Magnifying endoscopy in detecting early gastric cancer

A network meta-analysis of prospective studies

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Abstract

Background: Conventional white-light imaging endoscopy (C-WLI) had a significant number of misdiagnosis in early gastric cancer (EGC), and magnifying endoscopy (ME) combined with different optical imaging was more accurate in the diagnosis of EGC.

Methods: A comprehensive literature search was conducted to identify all relevant studies. Pair-wise meta-analysis was conducted to evaluate the accuracy of ME, and Bayesian network meta-analysis was performed to combine direct and indirect evidence and estimate the relative effects.

Results: Eight prospective studies were identified with a total of 5948 patients and 3 optical imaging in ME (ME with WLI (M-WLI), ME with narrow-band imaging (M-NBI), and ME with blue laser imaging (M-BLI)). Pair-wise meta-analysis showed a higher accuracy of ME than C-WLI (OR: 2.97, 95% CI: 1.68–5.25). In network meta-analysis, both M-NBI and M-BLI were more accurate than M-WLI (OR: 2.56, 95% CI: 2.13–3.13; OR: 3.13, 95% CI: 1.85–5.71). There was no significant difference between M-NBI and M-BLI.

Conclusion: ME was effective in improving the detecting rate of EGC, especially with NBI or BLI.

Abbreviations: BLI = blue laser imaging, CI = confidence interval, C-WLI = conventional white-light imaging, EGC = early gastric cancer, LCI = linked color imaging, ME = magnifying endoscopy, NBI = narrow-band imaging, NOS = Newcastle-Ottawa Scale, OR = odds ratio.

Keywords: blue laser imaging, magnifying endoscopy, narrow-band imaging, network meta-analysis

1. Introduction

Gastric cancer (GC) is one of the most common cancers worldwide, with an estimated 951,600 new cases and 723,100 deaths per year.[1] Although the death rate has declined during the past years, the rate of early diagnosis was still low. Early gastric cancer (EGC) was considered curative, and after endoscopic resection, the 5-year survival rate was more than 95%.[2] Thus, if GC could be early detected, we would be able to improve the prognosis.[3]

Conventional white-light imaging (C-WLI) has been applied in clinical practice for many years, but the accuracy in diagnosing gastric cancer was still low, with a sensitivity of 40% to 60% and a specificity of 67.9% to 94.3%.[4] It was really difficult to detect EGC and conduct accurate biopsies using C-WLI alone. To overcome the limitation, several enhanced endoscopic imaging techniques have occurred, including narrow-band imaging (NBI), blue laser imaging (BLI) and linked color imaging (LCI).

Magnifying endoscopy (ME) combined with these optical imaging could help improve EGC detection. Several meta-analyses reported the superiority of magnifying endoscopy with NBI (M-NBI) to C-WLI in detecting EGC.[5-7] However, these studies ignored ME with other optical imaging, such as WLI, and the newly occurred systems of BLI and LCI.[8] Furthermore, no studies compared the accuracy between different optical imaging. Thus, we conducted a pair-wise meta-analysis to evaluate the accuracy of ME, and then a network meta-analysis to compare the accuracy of ME with different optical imaging in detecting EGC.

2. Materials and methods

2.1. Search strategy

The database of PubMed and Web of Science were searched for related studies published up to March 8th, 2020, using the Key...
words: (“magnifying endoscopy (ME)” OR “blue laser imaging (BLI)” OR “narrow-band imaging (NBI)” OR “linked color imaging (LCI)”) AND “early gastric cancer (EGC).” Studies in languages other than English were excluded. Moreover, the references of all relevant studies, reviews and meta-analyses were reviewed for undetected studies. This study was approved by the ethics committee of The Central Hospital of Enshi Tujia And Miao Autonomous Prefecture.

2.2. Study selection and exclusion

Two authors reviewed the studies independently. The inclusion criteria were as follows:

(1) prospective designed study;
(2) compared the accuracy of conventional white-light imaging (WLI) endoscopy, ME-BLI, ME-NBI and ME-LCI in detecting early gastric cancer;
(3) The endoscopic diagnosis was confirmed by pathology.

The exclusion criteria were as follows:

(1) abstracts without full text,
(2) case-control studies and
(3) reviews.

