Flexible magnifying endoscopy with narrow band imaging versus colposcopy for diagnosing uterine cervical neoplasms: a multicenter, prospective, non-randomized, paired comparison study

Hideki Kobara,[a] Kunihisa Uchita,[b] Noriya Uedo,[c] Jun Kunikata,[d] Kenji Yorita,[e] Naoya Tada,[a] Noriko Nishiyama,[a] Yuriko Shigehisa,[b] Chihiro Kuroiwa,[b] Noriko Matsuura,[c] Yohei Takahashi,[f] Yuka Kai,[f] Uiko Hanaoka,[g] Yumiko Kiyohara,[h] Shoji Kamiura,[h] Kenji Kanenishi,[g] Tsutomu Masaki,[a] Koki Hirano[f]

[a] Department of Gastroenterology and Neurology, Faculty of Medicine, Kagawa University, Kagawa, Japan [b] Department of Gastroenterology, Kochi Red Cross Hospital, Kochi, Japan [c] Department of Gastrointestinal Oncology, Osaka International Cancer Institute, Osaka, Japan [d] Department of Clinical Research Support Center, Faculty of Medicine, Kagawa University, Kagawa, Japan [e] Department of Diagnostic Pathology, Kochi Red Cross Hospital, Kochi, Japan [f] Department of Gynecology, Kochi Red Cross Hospital, Kochi, Japan [g] Department of Gynecology, Faculty of Medicine, Kagawa University, Kagawa, Japan [h] Department of Gynecology, Osaka International Cancer Institute, Osaka, Japan

*Corresponding author: Hideki Kobara, MD, PhD

Department of Gastroenterology and Neurology, Faculty of Medicine, Kagawa University

1750-1 Ikenobe, Miki, Kita, Kagawa 761-0793, Japan

Telephone: +81-87-891-2156 Fax: +81-87-891-2158

E-mail: kobara@med.kagawa-u.ac.jp

Running title ME-NBI for cervical neoplasms

Abstract

Objective To investigate the detection ability of flexible magnifying endoscopy with narrow band imaging (ME-NBI) for cervical intraepithelial neoplasia grade two or worse (CIN2+) compared with colposcopy.

Design Multicenter, prospective, non-randomized, paired comparison study.

Setting Three Japanese medical centers.

Population Japanese women.

Methods Eligible patients had positive PAP smear test results, suspicious high-grade CIN in previous colposcopy, or definitive CIN3 diagnosed previously. A gastrointestinal endoscopist examined the cervix using ME-NBI in an endoscopy room and, subsequently, a gynecologist blinded to the ME-NBI findings performed colposcopy in a different room. CIN2+ locations were documented in a scheme immediately after each examination. Punch biopsy samples were obtained from all areas diagnosed as CIN2+ with both methods and from one normal area. The reference standard was the presence of at least one histological diagnosis of CIN2+ among all biopsy specimens.

Main outcome measures The primary outcome was the detection sensitivity of patients with CIN2+, comparing ME-NBI and colposcopy.

Results We enrolled 88 patients. The detection sensitivity for patients with CIN2+ was not statistically different between the two methods (both: 79%, 95% CI: 66%–88%). For diagnosing CIN2+, ME-NBI tended to show a higher sensitivity than colposcopy (69% vs. 58%, respectively), while its specificity tended to be lower vs. colposcopy (55% vs. 70%, respectively). Patients reported significantly less discomfort and embarrassment with ME-NBI vs. colposcopy.

Conclusion ME-NBI showed comparable sensitivity to colposcopy for detecting CIN2+

lesions, and ME-NBI was more patient-acceptable.

Funding Japan Society for the Promotion of Science (JSPS) KAKENHI Grant Number 17K15775.

Keywords Uterine Cervical Neoplasms, Cervical Intraepithelial Neoplasia, Endoscopy, Colposcopy

The trial registration number University Hospital Medical Information Network (UMIN) Clinical Trials Registry Number 000033189

Tweetable abstract ME-NBI had comparable detection to colposcopy of high-grade CIN, and ME-NBI was more patient-acceptable.

Introduction

Uterine cervical cancer is caused by human papillomavirus (HPV) infection, and proper screening programs promise cancer detection at an early stage. Cervical intraepithelial neoplasm grade three (CIN3) or intraepithelial cancer can be treated by cervical conization; thereby, preserving fertility by avoiding hysterectomy.

