe. Widespread studies using pCLE are limited at the current time. We aimed to investigate the diagnostic efficacy of this modality for the detection of GC.

Methods Multiple databases were searched from inception until November 2021. The diagnostic performance of pCLE was assessed by calculating its sensitivity, specificity and accuracy for the detection of GC, using pooled proportions and 95% confidence intervals (CI) with a random-effects model. Heterogeneity was assessed using I^2.

Results Seven studies were included, with a total of 567 patients (mean age 61.7 years, 364 males). Pooled performance metrics of pCLE included a sensitivity of 87.9% (95%CI 81.4-92.4; P<0.001; I^2=0%), specificity 96.5% (95%CI 91.5-98.6; P<0.001; I^2=51.84%), and an accuracy of 94.7% (95%CI 89.5-97.4; P<0.001; I^2=65.44%).

Conclusions pCLE is a highly effective diagnostic modality for detecting GC. Larger, randomized controlled studies are needed to determine its role in daily practice compared to conventional endoscopic practices.

Keywords Probe-based confocal laser endomicroscopy, gastric adenocarcinoma, gastric cancer, screening

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Conflict of Interest: None

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Introduction

Gastric cancer (GC) represents a significant clinical burden on the global healthcare system. The worldwide incidence of GC in 2020 was 1,089,103 and there were 768,793 deaths [1]. The prognosis is largely dependent on the stage of GC, but is typically poor, with a 5-year survival rate of 32% [2]. Therefore, detecting GC early is paramount to improve survival outcomes. Endoscopic screening in high-risk populations can detect lesions amenable to endoscopic or surgical resection and improve survival rates [3]. However, early detection continues to remain a challenge, especially given the varying geographical incidences and resources around the world [4]. In 2018, South Korea had the highest rate of GC, with 39.6 per 100,000 people [4]. In the setting of a significantly high disease burden, South Korea has effectively instituted a National Cancer Screening Program to reduced cancer-related morbidity and mortality [5,6]. However, cost-effective endoscopic screening programs in countries with intermediate-to-low incidence have yet to be established [7].

The need for reliable detection can reduce major costs by diagnosing lesions that are curable at early stages and prevent advanced-stage mortality [8,9]. What further complicates this matter is that upper gastrointestinal endoscopy can miss GC at a rate of 9.4% [10]. This has led to recent advances in endoscopic technology in an effort to improve detection rates. Probe-based confocal laser endomicroscopy (pCLE) is one such technology: it provides high-resolution images at the cellular and microvascular levels through the use of a confocal probe that reflects laser light at varying tissue depths [11]. With real-time tissue illumination at 1000× magnification, making an endoscopic optical biopsy holds tremendous potential to reduce biopsy costs and biopsy-related adverse events, while improving real-time treatment decisions [12]. However, there are limited data regarding the effectiveness of pCLE in detecting GC. Hence, our aim was to determine the diagnostic performance of pCLE in detecting GC.

Materials and methods

Protocol

This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement (PRISMA) and Meta-analyses of Observational Studies in Epidemiology (MOOSE) reporting standards [13,14].

Search strategy

Multiple databases were searched (Medline, Embase, Scopus, Web of Science and the Cochrane Library) to identify studies that used pCLE for GC detection *in vivo* from inception to October 2021. An experienced librarian assisted with the literature search, using medical subject headings and inputs provided by the study authors. The search strategy included the following terms: "probe-based confocal laser endomicroscopy", "gastric" or "stomach", and "cancer", "neoplasm", "lesion", and "adenocarcinoma".

Study selection and data abstraction

This meta-analysis was aimed at evaluating the diagnostic performance of pCLE in patients with GC. All study titles and abstracts were independently reviewed by 2 reviewers (AC, JK). Exclusion criteria included non-human, non-English, pediatric studies, systematic reviews, abstracts with less than 10 subjects and case reports. Data abstraction included: study authors, publication year, country of origin, study design, age, sex, equipment used, level of experience, number of gastric lesions, lesion size, lesion location, true positive, true negative, false positive, and false negative.

Quality assessment

Quality assessment of diagnostic accuracy and risk of bias was conducted using the Quality Assessment of Diagnostic Studies-2 (QUADAS-2) tool, and reviewed by 2 authors (AC, JK) [15].

Outcomes assessed

The primary performance outcomes assessed were the sensitivity, specificity, and accuracy of pCLE.

