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Usefulness of endocytoscopy in evaluating transbronchial biopsy specimens

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Abstract

Background: Endocytoscopy (ECS) provides a magnification of approximately 450× for real-time observation of lesion nuclei.

Using ECS, we aimed to evaluate whether sufficient samples for diagnosis can be obtained during bronchoscopy. We also investigated whether ECS can enable two-class diagnosis of malignant or non-malignant transbronchial biopsy specimens in real-time during bronchoscopy.

Methods: This was a single-facility, prospective, observational, ex vivo study. Forty cases with localized peripheral pulmonary lesions underwent transbronchial biopsy with endobronchial ultrasonography using a guide sheath. Each biopsy specimen was immediately observed and evaluated endocytoscopically after the collection by the bronchoscopic procedure.

Results: Thirty-seven cases were enrolled. The diagnostic accuracy achieved by ECS was 91.9% (34/37). The agreement rate between the endocytoscopic evaluation and pathological diagnosis of each specimen (170 specimens) was 65.3% (111/170). The median time required for endocytoscopic evaluation per specimen was 70 s. When we judged a specimen to be malignant a second time on ECS evaluations of five specimens in one case, pathologically malignant specimens were collected in 26 of 27 cases (96.3%).

Conclusions: ECS with methylene blue staining may aid in the two-class diagnosis of malignant or non-malignant transbronchial biopsy specimens during bronchoscopy. This may reduce the number of tissue biopsies.

KEYWORDS
biopsybronchoscopyendocytoscopy

INTRODUCTION

When lung cancer is suspected on chest X-ray or computed tomography (CT), diagnosis is based on accurate analyses of cells and/or tissues obtained from the lesion via bronchoscopy, percutaneous needle biopsy, thoracoscopy, or a surgical procedure. In recent years, treatable driver oncogenes have been discovered and targeted drugs have been developed.[1–4] Hence, more specimens are now required for genomic analysis. However, the optimal number of specimens and optimal specimen size required for genome analysis has not been clearly defined.

Endocytoscopy (ECS) is an ultra-magnifying imaging technique for the evaluation of mucosal surfaces that has been applied during clinical gastroenterological endoscopy.[5–7] There are two types of ECS, the integrated-type and the catheter-type. The principal ECS procedure is called contact endoscopy, during which the objective lens is in contact with

the target with a magnification of ∼450× for observation. ECS can be used to observe cells and nuclei in real time. Shibuya et al.[8] observed the bronchial epithelium in real-time using ECS in 22 patients, reporting that ECS was useful in discriminating between normal epithelial cells and dysplastic or malignant cells.

The ability to determine whether a sample obtained during bronchoscopy is qualitatively appropriate in real time would aid in the prevention of delays in diagnosis and treatment because of insufficient specimen size. In addition, obtaining sufficient specimens would reduce the risk of bleeding and pneumothorax because of excessive biopsy and decrease the overall examination time.

This study aimed to observe transbronchial biopsy (TBB) specimens using ECS during bronchoscopy and to determine the possibility of performing two-class diagnosis of malignant or non-malignant TBB specimens in real-time during bronchoscopy. In addition, the time required for ECS observation and evaluation was measured, and the feasibility of the ECS procedure during the routine bronchoscopic procedure was examined.

METHODS

Patients

This single-facility, prospective, observational, ex vivo study was approved by the Institutional Review Board of Shimane Universal Hospital (approval number: 3014) and registered with the UMIN Clinical Trials Registry (UMIN 000033817). All participants provided written informed consent. There were no reports of ECS for transbronchial biopsy specimens, and it was challenging to set the sample size. For an exploratory study, we set the sample size of 40 cases that could be accumulated in 1 year from the number of cases in our division. Forty bronchoscopic procedures performed in 38 patients were enrolled from November 2018 to March 2019. Hereafter, 40 bronchoscopic procedures were referred to 40 cases. Forty cases with localized peripheral lung lesions distal to the subsegmental bronchus were enrolled and referred for diagnostic bronchoscopy.

Procedures

Before the bronchoscopy, the bronchoscopist identified the leading bronchi to the target lesion using a chest CT scan with a slice thickness of 0.5 to 2 mm.[9] The bronchoscopy and biopsy procedures are outlined in the Appendix S1. We performed endobronchial ultrasonography using a guide sheath (EBUS-GS) to get five biopsy specimens per one case.

The tissue specimen obtained using the biopsy forceps was soaked in 10% formalin for 30 seconds and placed on gauze, following which 0.5% methylene blue was dropped on the surface of the specimens using a 1-mL syringe with a 25-G needle. Each biopsy specimen was immediately observed and evaluated endocytoscopically after the collection by the bronchoscopic procedure.