The WHO has established a strategy to achieve a one-third reduction in premature mortality by 2030.[1] They emphasize the importance of triple intervention targets to increase HPV vaccination rates, and screening and treatment for cervical cancer. The current standard steps for screening are a “Pap” smear test followed by colposcopy. The main objective of colposcopy is to detect CIN grade two or worse (CIN2+). A recent quality-controlled review found moderate sensitivity of colposcopy for CIN2+ of 75.1%, specificity of 71.0%, and positive predictive value of 72.0%.[2]

Moreover, of 44,446 women treated surgically for CIN, the proportion of positive margins was 23.1%, which gave an overall rate of residual or recurrent CIN2+ of 6.6%.[3] The diagnostic inaccuracy of colposcopy may be associated with the low image quality of conventional colposcopy and limited visual field when using a Cusco speculum. Most screened women have a favorable attitude toward colposcopy, but some complain of pain during insertion of the speculum.[4] Thus, new methods are required to reduce discomfort. Moreover, the acceptability, including embarrassment, remain unevaluated in Asian cultures.

Currently, image-enhanced endoscopy technology involving narrow band imaging (NBI) plays an important role in the diagnosis of gastrointestinal neoplasms.[5–9] NBI systems use narrow band illumination of 415-nm and 540-nm wavelengths, which are well-absorbed by hemoglobin. Flexible magnifying endoscopy with narrow band imaging (ME-NBI) allows clear visualization of the micro-structure as well as the micro-vascularity of mucosal surfaces. Thus, we expected ME-NBI to be useful for CIN diagnosis, and our previous investigation suggested high potential with the method.[10,11] The advantages of ME-NBI are its high resolution with magnification power (maximum 85 times), and the endoscope maneuvers freely, close to the lesion. Currently, there are no comparative data regarding the diagnostic ability of ME-NBI vs. colposcopy. Hence, we aimed to compare the detection ability of ME-NBI and colposcopy in cancer screening. We also compared patients' acceptability of both methods in a Japanese

population.

Methods

Study design

This was a prospective, non-randomized, paired comparative study, conducted to investigate the diagnostic ability of ME-NBI for CIN diagnosis compared with standard colposcopy at three medical centers: Kochi Red Cross Hospital, Kagawa University Hospital, and Osaka International Cancer Institute. ME-NBI was used for the index test, while we assigned colposcopy for comparison and histological diagnosis obtained from punch biopsy, for the reference standard. All data were extracted and compiled into a REDCap database.

Participants

Between September 2018 and June 2020, we enrolled 95 patients with positive PAP smear test results or follow-up of high-grade squamous cell intraepithelial lesions (HSIL) or definitive CIN3 confirmed by a referral hospital. Both ME-NBI and colposcopy were performed for the same patient, and the diagnostic ability of both examinations were compared. All patients provided written informed consent to undergo the procedures and participate in the study.

Inclusion and exclusion criteria

The inclusion criteria were adults aged 20 years to < 70 years of age and written informed consent. Exclusion criteria were: patients with past history of uterine cervical operation, patients with mental illness or symptoms, pregnant or possibly pregnant, and patients judged as inappropriate by the attending physician.

Examination protocol

Prior to colposcopy, a gastrointestinal endoscopist examined the cervix using ME-NBI and recorded the endoscopic findings and illustrations in the dedicated report. Then, with the endoscopic report masked, a gynecologist performed colposcopy and recorded the findings. The main lesion was defined as the highest-grade suspected neoplasm in each examination. Accessory lesions were defined as lesions suspected of being abnormal other than the main lesion in each examination. Finally, the gynecologist obtained punch biopsies from all abnormal areas, including the main and accessory lesions as well as one negative biopsy, according to the written reports of the ME-NBI and colposcopy findings. A negative biopsy was defined as acquiring one sample from an area where no lesion was noted, to improve the accuracy of the reference standard. The reference standard was defined as the highest-grade lesion confirmed by histopathological results from all biopsies, including the negative biopsy. This was why all patients did not necessarily require surgical intervention even though whole cervical resection by conization was ideal. If no abnormal findings were identified, a single biopsy was obtained from any location.

ME-NBI procedure

Magnifying endoscopes (GIF-H260Z or H290Z; Olympus Corporation, Tokyo, Japan)

with an NBI system (EVIS LUCERA SPECTRUM ELITE system; Olympus) and a carbon dioxide insufflation device (UCR; Olympus) were used during all procedures. A soft black hood (MAJ1990, Olympus) was attached to the endoscope tip to obtain focused images in high-definition. Each patient underwent ME-NBI examination in the endoscopy unit in the left lateral decubitus position (Fig. S1). Using a developing balloon (Fuji Systems Corporation, Tokyo, Japan) mounted on the endoscope tip, the vaginal orifice was occluded, and the field of view of the cervix and vagina was expanded. Mucus adherent to the cervix was removed using the water jet function of the endoscope. After the circumference of the cervix was observed under white light imaging, the endoscope was changed to NBI mode. The squamo-columnar junction where CIN occurs was circumferentially observed at long, middle, and short distances (maximum: 85 power magnification) by freely moving the endoscope. Finally, the cervix was covered in 3% acetic acid (20–30 ml) for 1 minute. and findings were captured. The inspection time was set at < 10 minutes. The endoscopic procedure was performed by four endoscopists with experience performing more than 600 ME-NBI examinations for gastrointestinal neoplasms (HK, KU, NU, and NN).