2.3. Data extraction and quality assessment

Two authors extracted the data by a standardized collection form. Disagreements were solved by discussion. The following information was extracted from each study: first author, publication year, study area, study duration, study design, number of included patients, sex, age, lesion number, lesion size, endoscopy equipment, optical imaging type, assessment, and number of total cases and cases with accurate diagnosis. The Newcastle-Ottawa Scale was used to assess the methodological quality of included studies.

2.4. Statistical analysis

Pair-wise meta-analysis was conducted by Review Manager 5.2 to evaluate the accuracy of ME in comparison to C-WLI. Odds ratios (OR) with 95% confidence intervals (CI) were used to report the estimates following the Mantel-Haenszel method. The heterogeneity between studies was estimated by Q test and I² statistic. I² > 50% represented substantial heterogeneity, and a random-effects analysis was conducted. Otherwise, a fixed-effects model was used. Furthermore, subgroup analysis on the main confounders and sensitivity analysis by omitting 1 study at a time during repeated analyses were conducted to evaluate the stability of the primary result. Egger test was used to detect publication bias. All tests were sided with a significance level of 0.05.

To incorporate the indirect comparisons among ME, ME-BLI and ME-NBI, we conducted a Bayesian network meta-analysis by using the R packages of “gemtc” and “coda” and following the methods described by Dias et al.[9] Fixed- and random-effect model were evaluated, and the goodness fit of each model was assessed by the Deviance Information Criterion. The posterior densities for the outcome were estimated using the Markov Chain Monte Carlo simulations for each model. The results were based on 1000 simulation iterations and 5000 adaptation iterations.

3. Results

3.1. Study characteristics

The search strategy resulted in 457 records: 118 from PubMed, 296 from Web of Science, and 43 through other sources (Fig. 1). After excluding duplicated and irrelevant records, 8 studies were included in this meta-analysis with a total of 5948 patients and 5731 lesions (Table 1).[6,10–16] Three studies were conducted in multiple centers, while 5 studies were crossover designed. Six studies took the endoscopy of Olympus, while 2 selected Fujifilm. Six studies conducted a real-time assessment, while 2 studies made a diagnosis after the procedure. In quality assessment, the included studies had an average score of 7.78.

3.2. The accuracy of ME in detecting EGC

Yu et al study compared C-WLI with M-NBI and M-BLI respectively, and thus it was regarded as 2 separate studies in the pair-wise meta-analysis. Finally, 8 studies were included. ME showed a higher accuracy than C-WLI in detecting EGC (OR: 2.97, 95% CI: 1.68~5.25) (Fig. 2). Sensitivity analysis showed that the result was robust. Egger test detected no significant publication bias (P = .116).

Subgroup analysis was conducted on study design, number of lesions, EGC proportion, endoscopy equipment, optical imaging, and assessment (Table 2). No substantial changes of the primary result were found between subgroups, except for the comparison between M-WLI and C-WLI which contributed to the limited number of included studies (n = 1).

3.3. Network meta-analysis of ME with different optical imaging in detecting EGC

Five subgroups were included into the network meta-analysis, namely C-WLI, ME, ME-BLI and ME-NBI. There existed direct comparisons between M-BLI and C-WLI, M-NBI and C-WLI, M-WLI and C-WLI, and M-NBI and M-WLI (Fig. 3). Compared with C-WLI, the diagnostic accuracy was higher in M-WLI (OR: 1.43, 95% CI: 1.12–1.85), M-NBI (OR: 2.56, 95% CI: 2.13–3.13) and M-BLI (OR: 3.13, 95% CI: 1.85–5.71) (Table 3). Among the 3 types of ME, both M-NBI and M-BLI were more accurate than M-WLI (OR: 2.56, 95% CI: 2.13~3.13; OR: 3.13, 95% CI: 1.85~5.71). However, there was no significant difference between M-NBI and M-BLI.