The tip of the endocytoscope (prototype, XEC-300-2; Olympus Medical Systems) was placed on the surface of the biopsy specimen, and the ECS image of the specimen was observed and recorded using a video recorder (Image Management Hub: IMH-20; Olympus Medical Systems). Specimens were stored in a separate formalin container and submitted to the Department of Pathology. After completion of five biopsies, the guide sheath (GS) (SG-200C, Olympus Medical Systems) was left in situ for 2 to 3 minutes to stop the bleeding and was then removed. The starting (when methylene blue was dropped on the specimens) and ending times (completion of ECS evaluation) of each ECS evaluation were recorded.

Endocytoscopy system

The endocytoscope consisted of a flexible catheter-type endoscope that was 380 cm long and 3.2 mm in diameter. The ECS provided an observation field of 300 × 300 μm, an observation depth of ∼0 to 30 μm, and horizontal resolution of 4.2 μm. A 450-fold magnified image of the biopsy tissue was displayed on a 14-inch monitor. The tissue was observed with the objective lens using scattered light emitted from the tip of the endocytoscope (Figure 1).

Evaluation method

ECS evaluation method for each sample

Abad et al.[10] proposed classifying ECS images of the esophagus and stomach into three categories: (a) non-neoplastic lesions (EC 1) with regular cellular arrangement and a uniform pattern of small, rounded nuclei; (b) borderline lesions (EC 2) with changes in cellular density, morphology, or arrangement, but containing a nucleus with a regular shape and size (or mild enlargement); and (c) neoplastic lesions (EC 3) with an irregular cellular arrangement and morphology and nuclei that are heterogeneous in shape and size.[10] However, to our knowledge, there are no criteria for ECS evaluation of TBB specimens. Therefore, we developed an endocytoscopy-for-biopsy (ECB) classification based on Abad's criteria[10] and Minami's endocytoscopic atypia (ECA) classification[11] used in the field of gastrointestinal endoscopy. The judgment of ECB classification was made based on the presence or absence of "heterogeneity of nuclei" and "irregular arrangement of nuclei." Heterogeneity of nuclei was defined as swelling of the nuclei accompanied by heterogeneity in size and shape. Irregular arrangement of nuclei was defined as non-uniform nuclear distribution and a significant increase in nuclear density based on a comparison of four segments displayed simultaneously on the monitor.