Statistical analysis

Statistical analysis was performed using Comprehensive Meta-Analysis (CMA 3.0) software (Biostat, Englewood, NJ). Pooled estimates and corresponding 95% confidence intervals (CI) for dichotomous variables were calculated using the random-effects inverse variance/DerSimonian-Laird method [16]. Heterogeneity was measured by Cochrane Q and I^2 statistics, with values of <30%, 31-60%, 61-75%, and >75% suggesting low, moderate, substantial and considerable heterogeneity, respectively [17,18]. Prediction intervals were also calculated. Three levels of impact were reported, based on the concordance between the reported results and the actual estimate if there was no bias. The impact was reported as minimal if both versions were estimated to be the same, modest if the effect size changed substantially, but the final finding would remain the same and severe if the bias threatened the conclusion. A funnel plot combined with Egger's tests was performed to assess publication bias. A P-value of 0.05 or less, combined with asymmetry in the funnel plots, was used to measure significant publication bias and, if <0.05, the trim-and-fill computation was used to evaluate the effect of publication bias on the interpretation of the results [19].

Results

The systematic search yielded 3389 studies, after removal of duplicates (n=1803) and irrelevant studies based on title/abstract (n=1575), there were 11 studies remaining for full-text review (Fig. 1). Seven studies met the inclusion criteria for the final analysis [20-26]. These included 567 patients (mean age 61.7 years, 364 male) with 611 gastric lesions. The majority of studies were from Asia (South Korea [20], China [21,24], Japan [22,25,26]) and one study was conducted in Brazil [23]. All studies used the Gastroflex ultrahigh definition (UHD) miniprobe (Cellvizio

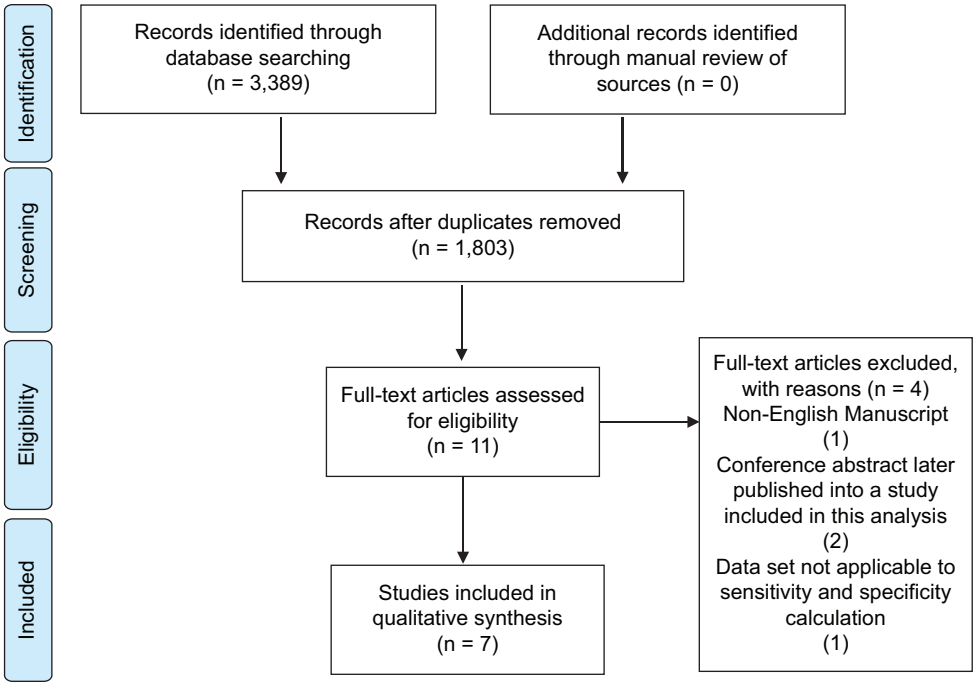

Figure 1 Flow chart of selected studies
From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *Preferred Reporting items* for Systematic Reviews and *Meta-Analyses*: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Mauna Kea, Paris). In terms of expertise, all studies employed experienced operators to analyze the gastric lesions.

Quality assessment

Using the QUADAS-2 tool, there was a low-to-moderate risk of bias (Fig. 2). All of these studies used an index test (i.e., Miami Classification by Wallace *et al* [12]) with a reference standard related to histopathology. The primary source of bias detected was related to patient selection, whereby the patient population and/or exclusion criteria were not specified in some cases (primarily publications that were abstracts).

Meta-analysis outcomes

Sensitivity

The pooled sensitivity of all 7 studies was 87.9% (95% confidence interval [CI] 81.4-92.4; P<0.001; I^2=0%) (Fig. 3). The true effect size in 95% of all comparable populations falls in the interval 0.72-0.95.