4. Discussion

GC is the fourth most common cancer and the second most common cause of cancer death worldwide. Although the early detection of GC is necessary to improve patient survival, the identification of small GC is difficult. High-resolution endoscopic system has increased the probability of finding small and depressed lesions in the stomach, which include gastritis and EGC. Thus, the differential diagnoses are clinically important. For the images obtained using WLE, the endoscopic distinctive diagnosis between cancer and non-cancer for each lesion is made based on an assessment of the color and appearance. Therefore, the accurate diagnosis of EGC by C-WLI is difficult, and it also increases the number of unnecessary biopsies.

Magnifying endoscopy could visualize the microstructures and microvessels of the lesions. Endoscopic changes in these structures were useful for the early and differential diagnosis.
of GC.[10] The diagnosis criteria by Yao et al were as following: an irregular microvascular pattern with a demarcation line and/or the presence of an irregular microsurface pattern with a demarcation line.[17] However, as for the low contrast of imaging in M-WLI, it is not easy to accurately visualize and evaluate the magnifying endoscopic findings such as demarcation line and microvascular pattern. A novel technique and an excellent diagnostic capacity for magnifying endoscopy are required for an accurate diagnosis when using M-WLI.

ME-NBI is an advanced endoscopic imaging technology launched recently, in which spectral bandwidth filters in a red-green-blue (R/G/B) sequential illumination system, and could be used to improve the diagnostic accuracy.[17] It has been developed to enhance the visualization of the superficial mucosal structure and vascular architecture. Several meta-analyses reported the superiority of magnifying endoscopy with NBI (M-NBI) to C-WLI in detecting EGC.[5] Moreover, it has also been applied to evaluate the histological type of EGC and measure the horizontal

![Table 1](image)

**Table 1**

| Study   | Area            | Study design | No. of patients | Sex (M/F) | Age (y)       | Lesion number | Lesion size (mm) | Endoscopy equipment | Optical imaging | Assessment |
|---------|-----------------|--------------|-----------------|-----------|---------------|---------------|------------------|-------------------|-----------------|------------|
| Ezoe 2010| Kashiwa, Japan  | Crossover    | 53              | NA        | NA            | 57 (30 CA)    | ≤10              | GIF-Q240Z, GIF-H260Z | M-WLI, M-NBI | Real-time |
| Kato 2010| Tokyo, Japan    | Crossover    | 111             | 98/13     | 66.3±9.8      | 201 (14 CA)   | 7.0±4.0          | GIF-H260Z          | C-WLI, M-NBI | Real-time |
| Ezoe 2011| Multicenter, Japan | Parallel | 353             | 278/75    | 69 (37–93)    | 353 (40 CA)   | ≤10              | GIF-Q240Z, GIF-H260Z | C-WLI, M-NBI | Real-time |
| Tao 2014| Beijing, China  | Crossover    | 508             | 316/192   | 64 (41–78)    | 643 (24 CA)   | 7 (5–20)         | GIF-H260Z          | C-WLI, M-NBI | Post-procedure |
| Yu 2015 | Multicenter, China | Crossover | 3616           | 1910/1706 | 56 (40–90)    | 3675 (257 CA) | NA               | GIF-H260Z          | C-WLI, M-WLI, M-NBI | Post-procedure |
| Ang 2015| Multicenter, Asia | Parallel | 579             | 236/343   | 62±9          | 579 (10 CA)   | NA               | Olympus            | C-WLI, M-NBI | Real-time |
| Dohi 2017| Kyoto, Japan    | Crossover    | 132             | 95/23     | 70 (41–91)    | 127 (32 CA)   | NA               | EG-L590ZW          | C-WLI, M-BLI  | Real-time |
| Dohi 2018| Kyoto, Japan    | Parallel     | 596             | 385/211   | 73 (66–80)    | 90 (53 CA)    | NA               | EG-L590ZW, EG-L600ZW | C-WLI, M-BLI  | Real-time |

CA = cancer, C-WLI = conventional white-light imaging, M-BLI = magnifying blue laser imaging, M-NBI = magnifying narrow-band imaging, M-WLI = magnifying white-light imaging, NA = not available.
extent of the stomach tumor before endoscopic submucosal dissection (ESD).\cite{18,19}

Recently, Fuji film developed an endoscope system with a semiconductor laser as a light source.\cite{20} The system includes 2 types of lasers with wavelengths of 410 and 450 nm. The 450 nm laser irradiates phosphor to produce illumination light similar to that obtained with a xenon lamp. The combination of strong 410 nm laser light, weak 450nm laser light, and fluorescent light