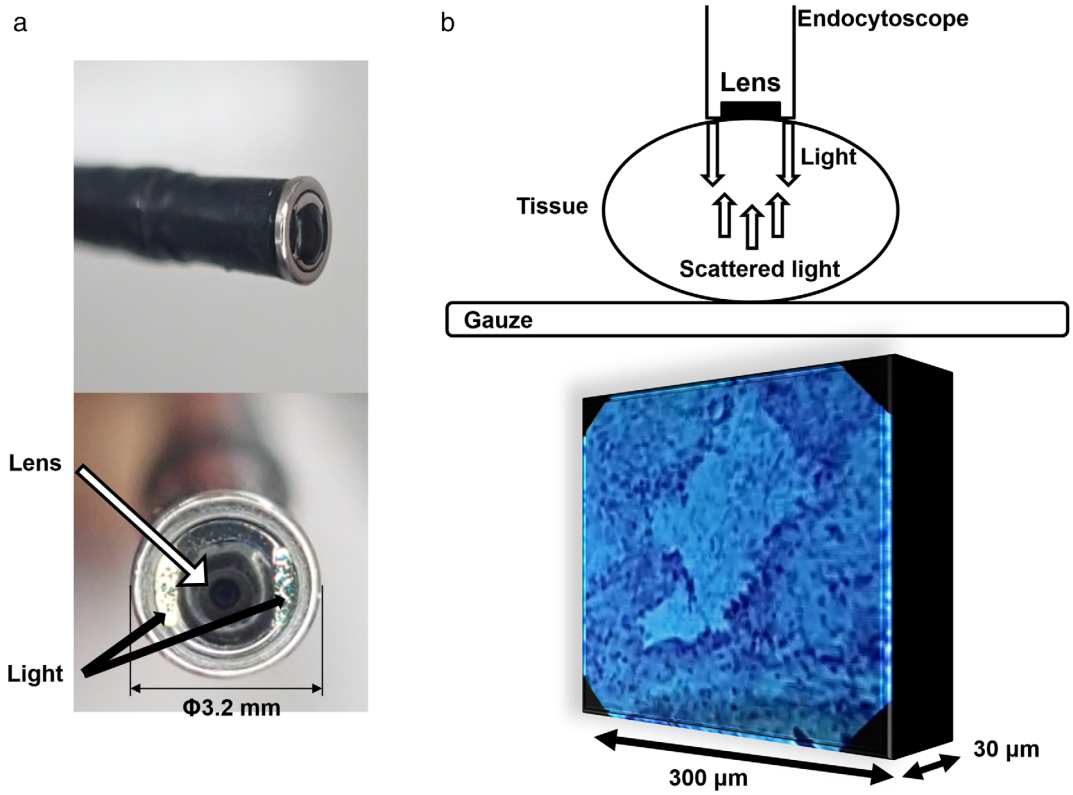

FIGURE 1 Endocytoscopy (ECS). (a) An endocytoscope consisting of a flexible catheter-type endoscope 380 cm long and 3.2 mm in diameter (Source: courtesy of Olympus medical systems). (b) The light emitted from the tip of the endocytoscope is scattered in the tissue, and the tissue can be observed with the objective lens using scattered light. The ECS system provides a magnification of 450-fold on a 14-inch monitor, observation field of 300 × 300 μm, observation depth of 0–30 μm, and horizontal resolution of 4.2 μm.

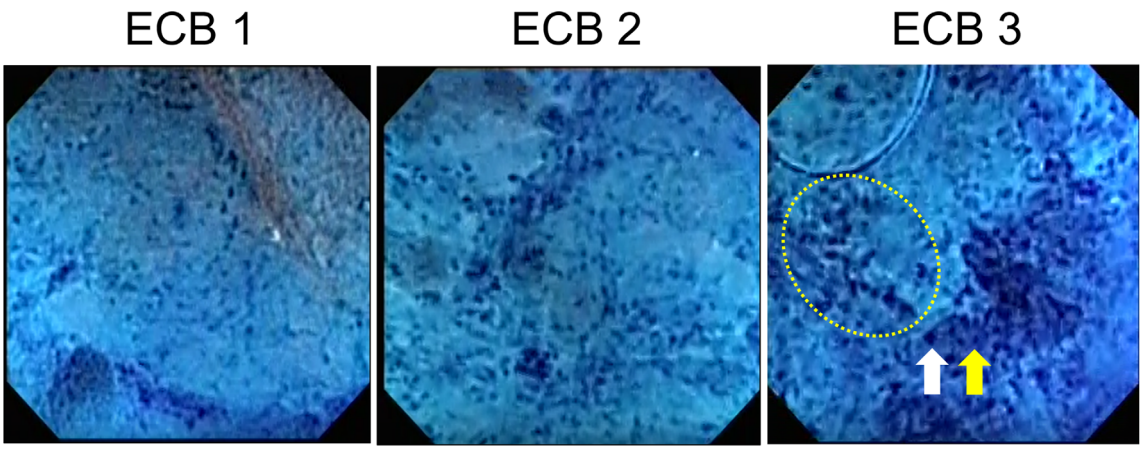

FIGURE 2 Endocytoscopy-for-biopsy (ECB) classification. ECB 1: endocytoscopy (ECS) indicates homogeneity of nuclei and regularity of nuclear arrangement. ECB 2: ECS indicates either heterogeneity of nuclei or irregularity of nuclear arrangement. This image shows irregularity of nuclear arrangement. ECB 3: ECS indicates both heterogeneity of nuclei (white arrow, yellow arrow) and irregularity of nuclear arrangement (circle on broken line). ECB 1 and ECB 2 specimens are classified as non-malignant, whereas ECB 3 specimens are classified as malignant.

We established the following ECB classifications:

- ECB 1: ECS indicating homogeneity of nuclei and regular arrangement of nuclei.
- ECB 2: ECS indicating either heterogeneity of nuclei or irregular arrangement of nuclei.
- ECB 3: ECS indicating both heterogeneity of nuclei and irregular arrangement of nuclei.

ECB 1 and ECB 2 specimens were classified as non-malignant, whereas ECB 3 specimens were classified as malignant (Figure 2).

ECS evaluation method for each case

When at least one biopsy specimen was classified as ECB 3, the case was considered malignant. When all five biopsy specimens were classified as ECB 1 or ECB 2, the case was considered non-malignant.

Diagnosis of biopsy specimens

The biopsy specimens were evaluated by an experienced pathologist. Specimens with obvious malignant findings based on pathological examination were classified as "malignant". The diagnosis of "non-malignant" was made based on pathological findings, and "suspicious" findings were considered non-malignant in our study.

Outcome measures

The outcome measures were as follows: (a) diagnostic accuracy using ECS; (b) agreement rate between ECS evaluation and pathological diagnosis in each specimen; (c) duration of ECS evaluation; (d) cumulative diagnostic yield of sequential biopsies of lesions pathologically diagnosed as malignant; (e) correlation between collection of malignant tissue and the number of specimens evaluated as malignant based on ECS; and (f) inter-observer and intra-observer agreement.