Endoscopic diagnostic criteria

The ME-NBI findings were evaluated by the presence or absence of thin- or thick-white epithelium, and abnormal intra-epithelial papillary capillary loops (IPCL), which

generally appear in esophageal neoplasms with squamous epithelium,[6] as in previous studies.[10,11] White epithelium was defined as thin-white epithelium when the underlying vessel was visible, and as thick-white epithelium when the underlying vessel was invisible. Atypical IPCL was defined as a micro-vessel that satisfied more than two of the following four findings: dilatation, crawling, irregular arrangement, and caliber change according to the IPCL classification.[6] The acetowhite findings with acetic acid spray conformed to colposcopic cervical terminology recommended by the criteria of the Rio 2011 Colposcopy Nomenclature of the International Federation for Cervical Pathology and Colposcopy (IFCPC) as follows:[12] thin acetowhite epithelium: W1 or dense acetowhite epithelium: W2. The diagnostic criteria for CIN2+ under ME-NBI were: the presence of thick-white epithelium or thin-white epithelium plus atypical IPCLs or acetowhite W2, according to a previous study.[11]

Colposcopic procedure

Patients underwent standard colposcopic examination in the lithotomy position in a gynecology unit (Fig. S1). After visualizing the cervix using a Cusco speculum (SANRITU, Tokyo, Japan), a colposcopic instrument (ZEISS Colposcope KSK 150 FC; Carl Zeiss Meditec AG, Jena, Germany) with maximum 21.5 power magnification was applied. First, the cervix was stained with 3% acetic acid to detect acetowhite epithelium. Punch biopsies were obtained from the abnormal areas according to the Rio

2011 Colposcopy Nomenclature of the IFCPC.[12] The colposcopic procedures were performed by four gynecologists who had performed more than 600 colposcopic examinations (YK, UH, KK, and KH).

Colposcopic diagnostic criteria

Colposcopic terminology was according to the Rio 2011 Colposcopy Nomenclature of the IFCPC.[12] The most frequent abnormal colposcopic findings were acetowhite epithelium, mosaic, and punctation. Abnormal colposcopic findings were categorized as: grade 1 (minor): thin acetowhite epithelium, fine punctation, fine mosaic; grade 2 (major): dense acetowhite epithelium, coarse punctation, coarse mosaic; suspicious for invasion: atypical vessels; additional signs: fragile vessels, irregular surface, exophytic lesion, necrosis ulceration (necrotic), tumor, or gross neoplasm; and nonspecific: columnar epithelium (adenosis).

Pathological evaluation

Histological results were confirmed with punch biopsies obtained during colposcopy. Tissues were fixed in 10% neutral-buffered formalin and processed into paraffin-embedded blocks; sections (3 μm) were then cut from each paraffin block. The final diagnosis was performed by experienced pathologists using hematoxylin and eosin staining.

Agreement between endoscopic and colposcopic images

To ensure consistency between the endoscopic and colposcopic sites, the side of the inserted endoscope where fluid accumulates in the left lateral decubitus position was described as the 3 o'clock position in the colposcopic images. The endoscopic axis was made concordant with the colposcopic axis by rotating the endoscopic images clockwise 180 degrees.

Outcome measures

Primary outcome

The primary outcome was the detection sensitivity of CIN2+ for ME-NBI or colposcopy in main lesions, for which the reference standard confirmed the presence of CIN2+. This outcome was determined by the following reason: clinically, lesion detection can play a role in screening regardless of the predicted diagnosis. True positive (TP) was defined as successful detection with confirmed histological results of CIN2+ for both the main lesion and the reference standard. False negative (FN) was defined as overlooked detection with histological results of < CIN2 for the main lesion and CIN2+ for the reference standard.

Secondary outcomes

The secondary outcome measures were the rates of visible whole circumferential transition zones, visible cervical orifice, and complications. Patient acceptance of both

methods was compared by a questionnaire survey evaluating patients' discomfort and embarrassment. Increasing degrees of discomfort and embarrassment were scored from 1–5. Patients were also asked which examination they would choose in future.

Subanalysis I was performed to evaluate whether the diagnostic prediction of each examination for the main lesion was concordant with the reference standard in each patient. Subanalysis II attempted to evaluate whether the diagnostic prediction for the main lesion was concordant with the final histological results for each lesion. The subanalyses measured the sensitivity, specificity, and accuracy of ME-NBI and colposcopy.

Sample size calculation

According to a previous systematic review,[13] the detection rate of CIN2+ as a primary outcome was assumed to be 90% in patients with definitive CIN3 confirmed by a referral hospital, while the rate was estimated at 40% in patients with positive PAP smear results. Moreover, the sensitivity of colposcopy to detect CIN2+ was considered approximately 70%;[2,13] thus, a minimum of 48 patients with CIN2+ were required when 95% confidence intervals (CI) required a sensitivity of ± 13%. Accordingly, the required number of patients with positive PAP smear results was calculated to be 75. Additionally, the maximum number of cases with definitive CIN3 was considered 20, so that the possibility of detecting lesions would not be too high. The calculated final

sample size was 95 patients.

