Study on the Diagnostic Accuracy of Endoscopic Ultrasound for Colorectal Subepithelial Lesions

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1. Background

On endoscopic ultrasound (EUS), the normal intestinal wall is typically visualized as a five-layer structure with alternating hyperechoic and hypoechoic layers, corresponding to the superficial mucosal interface, deep mucosa/muscularis mucosa, submucosa, muscularis propria, and serosa. For subepithelial lesions (SELs), EUS can measure lesion size and assess sonographic features such as margins, homogeneity, and acoustic shadowing. It also provides information on the layer of origin, lesion location, and relationship to surrounding tissues. By integrating these findings, EUS may help predict pathological nature and guide subsequent management.

However, compared with final histopathology, the reported diagnostic accuracy of EUS for gastrointestinal SELs is approximately 43%–79%, which may not fully meet current clinical needs.

2. Objectives

2.1 Primary Objective

To identify factors associated with the coincidence (concordance) between EUS diagnosis and pathological diagnosis for colorectal subepithelial lesions.

3. Endpoints

3.1 Primary Endpoint

Coincidence rate between EUS diagnosis and pathological diagnosis.

4. Study Design

This is a single-center, retrospective, observational study. All patients who underwent colorectal EUS at Shenzhen Hospital of Southern Medical University between 2015 and 2023 will be screened, and their endoscopy/EUS reports and pathology reports will be retrospectively reviewed and analyzed.
If a patient had two or more colorectal lesions evaluated by EUS, lesions at different sites will be treated as independent EUS examinations. Only SEL cases with histopathologic confirmation will be included for further analysis.

During the study, no randomization will be performed and no protocol-driven treatment will be administered or provided. When clinically indicated, treatment decisions and treatment selection will be made at the discretion of the treating physician.

5. Study Population

The study population consists of patients with colorectal subepithelial lesions.

5.1 Diagnostic Criteria

Diagnosis of colorectal submucosal tumors/subepithelial lesions will be based on the Chinese expert consensus on endoscopic diagnosis and treatment of gastrointestinal submucosal tumors (2023 edition).

5.2 Inclusion Criteria

1. Patients admitted to Shenzhen Hospital of Southern Medical University from 2015 to 2023 who underwent colorectal EUS.

2. Patients diagnosed with colorectal submucosal tumors (subepithelial lesions) according to the Chinese expert consensus on endoscopic diagnosis and treatment of gastrointestinal submucosal tumors (2023 edition) and related criteria.

5.3 Exclusion Criteria

1. Patients whose EUS diagnosis indicated non-submucosal tumors (i.e., not consistent with submucosal tumors/subepithelial lesions).

5.4 Withdrawal and Loss to Follow-up

All enrolled participants have the right to withdraw from this study at any time. Reasons for withdrawal include:

- Participant requests withdrawal and does not wish to continue participation;
- Participant is lost to follow-up;
- Participant refuses further follow-up;
- Other reasons deemed by the investigator to make the participant unsuitable to continue in the study.

Participants who withdraw during the study will be considered dropouts. After dropout, efforts should be made to contact the participant to complete assessments as feasible and to complete the study summary page.

6. Methods and Procedures

As this is an observational study, no additional study visits, laboratory testing, or assessments beyond routine clinical practice are required. Treating physicians will determine clinical management according to product labeling and local standards of care. Investigators will review medical history and laboratory reports and determine eligibility based on the inclusion and exclusion criteria.

A waiver of informed consent will be requested because the samples and information are derived from medical records and specimens collected during routine clinical care; the study poses no more than minimal risk to participants; the waiver

will not adversely affect participants' rights or welfare; obtaining consent would make the study impracticable; and participants' privacy and personal identifiers will be protected.

The number and timing of clinical visits will be determined by physicians according to local routine practice.

6.1 Informed Consent and Enrollment

A waiver of written informed consent will be applied for. Participants who meet all other inclusion/exclusion criteria will be considered enrolled.

6.2 Participant Identification Number

Each participant will be assigned a unique identification number in chronological order based on the date of examination. All study documents (e.g., case report forms, clinical records) will use this identification number. In accordance with data privacy regulations, the identification number must not include combinations that could identify the participant (e.g., initials plus date of birth should not be used together).

6.3 Data Source / Data Collection Process

Study data will be obtained by extracting routine clinical medical records of enrolled participants. Investigators will enter information from source medical records into study record forms throughout the monitoring period.

6.4 Data Collection Items

1. Demographics: age, sex, initials;
2. Lesion location and size (maximum diameter);
3. EUS echogenic features, layer-related characteristics, EUS diagnosis (primary diagnosis), operator, and device information;
4. Pathology acquisition method, pathological layer, and pathological diagnosis.

7. Criteria for Study Termination / Suspension

7.1 The sponsor has the right to terminate or suspend the study. Before termination/suspension, the sponsor must notify the investigator, the ethics committee, and relevant regulatory authorities and provide the rationale. If the study is terminated/suspended early, restarting the study requires ethics committee approval.
7.2 Termination or suspension as required by the ethics committee.

8. Study Completion

The study will be completed when data collection reaches the predefined time interval.