Inter-observer and intra-observer agreement

Observers (two pulmonologists) evaluated the movies of endocytoscopic images for classifying malignant or non-malignant using ECB classifications on an inter-observer agreement and intra-observer agreement. The intra-observer agreement was evaluated 3 months after the initial assessment of the inter-observer agreement. All observers were blinded to the information regarding the patients.

Data analysis

Means, percentages, sensitivity, specificity, and diagnostic accuracy were presented as appropriate. The reproducibility of the diagnoses between the two observers was evaluated using κ statistics. Cohen's κ values were used to evaluate the degree of agreement, which was classified as poor, $\kappa < 0$; slight, $\kappa = 0$–0.20; fair, $\kappa = 0.21$–0.40; moderate, $\kappa = 0.41$–0.60; substantial, $\kappa = 0.61$–0.80; or almost perfect, $\kappa = 0.81$–1.00.[12]

Statistical analysis was performed using R version 4.0.3[13] and the irr package[14] to obtain Cohen's κ coefficients. The missing data were excluded from the analysis.

RESULTS

Characteristics of patients and lesions

Among the 40 cases enrolled, two cases were excluded because fewer than five specimens had been collected, whereas another was excluded because cancer was diagnosed without endocytoscopic evaluation. Specimens from the remaining 37 cases were evaluated (Figure 3).

Of 37 cases, 28 were male and nine were female, with a median age of 72 (57–87) years. Twenty-seven lesions were pathologically diagnosed as malignant based on bronchoscopic biopsy specimens, comprising 17 adenocarcinomas, seven squamous cell carcinomas, and three small cell carcinomas. Ten lesions were not pathologically diagnosed as malignant based on bronchoscopic biopsy specimens.

Representative cases

Case 1

Chest CT showed an adenocarcinoma in the left upper lobe (Figure 4(a)). ECS revealed swelling, heterogeneous nuclei, and accumulation of nuclei in the lesion (Figure 4(b)). The pathological findings closely resembled ECS findings (Figure 4(c)).

Case 2

Chest CT showed a squamous cell carcinoma in the left lower lobe (Figure 4(d)). Elongated nuclei formed nests (Figure 4(e)), and pathological findings closely resembled ECS findings (Figure 4(f)).

Diagnostic accuracy using ECS

Of the 37 cases, 30 were judged to be malignant based on ECS, whereas seven were not. Pathologically, 27 cases were identified as malignant, whereas 10 were identified as non-malignant. The diagnostic accuracy, sensitivity, specificity, positive predictive value, and negative predictive value were 91.9% (34/37), 100% (27/27), 70.0% (7/10), 90.0% (27/30), and 100% (7/7), respectively (Table 1).

Agreement rate between ECS evaluation and pathological diagnosis in each specimen

A total of 185 specimens were obtained from 37 cases, among which a total of 170 specimens were evaluated. Among the 15 specimens that could not be evaluated, six could not be embedded, eight with blood clots could not be evaluated via ECS, and one could not be evaluated pathologically because of sample destruction (Figure 3). Eighty specimens were classified