Statistical analysis

The sensitivity, specificity, and accuracy of ME-NBI and colposcopy were calculated as 95% CIs using 2 × 2 tables, and these measures were compared between the two methods using McNemar's test or the chi-square test. Other categorical variables are presented as frequencies and percentages, and continuous variables as median and range. For all statistical tests, two-tailed $P < 0.05$ was considered significant. All statistical analyses were conducted using R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria; 2019).

Results

Patient enrollment

Seven of 95 patients were excluded because of inadequate data for the main lesion; the remaining 88 patients were assessed in the final analysis. Figure 1 is a flow diagram of patient enrollment and the examination protocol.

Patients' characteristics

Patients' baseline demographics and clinical characteristics are summarized in Table 1. The 88 consecutive patients (median age: 40.5 years, range: 21–67 years) comprised 72 with positive PAP smear test results, 13 with follow-up HSIL, and 3 with definitive CIN3 confirmed by a referral hospital. HPV infection history was positive in 25 patients, negative in 5, and undetermined in 58. A history of HPV vaccination was

present in 5 patients and absent in 83. The final diagnoses comprised non-cancerous lesions (n = 8), CIN1 (n = 32), CIN2 (n = 13), CIN3 (n = 34), and microinvasive carcinoma (n = 1).

Outcomes results

The primary and secondary outcomes are summarized in Table 2.

The detection sensitivity of CIN2+ showed no significant differences between the two methods (both: 79.2%; 95% CI: 65.7%–88.3%; $P > .99$).

The rates of visible whole circumferential transition zones and a visible cervical orifice were 97.7% and 96.6%, respectively, for ME-NBI, and 90.9% and 89.8%, respectively, for colposcopy ($P > 0.05$). No complications occurred during or after either procedure. 86 of 88 patients answered questionnaire. ME-NBI had significantly lower mean scores than colposcopy for discomfort (ME-NBI vs. colposcopy: 1.34 vs. 3.51, respectively; $P < 0.05$) and embarrassment (1.72 vs. 3.15, respectively; $P < 0.05$). As a future examination, 65/86 patients stated they would select ME-NBI (75.6%), 2 patients indicated colposcopy (2.3%), and 19 patients replied that both methods were acceptable (22.1%).

Subanalysis I

Regarding the prediction ability of CIN2+ for the reference standard, the sensitivity, specificity, and accuracy of ME-NBI vs. colposcopy was 68.8% (95% CI: 54.7%–80.5%) vs. 58.3% (95% CI: 44.3%–71.2%), 55.0% (95% CI: 39.8%–69.3%) vs. 70.0% (95% CI: 54.6%–81.9%), and 62.5% (95% CI: 52.1%–71.9%) vs. 63.6% (95% CI: 53.2%–72.9%), respectively, with no significant differences.

Subanalysis II

Regarding the prediction ability of CIN2+ for the histological results, the sensitivity, specificity, and accuracy of ME-NBI vs. colposcopy was 86.8% (95% CI: 72.7%–94.3%) vs. 73.7% (95% CI: 58.0%–85.0%), 50.0% (95% CI: 36.6%–63.4%) vs. 68.0% (95% CI: 54.2%–79.2%), and 65.9% (95% CI: 55.5%–75.0%) vs. 70.5% (95% CI: 60.2%–79.0%), respectively, with no significant differences. The results of the subanalysis are summarized in Table 3**.**

Diagnostic concordance between ME-NBI and colposcopy according to the reference standard of CIN2+ (n = 48) was distributed as follows (Table S1): TP with both methods (n = 34), TP with ME-NBI and FN with colposcopy (n = 4), TP with colposcopy and FN with ME-NBI (n = 4), and FN with both methods (n = 6). A representative case of CIN3 with positive results with both methods is shown in Figure S2**.** A representative case with TP with ME-NBI and FN with colposcopy is shown in Figure S3.

Discussion

Main findings

We identified two important findings. First, ME-NBI showed a diagnostic ability similar to colposcopy for detecting CIN2+, despite ME-NBI alone having a disadvantage regarding the target biopsy. Second, ME-NBI was superior to colposcopy regarding patient acceptance.

Strengths and limitations

This study has several strengths. First, this is the first prospective study comparing novel ME-NBI with standard colposcopy for diagnosing CIN. Second, gastrointestinal ME-NBI with high-quality imaging was diverted to diagnose CIN, representing cost-efficiency. Third, our developed vaginal-occluding balloon is a new alternative to obtain a clear cervical visual field.