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**Table 2**

| Subgroup analysis of magnifying endoscopy in detecting early gastric cancer. | Odds Ratio (95% CI) | $I^2$ |
|---|---|---|
| **Study or Subgroup** | **No. of studies** | **OR (95% CI)** | **$I^2$** |
| **Study design** | | | |
| Parallel | 3 | 2.34 (1.00–5.48) | 83% |
| Crossover | 5 | 3.50 (1.53–7.99) | 94% |
| **No. of lesions** | | | |
| $>500$ | 4 | 2.05 (1.10–3.82) | 90% |
| $<500$ | 4 | 4.39 (2.61–7.39) | 57% |
| **EGC proportion** | | | |
| $>10\%$ | 3 | 3.64 (1.93–6.87) | 55% |
| $<10\%$ | 5 | 2.71 (1.34–5.48) | 93% |
| **Endoscopy equipment** | | | |
| Olympus | 5 | 4.21 (2.03–8.75) | 87% |
| Fuji film | 2 | 1.23 (1.00–1.51) | 0% |
| **Optical imaging** | | | |
| NBI | 4 | 3.79 (1.64–8.77) | 93% |
| BLI | 2 | 2.86 (1.05–7.78) | 66% |
| WLI | 1 | 1.17 (0.88–1.56) | – |
| **Assessment** | | | |
| Real time | 5 | 3.33 (1.66–6.68) | 85% |
| Post-procedure | 3 | 2.46 (1.00–6.02) | 94% |

BLI = blue laser imaging, CI = confidence interval, NBI = narrow-band imaging, OR = odds ratio, WLI = white-light imaging.

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**Table 3**

| Network meta-analysis of magnifying endoscopy with different optical imaging in detecting early gastric cancer. | Odds ratio (95% confidence interval) |
|---|---|---|---|---|
| **Optical imaging** | **C-WLI** | **M-WLI** | **M-NBI** | **M-BLI** |
| C-WLI | – | 1.43 (1.12–1.85) | 2.56 (2.13–3.13) | 3.13 (1.85–5.71) |
| M-WLI | 0.70 (0.54–0.89) | – | 1.79 (1.37–2.38) | 2.22 (1.20–4.17) |
| M-NBI | 0.39 (0.32–0.47) | 0.56 (0.42–0.73) | – | 1.22 (0.69–2.22) |
| M-BLI | 0.32 (0.18–0.54) | 0.45 (0.24–0.83) | 0.82 (0.45–1.45) | – |

CA = cancer, C-WLI = conventional white-light imaging, M-BLI = magnifying blue laser imaging, M-NBI = magnifying narrow-band imaging, M-WLI = magnifying white-light imaging, NA = not available.
This meta-analysis has several strengths. First, to our knowledge, this is the first meta-analysis to evaluate the accuracy of ME with different optical imaging in detecting EGC. Previous studies mainly focused on the comparison between ME and C-WLI to emphasize on the clinical significance of endoscopic magnification. However, no studies have compared the accuracy between M-NBI and M-BLI in detecting EGC. As M-NBI was base on the platform of Olympus endoscopic system and M-BLI on the platform of Fujifilm, it was difficult to make a direct comparison of M-NBI and M-BLI on the same patient. Our network meta-analysis solved this problem. To our knowledge, this is also the first network meta-analysis to compare the efficacy of ME with different optical imaging in detecting EGC. Our findings could help the endoscopic physicians to make a better choice in the EGC screening. There were also a few limitations in this meta-analysis. First, the number of included studies was relatively small. Second, not all included studies had a large sample size. Third, not all potential confounders were adjusted in every study, like the operator’s experience and the equipment generation. Nevertheless, these limitations could not prevent us from investigating an effective endoscopic pattern to improve the detecting rate of EGC. We thought that its clinical significance was far greater than its limitations. We expected large-scale prospective designed studies in the future to overcome the shortcomings in this study.

In conclusion, ME was effective in improving the detecting rate of EGC, and there was no significant difference between M-NBI and M-BLI.

Author contributions

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