Specificity

Six studies were used to calculate a pooled specificity of 96.5% (95%CI 91.5-98.6; P<0.001; I^2=51.84%) (Fig. 4) [20-25]. The true effect size in 95% of all comparable populations falls in the interval 0.64-1.00.

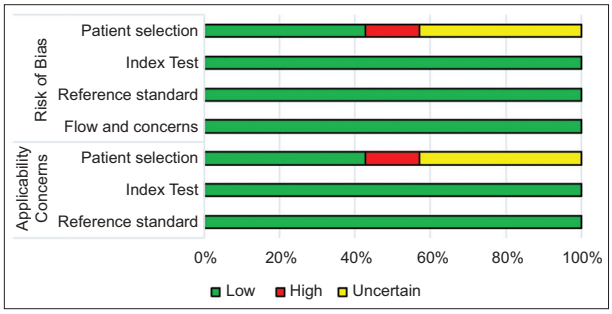

Figure 2 QUADAS-2 tool for the quality assessment of diagnostic accuracy studies
Patient Selection: 42.9% low, 14.3% high, 42.9% unclear for both risk of bias and applicability

Accuracy

The pooled accuracy of all 7 studies was 94.7% (95%CI 89.5-97.4; P<0.001; I^2=65.44%) (Fig. 5). The true effect size in 95% of all comparable populations falls in the interval 0.76-0.99.

Validation of meta-analysis results

Sensitivity analysis

A one-study removal sensitivity analysis was performed to assess any dominant effect on the meta-analysis. The statistical significance and direction of findings for all outcomes remained unchanged.

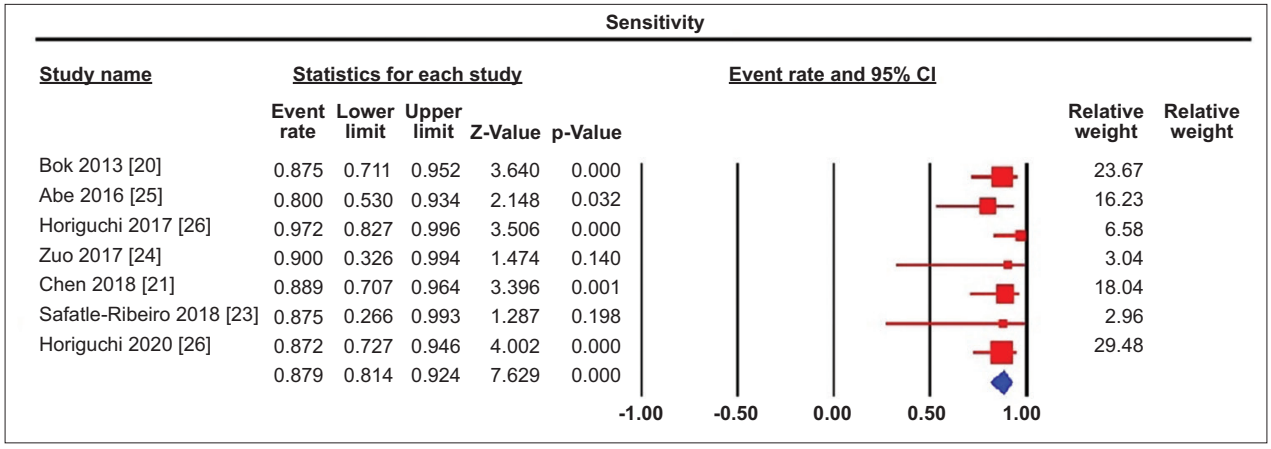

Figure 3 Pooled sensitivity of probe-based confocal laser endomicroscopy
CI, confidence interval