This study has several limitations. First, the site designated by ME-NBI was biopsied under colposcopy, which could be disadvantageous when using only ME-NBI. Tissue sample quality using endoscopic biopsy forceps is still undergoing investigation, which is why we adopted this two-method approach. Second, the diagnostic criteria for ME-NBI for CIN remain immature, which suggests future modification of the approach after verification of our results. Third, evaluating patients' acceptance of the diagnostic methods was limited to Japanese women.

Interpretation

A meta-analysis of eight studies published in 1998 estimated the sensitivity and specificity of colposcopy at 85% and 69%, but values ranged widely from 30% to 99% for sensitivity and from 39% to 93% for specificity.[14] Another meta-analysis of 25 studies published in 2012 provided pooled values of 91.3% for sensitivity and 24.6% for specificity, but also demonstrated wide ranges of 65.9%–100% for sensitivity and 5%–80% for specificity.[15] Most studies appeared to be subject to bias, especially verification bias, which is problematic in colposcopy studies. Moreover, as these studies defined sensitivity and specificity differently according to the biopsy-associated

values/evaluation and the reference standard, direct comparison is difficult. Therefore, in this study, we focused on fairly comparing the two methods. Specifically, we compared the diagnostic performance of each method for only the main lesion suspected as the highest grade. The other lesions, including one negative biopsy, were used only to determine the reference standard. This approach meant that verification bias and evaluating the reference standard did not affect the fairness when comparing the methods. However, sensitivity and specificity results do not necessarily indicate general diagnostic performance.

NBI is a reliable image-enhanced technology for detecting and diagnosing early gastrointestinal neoplasms. A prospective, randomized, controlled trial showed a higher detection rate of superficial carcinoma in the head and neck and the esophagus for NBI compared with conventional white-light imaging (97% vs. 55%, respectively).[16] Furthermore, ME-NBI is useful for evaluating microvascular structures (IPCLs) of squamous epithelium and permits distinguishing cancerous lesions from non-cancerous lesions[17] and predicting the invasion depth.[18] A multicenter prospective study reported excellent diagnostic performance of ME-NBI for diagnosing early gastric cancer, with accuracy, sensitivity, and specificity of 98.1%, 85.7%, and 99.4%, respectively.[19] The study was followed by a meta-analysis.[20] Consequently, high evidence supports ME-NBI as a productive diagnostic modality.

In this study, no significant differences were observed in the detection

sensitivity of CIN2+ between the two methods although we assumed a higher detection sensitivity of ME-NBI over colposcopy, similar to gastrointestinal-related data. The subanalyses also showed no significant differences in prediction ability of CIN2+ for the reference standard or the histological results. This may be because lesions detected by ME-NBI may have resulted in FN biopsy results because punch biopsy under colposcopy was performed at the site indicated in the ME-NBI report. This factor may be associated with different cervical extensibility and appearance between the two methods and information transmission error from endoscopic report to gynecologists. In comparison, colposcopy appeared to have low sensitivity and relatively high specificity because acetowhite epithelium was generally considered the main finding, and random biopsy was not performed in this study. As shown in Table S1, there were four ME-NBI-positive patients with FN results with colposcopy. The details of these four cases are as follows: in one case, whole circumferential observation was not possible using a Cusco speculum; one middle-aged case had transition zones regressed toward the cervical orifice; one case had no acetowhite findings; and one case had a lesion hidden behind a benign polyp. In comparison, four colposcopy-positive patients with ME-NBI FN results were seen. When ME-NBI findings and reports were reviewed for these cases, we considered the following failure factors: three cases may have involved unsuccessful colposcopic target biopsy, one may have involved schema description error because of an axis discrepancy between the methods.

Among several new instruments, three adjunctive colposcopy technologies were introduced to assist in colposcopy: Dynamic Spectral Imaging System (DySIS),[21] LuViva Advanced Cervical Scan using optical spectroscopy,[22] and Niris Imaging System utilizing optical coherence tomography.[23] DySIS maps of acetowhite epithelium help examiners identify the target biopsy site. A recent comparative study showed no significant differences for identifying CINs between colposcopic-directed biopsies and DySIS-directed biopsies.[24] The studies of LuViva and Niris systems were associated with high bias and lack of advantageous outcomes; thus, clinical evaluations have been discontinued. Currently, novel microendoscopy[25] and flexible gastrointestinal endocytoscopy[26] provided a high level of diagnostic accuracy compared with colposcopy. However, these devices require further evidence, including the cost–benefit.

The rates for visible whole circumferential transition zones and the cervical orifice tended to be higher with ME-NBI than with colposcopy. The cervical visual field influences diagnostic accuracy. Cusco's speculum is sometimes associated with limited ability to obtain these visual fields in patients with a thick cervix, and middle-aged patients with regressed transition zones. Conversely, with ME-NBI, our developed vaginal-occluding balloon enables examiners to secure the cervical visual field without advanced skills. This innovation may overcome colposcopic-associated issues and lead to a stable and sufficient visual field.