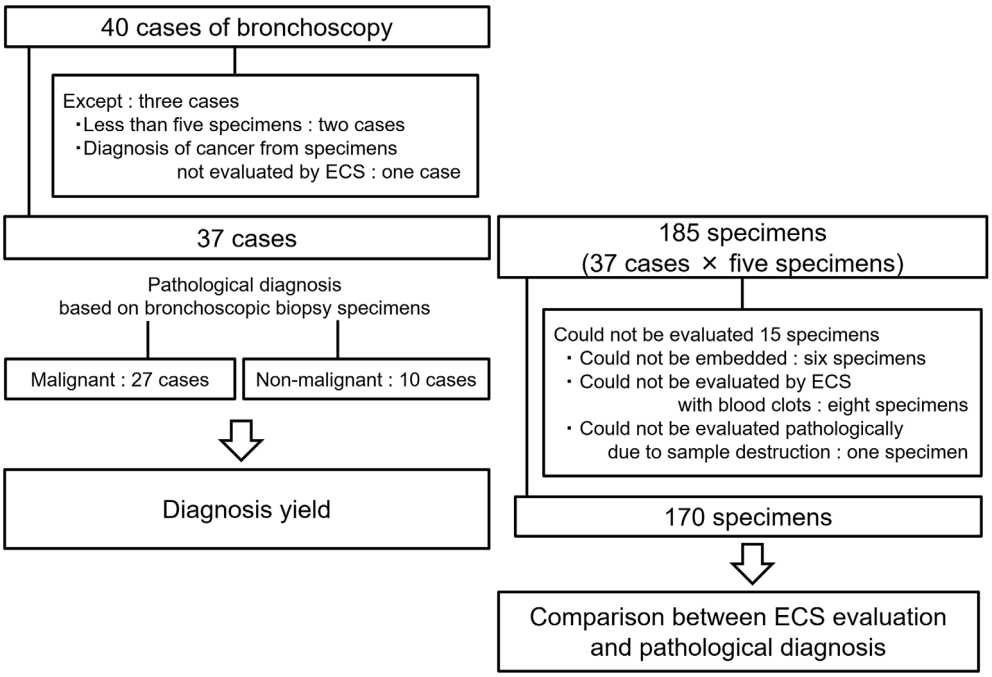

FIGURE 3 Flow chart of study enrollment. Forty cases were enrolled, and three inappropriate cases were excluded. Of the 37 cases evaluated, 27 were malignant, and 10 were pathologically non-malignant on bronchoscopic specimens. A total of 185 specimens were obtained from 37 cases. Among them, 170 specimens were evaluated following the exclusion of 15 inappropriate specimens. ECS, endocytoscopy

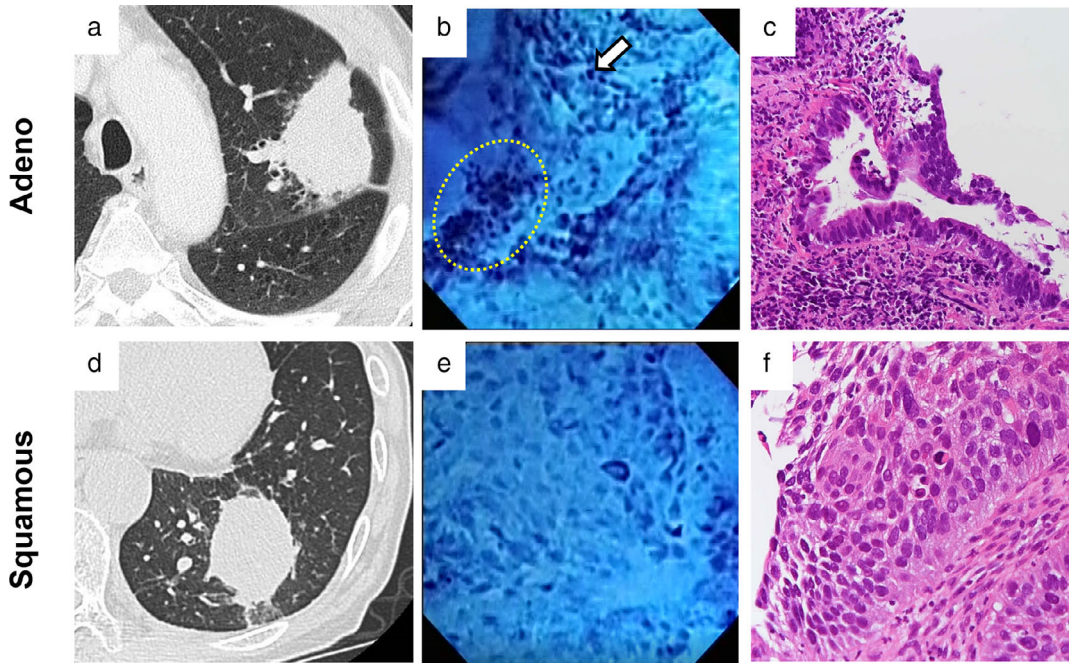

FIGURE 4 Representative cases. (a) Chest computed tomography (CT) image showing an adenocarcinoma in the left upper lobe. (b) Endocytoscopy (ECS) image showing swelling of the nuclei (arrow), heterogeneity in the size and shape of nuclei, irregular arrangement of nuclei, and abnormal proliferation and accumulation of nuclei (circle on broken line). (c) Pathological findings (hematoxylin and eosin staining [H&E]) closely resemble the ECS findings. (d) Chest CT image showing a squamous cell carcinoma in the left lower lobe. (e) ECS imaging showing swelling of nuclei, heterogeneity in the size and shape of nuclei, and irregular arrangement of nuclei. Elongated deformed nuclei can be observed. (f) Pathological findings (H&E staining) closely resemble the ECS findings.

as malignant based on ECS, whereas the remaining 90 were classified as non-malignant. On pathological examination, 91 specimens were identified as malignant, and 79 were identified as non-malignant. ECS evaluations were consistent with the pathological diagnosis for 111 specimens and inconsistent for 59 specimens. The agreement rate between the ECS evaluation and pathological diagnosis was 65.3% (111/170) (Table 2).