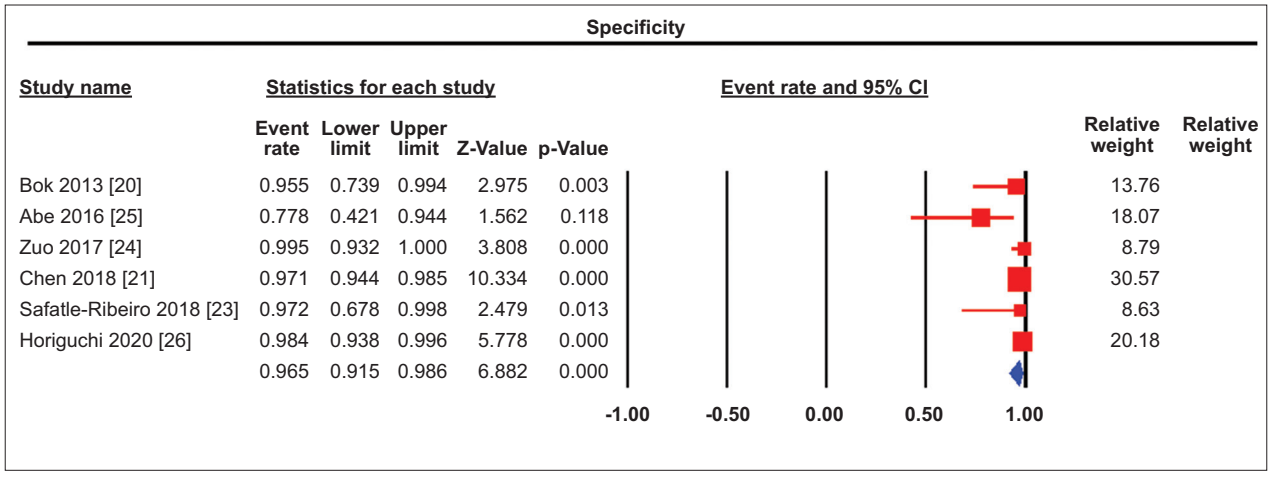

Figure 4 Pooled specificity of probe-based confocal laser endomicroscopy
CI, confidence interval

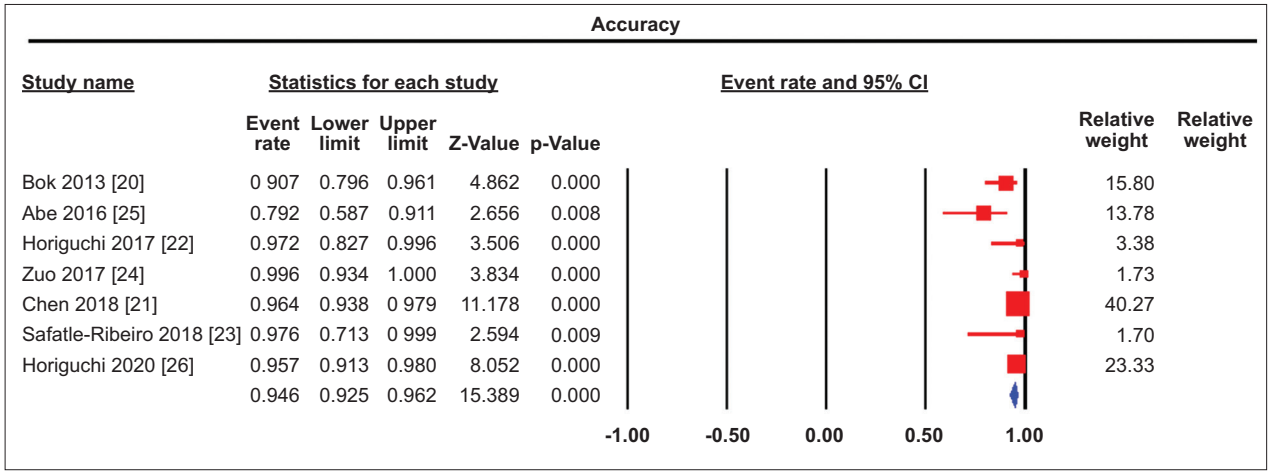

Figure 5 Pooled accuracy of probe-based confocal laser endomicroscopy
CI, confidence interval

Table 1 Characteristics of included studies using probe-based confocal endomicroscopy

First author, year [ref.]	Country	Study period	Study design	Equipment type	Number of subjects	Number of total lesions	Number of gastric cancer lesions
Bok, 2013 [20]	South Korea	2/2012 -52012	Single-center, prospective*	Gastroflex UHD miniprobe	46	54	32
Abe, 2016 [25]	Japan	2/2015 -4/2015	Abstract; multicenter, prospective*	Gastroflex UHD miniprobe	17	24	15
Horiguchi, 2017 [22]	Japan	1/2015 -12/2016	Single-center, prospective	Gastroflex UHD miniprobe	30	36	36
Horiguchi, 2020 [26]	Japan	4/2014 -8/2018	Abstract; single-center, prospective*	Gastroflex UHD miniprobe	34	41	39
Zuo, 2017 [24]	China	7/2014-8/2015	Multicenter, prospective*	Gastroflex UHD miniprobe	120	114	4
Chen, 2018 [21]	China	10/2014-12/2016	Single-center, retrospective	GastroFlex UHD mini probe	327	322	27
Safatle-Ribeiro, 2018 [23]	Brazil	n/a	Single-center	GastroFlex UHD mini probe	10	20	3

*Studies using recorded videos (offline)

UHD, ultrahigh definition

Heterogeneity

The I^2 was low-moderate across outcomes, suggesting moderate heterogeneity of our sample.