ME-NBI was significantly accepted by patients over colposcopy. In colposcopy, patients feel discomfort with the forced vaginal expansion with the Cusco speculum and feel embarrassed by the lithotomy position. Conversely, with ME-NBI, patients' discomfort and embarrassment was minimized. Moreover, most patients (75.6%) stated they would choose ME-NBI as a future examination. These results indicate that ME-NBI is more acceptable to patients than colposcopy.

Regarding future perspectives, with validation of sampling using endoscopic biopsy forceps, a prospective randomized controlled study of punch biopsy under colposcopy versus endoscopic biopsy under ME-NBI would be valuable to reveal the true ability of ME-NBI. Gynecologists must accept unfamiliarity with ME-NBI diagnosis and a lack of experience with endoscopic maneuvers to establish wide-spread ME-NBI examination. Training is mandatory, and artificial intelligence may assist accurate ME-NBI diagnosis for gynecologists. Moreover, a short rigid endoscope with ME-NBI function is expected to be developed so that gynecologists familiar with rigid laparoscopes can easily handle the endoscope.

Conclusion

ME-NBI was comparable to colposcopy for detecting high-grade CINs; therefore, target biopsy under ME-NBI is warranted. Furthermore, ME-NBI was more acceptable to patients than colposcopy.

Acknowledgements

We thank Jane Charbonneau, DVM, from Edanz Group (https://en-author-services.edanzgroup.com/ac) for editing a draft of this manuscript.

Disclosure of Interests

No authors have any conflict of interest.

Contribution to Authorship

Authors HK and KU were responsible for the study concept and design; authors KY, NT, NN, YS, CK, NM, YT, Y Kai, Y Kiyohara, SK, and UH were responsible for the acquisition of the data; authors NU and JK were responsible for the statistical analysis and data interpretation; authors KK and Masaki TM supplied the materials for the study; author NU was responsible for drafting the manuscript; and author KH was responsible for the study supervision.

Details of Ethical Approval

The present study was approved at April 26, 2018 by the Clinical Ethics Committee of each facility in accordance with the Declaration of Helsinki and was registered as University Hospital Medical Information Network Clinical Trials Registry Number UMIN 000033189 following the STARD checklist.

Funding

This work was supported by the Japan Society for the Promotion of Science (JSPS)

KAKENHI Grant Number 17K15775.

References

1. Canfell K, Kim JJ, Brisson M, Keane A, Simms KT, Caruana M, et al. Mortality impact of achieving WHO cervical cancer elimination targets: a comparative modelling analysis in 78 low-income and lower-middle-income countries. Lancet 2020;395:591–603.
2. Brown BH, Tidy JA. The diagnostic accuracy of colposcopy - A review of research methodology and impact on the outcomes of quality assurance. Eur J Obstet Gynecol Reprod Biol 2019;240:182–6.
3. Arbyn M, Redman CWE, Verdoodt F, Kyrgiou M, Tzafetas M, Ghaem-Maghami S, et al. Incomplete excision of cervical precancer as a predictor of treatment failure: a systematic review and meta-analysis. Lancet Oncol 2017;18:1665–79.
4. Selmouni F, Zidouh A, Alvarez-Plaza C, El Rhazi K. Perception and satisfaction of cervical cancer screening by Visual Inspection with Acetic acid (VIA) at Meknes-Tafilalet Region, Morocco: a population-based cross-sectional study. BMC Womens Health 2015;15:106.
5. Yao K, Oishi T, Matsui T, Yao T, Iwashita A. Novel magnified endoscopic findings of microvascular architecture in intramucosal gastric cancer. Gastrointest Endosc 2002;56:279–84.
6. Inoue H, Kaga M, Ikeda H, Sato C, Sato H, Minami H, et al. Magnification endoscopy in esophageal squamous cell carcinoma: a review of the intrapapillary

capillary loop classification. Ann Gastroenterol 2015;28:41–8.

7. Chiu PWY, Uedo N, Singh R, Gotoda T, Ng EKW, Yao K, et al. An Asian consensus on standards of diagnostic upper endoscopy for neoplasia. Gut 2019;68:186–97.
8. Nakanishi H, Doyama H, Ishikawa H, Uedo N, Gotoda T, Kato M, et al. Evaluation of an e-learning system for diagnosis of gastric lesions using magnifying narrow-band imaging: a multicenter randomized controlled study. Endoscopy 2017;49:957–67.
9. Banks M, Graham D, Jansen M, Gotoda T, Coda S, di Pietro M, et al. British Society of Gastroenterology guidelines on the diagnosis and management of patients at risk of gastric adenocarcinoma. Gut 2019;68:1545–75.
10. Nishiyama N, Kanenishi K, Mori H, Kobara H, Fujihara S, Chiyo T, et al. Flexible magnifying endoscopy with narrow band imaging for the diagnosis of uterine cervical tumors: a cooperative study among gastrointestinal endoscopists and gynecologists to explore a novel micro-vascular classiication system. Oncol Lett 2017;14:355–62.
11. Uchita K, Kanenishi K, Hirano K, Kobara H, Nishiyama N, Kawada A, et al. Characteristic findings of high-grade cervical intraepithelial neoplasia or more on magnifying endoscopy with narrow band imaging. Int J Clin Oncol 2018;23:707–14.