Duration of ECS evaluation

In the 37 cases, the starting and ending times of each ECS evaluation in 174 of 185 specimens were examined, excluding 11 data-deficient specimens. The mean time required for ECS evaluation per specimen was 77.4 seconds (median, 70 seconds per specimen).

TABLE 1 Diagnostic accuracy using ECS

	Pathology			
		Malignant	Non-malignant	Total
ECS	Malignant	27	3	30
	Non-malignant	0	7	7
	Total	27	10	37

Note: The diagnostic accuracy is 91.9% (34/37).
Abbreviation: ECS, endocytoscopy.

TABLE 2 Agreement rate between ECS evaluation and pathological diagnosis in each specimen

	Pathology			
		Malignant	Non-malignant	Total
ECS	Malignant	56	24	80
	Non-malignant	35	55	90
	Total	91	79	170

Note: The agreement rate between ECS evaluation and pathological diagnosis is 65.3% (111/170).
Abbreviation: ECS, endocytoscopy.

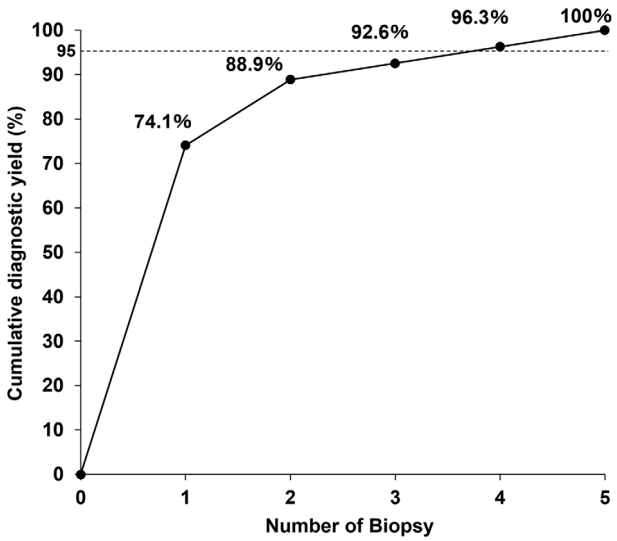

FIGURE 5 Cumulative diagnostic yield of sequential biopsies from lesions pathologically diagnosed as malignant. A total of 95% of the cumulative diagnostic yield was reached by the fourth biopsy specimen.

Cumulative diagnostic yield of sequential biopsies of lesions pathologically diagnosed as malignant

The cumulative diagnostic yield of sequential biopsy specimens from lesions pathologically diagnosed as malignant is shown in Figure 5. A cumulative diagnostic yield was established using the first, second, third, and fourth biopsy specimens for 74.1% (20/27), 88.9% (24/27), 92.6% (25/27), and 96.3% (26/27) of malignant lesions, respectively. A total of 95% of the cumulative diagnostic yield was attained by the fourth biopsy specimen.

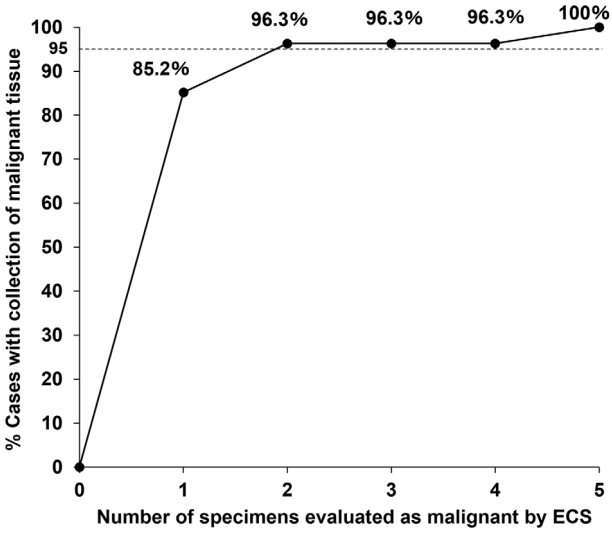

FIGURE 6 Correlation between collection of malignant tissue and the number of specimens evaluated as malignant based on ECS. When ECS revealed malignancy a second time of five biopsies in a malignant case, pathologically proven malignant specimens were collected in 26 of 27 cases (96.3%). ECS, endocytoscopy.