Publication bias

Publication bias could not be estimated because of the small number of studies included (n<10).

Discussion

The present study demonstrates that the diagnostic performance of pCLE is significantly high for *in vivo* detection of GC. The opportunity to make a real-time diagnosis after a lesion is detected during endoscopy (i.e., white light, narrow band imaging, or chromoendoscopy) through pCLE has the potential to reduce costs and enhance targeted biopsies, with a pooled sensitivity, specificity and accuracy of 87.9%, 96.5% and 94.7%, respectively. A prior meta-analysis in 2016 looked at both pCLE and endoscopic-based confocal laser endomicroscopy (eCLE), which together had a sensitivity of 91% and specificity of 99% [27]. That analysis was only limited to Asian countries, all studies were small, single-center designs, and they did not differentiate the diagnostic efficacy of pCLE vs. eCLE. In our meta-analysis, we examined only worldwide studies using pCLE, and found that it has high accuracy in detecting GC.

While esophagogastroduodenoscopy is typically the gold standard for screening, it is not uncommon for an endoscopist to miss GC because of inadequate detection, sampling errors, and locations such as the gastric cardia and proximal body of the stomach [10,28]. Consequently, creating an effective screening and surveillance program, especially in countries with intermediate-to-high incidences of GC, is important to detect early GC and hence reduce mortality and healthcare costs [7]. Widespread use of pCLE was enhanced by the Miami Classification, introduced in 2009 by Wallace *et al*, which created a standardized diagnostic classification system [12]. In an effort to further expand this classification, Bok *et al* and Lie *et al* expanded GC characterization based on differentiation of lesions, gastric pit patterns and vessel architecture according to location [20,29]. In addition to standardized diagnostic criteria, there also appears to be appropriate interobserver agreement for the differentiation between neoplastic vs. non-neoplastic lesions [29].

Despite a standardized system, the widespread use of pCLE for GC has been limited for several reasons. The first is probably its learning curve, since diagnostic accuracy is closely linked to experience and training [11,30]. Although other studies using pCLE for colon polyps, colorectal neoplasms and inflammatory bowel disease demonstrated an easy learning curve [31-33], it may stand to reason that GC lesions are inherently difficult for *in vivo* investigation, with significant gastric secretory products and appropriate positioning of the probe. Moreover, given the low incidence of early GC in the West, training endoscopists in the use of pCLE is likely to be more challenging.

That being said, the possibility of supplementing or even replacing physical biopsies is promising from a therapeutic standpoint. Taking biopsies prior to endoscopic resection can cause inflammatory changes or submucosal fibrosis that can make subsequent endoscopic resection challenging, and may even lead to incomplete endoscopic resection [20,34]. Diagnosing lesions with pCLE has the potential to prevent biopsy-induced fibrosis or desmoplasia when endoscopic submucosal dissection (ESD) is pursued [20]. In addition to ESD, the ability to determine if a lesion is even amenable to treatment can be enhanced by real-time magnification imaging, as pCLE can examine entire lesions, in contrast to the limitations of single biopsies. This also has the potential implication to reduce unnecessary ESD in situations where lesions are initially under-staged, and also reduce unnecessary surgery in cases where lesions are initially over-staged.

There are a few limitations to our analysis. First, these studies were conducted by experienced clinicians at high-volume centers with high-to-intermediate incidences of GC, primarily in Asia. Since pCLE cannot survey all the areas in the stomach, endoscopists need to diagnose the areas of concern. Thus, the evaluation of the diagnostic yield of pCLE alone might not be relevant in the clinical setting. Therefore, these results may not be generalizable in countries with a low incidence of GC. Second, the cost of applying pCLE in daily practice limits its widespread use. Consequently, directly comparing pCLE to other conventional endoscopic methods (such as narrow-band imaging) has not been extensively studied.

In conclusion, pCLE has the potential to influence real-time diagnoses when evaluating lesions suspicious for GC. The present study demonstrates its high diagnostic accuracy. However, larger, randomized controlled studies are needed to confirm these findings before widespread adoption can be considered.

Summary Box

What is already known:

- Early detection of gastric cancer can improve survival outcomes and reduce healthcare costs
- The ability to make a real-time optical diagnosis has led to advances in endoscopic technologies, such as probe-based confocal laser endomicroscopy

What the new findings are:

- In this meta-analysis, the pooled sensitivity, specificity and accuracy of probe-based confocal laser endomicroscopy were 87.9%, 96.5% and 94.7%, respectively
- As a highly accurate and reliable diagnostic modality, probe-based confocal laser endomicroscopy has the potential to supplement tissue diagnosis and improve gastric cancer screening

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