12. Bornstein J, Bentley J, Bosze P, Girardi F, Haefner H, Menton M, et al. 2011 Colposcopic terminology of the International Federation for Cervical Pathology and colposcopy. Obstet Gynecol 2012;120:166–72.
13. Wade R, Spackman E, Corbett M, Walker S, Light K, Naik R, et al. Adjunctive colposcopy technologies for examination of the uterine cervix--DySIS, LuViva Advanced Cervical Scan and Niris Imaging System: a systematic review and economic evaluation. Health Technol Assess 2013;17:1–240, v-vi.
14. Mitchell MF, Schottenfeld D, Tortolero-Luna G, Cantor SB, Richards-Kortum R. Colposcopy for the diagnosis of squamous intraepithelial lesions: a meta-analysis. Obstet Gynecol 1998;91:626–31.
15. Underwood M, Arbyn M, Parry-Smith W, De Bellis-Ayres S, Todd R, Redman CWE, et al. Accuracy of colposcopically-directed punch biopsies: a systematic review and meta-analysis. BJOG 2012;119:1293–301.
16. Muto M, Minashi K, Yano T, Saito Y, Oda I, Nonaka S, et al. Early detection of superficial squamous cell carcinoma in the head and neck region and esophagus by narrow band imaging: a multicenter randomized controlled trial. J Clin Oncol 2010;28:1566–72.
17. Ohashi S, Miyamoto S, Kikuchi O, Goto T, Amanuma Y, Muto M. Recent Advances From Basic and Clinical Studies of Esophageal Squamous Cell Carcinoma. Gastroenterology 2015;149:1700–15.

18. Goda K, Tajiri H, Ikegami M, Yoshida Y, Yoshimura N, Kato M, et al. Magnifying endoscopy with narrow band imaging for predicting the invasion depth of superficial esophageal squamous cell carcinoma. Dis Esophagus 2009;22:453–60.
19. Yao K , Doyama H , Gotoda T , Ishikawa H, Nagahama T, Yokoi C, et al. Diagnostic performance and limitations of magnifying narrow-band imaging in screening endoscopy of early gastric cancer: a prospective multicenter feasibility study. Gastric Cancer 2014;17:669–79.
20. Lv X, Wang C, Xie Y, Yan Z. Diagnostic efficacy of magnifying endoscopy with narrow-band imaging for gastric neoplasms: a meta-analysis. PLoS One 2015;10:e0123832.
21. Louwers JA, Zaal A, Kocken M, ter Harmsel WA, Graziosi GCM, Spruijt JWM, et al. Dynamic spectral imaging colposcopy: higher sensitivity for detection of premalignant cervical lesions. BJOG 2011;118:309–18.
22. Twiggs LB, Chakhtoura NA, Werner CL, Griffith WF, Flowers LC, Lashgari M, et al. Multimodal spectroscopy as a triage test for women at risk for cervical neoplasia: results of a 1,607 subject pivotal trial. J Low Genit Tract Dis 2010;14:248–9.
23. Liu Z, Belinson SE, Li J, Yang B, Wulan N, Tresser NJ, et al. Diagnostic efficacy of real-time optical coherence tomography in the management of preinvasive and invasive neoplasia of the uterine cervix. Int J Gynecol Cancer 2010;20:283–7.

24. Booth BB, Petersen LK, Blaakaer J, Johansen T, Mertz H, Dahl K, et al. Accuracy of colposcopy-directed biopsy vs dynamic spectral imaging directed biopsy in correctly identifying the grade of cervical dysplasia in women undergoing conization: A methodological study. Acta Obstet Gynecol Scand 2020;99:1064–70.
25. Guo J, Fu L, Zhao J, Lei L, Zhan Q, Liu M, et al. The value of microendoscopy in the diagnosis of cervical precancerous lesions and cervical microinvasive carcinoma. Arch Gynecol Obstet 2020;302:455–62.
26. Ono S, Nozaki A, Matsuda K, Takakuwa E, Sakamoto N, Watari H. In vivo optical cellular diagnosis for uterine cervical or vaginal intraepithelial neoplasia using flexible gastrointestinal endocytoscopy -a prospective pilot study. BMC Cancer 2020;20:955.