Correlation between collection of malignant tissue and the number of specimens evaluated as malignant based on ECS

We calculated the rate at which pathologically malignant specimens could be collected when a specimen was judged as malignant based on ECS findings. Each biopsy specimen was immediately observed and evaluated endocytoscopically after the collection by the bronchoscopic procedure. When we judged a specimen to be malignant a first time on ECS evaluations of five specimens in one case, pathologically malignant specimens were collected in 23 of 27 cases (85.2%). When we judged a specimen to be malignant a second time on ECS evaluations of five specimens in one case, pathologically malignant specimens were collected in 26 of 27 cases (96.3%) (Figure 6). When biopsy retrieval was stopped because of the second judgment of malignancy on ECS, the average number of biopsies (compared to the maximum of five biopsies) was reduced by 1.37 per malignant case (37 specimens/27 cases).

Inter-observer and intra-observer agreement

We used ECS images of 111 specimens in which the ECS evaluation was consistent with the pathological diagnosis. We selected three specimens as the teaching ECS images for the observers. Excluding these three specimens used as teaching materials, 108 specimens were used to evaluate

inter-observer and intra-observer agreement. Observer A (12 years of experience in respiratory medicine) and observer B (7 years of experience in respiratory medicine) evaluated movies of 108 specimens for inter-observer agreement.

On the results of the diagnostic yield of ECS for specimens, the sensitivity, specificity, and diagnostic accuracy of observer A using the ECS classification for malignancy were 75.9% (41/54), 72.2% (39/54), and 74.1% (80/108), respectively. The sensitivity, specificity, and diagnostic accuracy of observer B were 53.7% (29/54), 83.3% (45/54), and 68.5% (74/108), respectively.

The inter-observer agreement was moderate ($\kappa = 0.52$) (Appendix S1, Table S1). The intra-observer agreement of observer A was substantial ($\kappa = 0.70$), whereas that of observer B was moderate ($\kappa = 0.43$) (Appendix S1, Table S2, and Table S3).

Complications

In all 37 cases, the GS was left in situ for 2 to 3 minutes for hemostasis, and all the bronchoscopic biopsies were completed without serious bleeding. No major adverse events were observed.

DISCUSSION

In the present study, ECS imaging with methylene blue staining was useful for the two-class diagnosis of malignant or non-malignant TBB specimens during bronchoscopy. Although on-site evaluation is useful for detecting malignant cells, it cannot provide a tissue diagnosis. Given that tissue specimens are required for genetic testing in patients with lung cancer, even if the cytological diagnosis is malignant, we used ECS to determine whether the tissue could be harvested. To our knowledge, no studies have described the interference of pathological interpretation by methylene blue staining.

When ECS detected malignancy a second time, the malignant tissue was collected with a probability of 96.3%, and the pathological diagnosis could be determined with high possibility, even if the residual biopsies were canceled. Because no further biopsies were performed when we detected malignancy a second time on ECS, the average number of biopsies was reduced by 1.37 per case.

The median time required for ECS evaluation of one specimen was 70 seconds. Because the GS is left in situ to ensure hemostasis following specimen collection, a waiting time of 2 to 3 minutes is typically required. We used these 2 to 3 minutes to perform ECS evaluations. Our results indicate that it is acceptable to perform ECS evaluation during routine bronchoscopy.

The number of biopsy specimens is an important factor for increasing the diagnostic yield. The cumulative diagnostic yield increased stepwise, and the fourth biopsy specimen provided >95% of the diagnostic yield. Yamada et al.[15] reported that the cumulative diagnostic yield exceeded 95% in the fifth biopsy of 10, and the results were generally similar to those observed in the current study. At present, the collection of specimens based on genetic testing is becoming increasingly important, making it necessary to investigate the optimal number, size, and tumor cell-containing ratio in the future.

Clinically, ECS is used to evaluate the upper digestive tract and large intestine under optical magnification, allowing for real-time observation of structural abnormalities in nuclei and nuclear atypia. Minami et al.[11] used ECS to observe 146 esophageal lesions and classified them into five categories (ECA 1–5) according to size and uniformity of nuclei, cell count, and regularity of cellular arrangement. When compared with findings bases on hematoxylin and eosin staining (Vienna category), ECA 1 to 3 lesions corresponded to Vienna categories 1 to 3 at 91.0%, whereas ECA 4 or 5 lesions corresponded to Vienna categories 4 or 5 at 91.2%, with an overall accuracy of 91.3%.[11] Mori et al.[16] randomly assigned 203 colorectal lesions (≥5 mm) detected in 170 patients to either an ECS group or a standard biopsy group, in which lesions were assessed using microscopic examination. The diagnostic accuracy of ECS for the discrimination of neoplastic lesions was 94.1%, whereas that of standard biopsy was 96.0%, suggesting that ECS is not inferior to standard biopsy for the discrimination of neoplastic colorectal lesions.[16]