Tables

Table 1. Patients' baseline demographics and clinical characteristics

Characteristic	
Total number of patients	88
Median age, years (range)	40.5 (21–67)
Indications, *n*	
Positive PAP smear*	72
HSIL on follow-up	13
Definitive CIN3	3
HPV infection, *n*	
Positive	25
Negative	5
Undetermined	58
HPV vaccine, *n*	
Presence	5
Absence	83
Final diagnosis, *n*	
Non-cancerous lesion	8
CIN1	32
CIN2	13
CIN3	34
Microinvasive carcinoma	1

HSIL, high-grade squamous cell intraepithelial lesion; CIN1, cervical intraepithelial neoplasia grade 1; HPV, human papillomavirus. *Number of patients (*n*): low-grade squamous cell intraepithelial lesion (LSIL) (25), HSIL (35), atypical squamous cells of undetermined significance (ASC-US) (6), high-grade squamous intraepithelial lesion (ASC-H) (6).

Table 2. Comparison of the outcomes of ME-NBI versus colposcopy

	Measure	ME-NBI (*n* = 88)	Colposcopy (*n* = 88)	*P* value
Primary outcome	Detection sensitivity of CIN2+, % (95% CI*)	79.2 (65.7–88.3)	79.2 (65.7–88.3)	>.99※
Secondary outcomes	Rate of visible whole circumferential transition zones, %	97.7	90.9	0.05#
	Rate of visible cervical orifice, %	96.6	89.8	0.07#
	Complications rate	0	0	N/A#
	Patients' acceptance of the method, mean score (grade 1–5)	(*n* = 86)	(*n* = 86)	
	Discomfort	1.34	3.51	<.001†
	Embarrassment	1.72	3.15	<.001†
	Which choice as a future examination, % (*n*)$	75.6 (65)	2.3 (2)	<.001#

ME-NBI, magnifying endoscopy with narrow band imaging; CIN2, cervical intraepithelial neoplasia grade 2; N/A, not applicable.

*95% confidence interval (CI) according to Wilson's score interval, ※McNemar's test, #Chi-squared test, †Welch's t-test, $Both methods acceptable: 22.1% (19) of the 86 surveyed patients.

Table 3. Results of the subanalysis of ME-NBI versus colposcopy

Measure	ME-NBI (n = 88)	Colposcopy (n = 88)	P value
Prediction ability of CIN2+ for the reference standard, % (95% CI*)			
Sensitivity	68.8 (54.7–80.5)	58.3 (44.3–71.2)	0.30※
Specificity	55.0 (39.8–69.3)	70.0 (54.6–81.9)	0.21※
Accuracy	62.5 (52.1–71.9)	63.6 (53.2–72.9)	>.99※
Prediction ability for CIN2+ for the histological results, % (95% CI*)			
Sensitivity	86.8 (72.7–94.3)	73.7 (58.0–85.0)	0.15#
Specificity	50.0 (36.6–63.4)	68.0 (54.2–79.2)	0.07#
Accuracy	65.9 (55.5–75.0)	70.5 (60.2–79.0)	0.52#

ME-NBI, magnifying endoscopy with narrow band imaging; CIN2, cervical intraepithelial neoplasia grade 2; CI, confidence interval.

※McNemar's test, #Chi-squared test.

Table/Figure Caption List

Figure 1. Flow diagram of patient enrollment and the examination protocol.

Supporting Information

Figure S1. Schematic of the examinations.

a. Flexible magnifying endoscopy with narrow band imaging (ME-NBI).

b. Colposcopy.

ME-NBI, magnifying endoscopy with narrow band imaging.

Figure S2. Representative images of cervical intraepithelial neoplasm grade 3 (CIN3).

a. Narrow band imaging by endoscopy showing thick-white epithelium at the 6–7-o'clock position of the cervix (white arrows).
b. Magnifying endoscopy with narrow band imaging (ME-NBI) showing a well-demarcated neoplastic area with thick-white epithelium (yellow arrows) with atypical vessels (red arrows).
c. The lesion appears as thick acetowhite epithelium in acetic acid endoscopy (blue arrows).
d. Colposcopy with acetic acid application demonstrating dense acetowhite epithelium (grade 2) in the same area (black arrows).

ME-NBI, magnifying endoscopy with narrow band imaging; CIN3, cervical intraepithelial neoplasia grade 3.

Figure S3. Representative case of CIN3 that was detected by ME-NBI (yellow circle) but not with colposcopy with acetic acid. The red circle indicates CIN1 detected by colposcopy.

a. Narrow band imaging by endoscopy showing thin-white epithelium at the 1–2-o'clock position of the cervix.
b. ME-NBI showing thin-white epithelium with atypical vessels.
c. Acetic acid observation in a white-light image with flexible endoscopy showing no acetowhite epithelium in that area.
d. ME-NBI with acetic acid enhanced the thin-white epithelium with atypical vessels (blue arrows), confirmed histologically as CIN3.
e. Colposcopy with acetic acid application showing a thin acetowhite (grade 1) lesion at 11 o'clock, confirmed histologically as CIN1.
f. Close-up image with colposcopy.

ME-NBI, magnifying endoscopy with narrow band imaging; CIN3, cervical intraepithelial neoplasia grade 3.