Methods for computer-aided diagnosis (CAD) have evolved in recent years. Maeda et al.[17] developed a CAD system that uses ECS to predict persistent inflammation in ulcerative colitis. The authors reported that the sensitivity and specificity of CAD for histologic active inflammation were 74% and 97%, respectively, whereas the diagnostic accuracy was 91%.[17] Misawa et al.[17] investigated CAD based on ECS with narrow-band imaging (CAD system for endocytoscopic vascular pattern [ECV-CAD]), which enables microvascular evaluation to provide a two-class diagnosis of neoplastic or non-neoplastic colorectal lesions. ECV-CAD exhibited diagnostic accuracy that was better than that of trainees and similar to that of experts.[18]

In the gastrointestinal field, ECS and CAD systems are becoming alternatives to histopathological methods. In the respiratory field, ECS has been identified as a minimally invasive and highly accurate diagnostic method. In this study, the agreement rate between ECS evaluation and pathological diagnosis per sample was not high (65.3%). This may be because the observation sites were different in the ECS and pathological images. ECS is used to observe the surface of the tissue, whereas the pathological image presents an inside view of the biopsy tissue. When malignant cells sparsely exist in biopsy tissue, especially when the malignant cells lie on the surface of the biopsy specimen and necrotic tissues occupy at the center of the specimen, it could be evaluated as non-malignant by pathology despite being evaluated as malignant by ECS. Furthermore, we used two features for ECS evaluation: heterogeneity of nuclei and irregular arrangement of nuclei in the lesion. However, our ECS evaluation was subjective, and the inter-observer agreement between the two observers and the intra-observer agreement was relatively

low, which could hinder its general use in clinical practice. Therefore, although our findings suggest that ECS is useful for histological diagnosis during bronchoscopy, it remains unclear how much tissue is required for genomic analyses. Further studies are required to clarify this clinical issue.

This study had some limitations. First, it was conducted at a single facility, and our criteria for evaluating ECS images were subjective. We attempted to evaluate the relationship between tumor cell content based on ECS and the number of malignant cells based on pathological findings; however, it was difficult to measure tumor cell content because the boundary of the malignant tissue was unclear on ECS images; therefore, we could not evaluate this relationship. Future studies should aim to evaluate in the feasibility and validity of ECB classifications, and examine whether heterogeneity and irregularity of nuclei can be objectively evaluated using artificial intelligence for reducing any bias.

CONCLUSION

ECS imaging with methylene blue staining may be useful for the two-class diagnosis of malignant or non-malignant TBB specimens during bronchoscopy.

AUTHOR CONTRIBUTIONS

All the authors had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Conceptualization*: T.O. and N.K. *Methodology*: T.O. and N.K. *Investigation*: T.O., N.K., A.T, M.H., T.H., M.K., and Y.S. *Formal analysis*: T.O., N.K. and R.T. *Writing - original draft*: T.O. *Writing - review and editing*: T.O., N.K., T.H., R.T., S.H., T.I., and Y.T.

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CONFLICT OF INTEREST

Takae Okuno has no conflicts of interest. Noriaki Kurimoto received personal fees from Olympus Corporation. Noriaki Kurimoto received personal fees from Eli Lilly Japan K.K., and Chugai Pharmaceutical outside the submitted work. Akari Tanino has no conflicts of interest. Megumi Hamaguchi has no conflicts of interest. Takamasa Hotta has no conflicts of interest. Ryosuke Tanino has no conflicts of interest. Misato Kobayashi has no conflicts of interest. Yohei Shiratsuki has no conflicts of interest. Shunichi Hamaguchi has no conflicts of interest. Takeshi Isobe received grants from KONICA MINOLTA, IQVIA Services JAPAN K.K. and Insmed outside the submitted work. Takeshi Isobe received personal fees from DAIICHI SANKYO COMPANY, AstraZeneca K.K., and Nippon Boehringer Ingelheim outside the submitted work. Yukari Tsubata received grants from ONO PHARMACEUTICAL and Pfizer Health Research Foundation., outside the submitted work. Yukari Tsubata received personal fees from DAIICHI SANKYO COMPANY, AstraZeneca K.K., and Chugai Pharmaceutical, outside the submitted work.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, Noriaki Kurimoto, on reasonable request.

PATIENT CONSENT STATEMENT

All the participants provided written informed consent.

PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

No material.

CLINICAL TRIAL REGISTRATION

UMIN Clinical Trials Registry (UMIN 000033817).

ALL SOURCES OF SUPPORT IN THE FORM OF GRANTS, GIFTS, EQUIPMENT, AND/OR DRUGS

The Endocytoscopy System was borrowed from Olympus Medical Systems.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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