9. Data Management

9.1 Data Management Procedures

1. Investigators must ensure data are truthful, complete, and accurate.
2. Any correction to study records must be made by a single line through the original entry, with the corrected data annotated, the reason documented, and the investigator's signature and date provided; erasing or overwriting original records is not permitted.
3. Required laboratory examination items should be complete as applicable in routine care.

9.2 Data Recording and Document Retention

Participant data in case report forms will be recorded using coded identifiers; participants may only be identifiable via the participant code or initials.

This study will use an Excel database for data management, with double data

entry. After source data verification and confirmation of data integrity, the database will be locked. After database lock, the analysis dataset will be exported for statistical analysis. Locked data cannot be edited. If issues are identified after database lock, they may be corrected within the statistical analysis program after confirmation.

10. Statistical Analysis

10.1 Sample Size Determination

This is a single-center, retrospective, observational study. One-way analysis of variance (ANOVA) will be used to explore factors associated with concordance versus non-concordance between EUS diagnosis and pathological diagnosis. Using G*Power (version 3.1.9.7) with an effect size of 0.25, $\alpha = 0.05$, power $(1-\beta) = 0.80$, 10 predictors, and 2 groups, the required sample size was calculated to be 269 cases.

10.2 Statistical Methods

Analyses will include case distribution, demographic characteristics and baseline analyses, and outcome analyses.

10.3 Statistical Software and General Requirements

- Statistical analyses will be performed using SPSS.
- Continuous variables will be summarized using mean, standard deviation, median, minimum, and maximum values.
- Categorical variables will be summarized using frequencies and percentages.
- One-way ANOVA will be used to evaluate differences in potential factors between the concordant and non-concordant groups.
- Multivariable logistic regression will be performed to identify key factors independently associated with diagnostic concordance.

11. Study Management

11.1 Compliance With Regulations and Standards

1. Investigators will implement quality control (QC) and quality assurance (QA) systems in accordance with standard operating procedures (SOPs).

2. Source documents must comply with relevant regulations and standards.

3. Laboratory test results must be accurate and reliable.

4. All observations and findings will be verified to ensure data reliability.

5. A complete study organizational structure will be established with clearly defined responsibilities at each level.

6. The principal investigator (PI) will be responsible for overall quality control and ensuring that all personnel fulfill their responsibilities.

7. The PI will be responsible for study protocol development and related documents; the PI will prepare the study summary report after study completion.

8. Designated personnel will develop the study implementation procedures and SOPs for use during the study.

9. Before study initiation, the study team will organize training on the protocol; all study personnel must receive GCP training.

10. Physicians and nurses participating in the study must strictly follow the protocol and procedures and must not modify them arbitrarily.

11. Designated statisticians will be responsible for comprehensive

statistical processing of the study data.

11.2 Protection of Participant Privacy

All participant data collected during the study will be entered into a computer system for confidential storage and analysis. If necessary, relevant authorities may audit the records to verify the authenticity, accuracy, and completeness of the data. Study results may be published in academic journals; however, participant names will not be disclosed, and participant privacy will be protected.

11.3 Problems During the Study and Corrective Measures

1. Protocol amendments: After ethics approval, any revision requires a "protocol amendment statement" signed by the PI. Amendments may be made only after consultation and agreement between the investigators and the sponsor (and/or the registration applicant, as applicable).

2. After revision, the amended protocol must be submitted to the ethics committee for review and approval prior to implementation.

3. No study personnel may deviate from the protocol.

11.4 Quality Control and Quality Assurance

11.4.1 Quality Assurance

The sponsor and any collaborating organizations entrusted by the sponsor with all or part of the study responsibilities shall establish their own QA systems, fulfill their responsibilities, and strictly adhere to the protocol and applicable SOPs to ensure the implementation of QC/QA systems.

11.4.2 Quality Assurance for Study Conduct

Prior to study initiation, investigators will receive training on the protocol to ensure full understanding of the study procedures and endpoints. QC personnel will verify basic study conditions to ensure that the site can meet protocol requirements. During the study, investigators will follow institutional SOPs and the protocol,

perform clinical procedures accordingly, and maintain true, timely, complete, and standardized records. QC personnel will review study processes and corresponding source documents. After study completion, study documents will be compiled, checked by QC personnel, and archived. The institutional QA department may conduct feasibility audits; when noncompliance is identified, investigators and responsible personnel will be notified to implement corrective actions and to track the completion of corrections.

11.4.3 Expected Study Timeline and Completion Dates

- October 2023 to January 2024: completion of data collection
- January 2024 to April 2024: completion of data analysis

11.5 Responsibilities of Each Party and Other Related Work

1. **Sponsor responsibilities:** The sponsor is responsible for initiating, applying for, and organizing this study, and for providing study funding.

2. **Investigator responsibilities:** Investigators will conduct the study in accordance with the Declaration of Helsinki and relevant regulatory, ethical, and scientific principles, and in accordance with the protocol. Investigators should be familiar with procedures and requirements for reporting serious adverse events (SAEs) and record/report such events as required. Investigators will enter data into study records accurately, completely, timely, and legally, and will accept monitoring/audits by sponsor- or CRO-appointed monitors/auditors and inspections by regulatory authorities to ensure study quality.

3. **Publication of study data:** The sponsor holds exclusive rights to the study data. Unless written permission is obtained from the sponsor or specified in a collaboration agreement, no publication should be made in an individual capacity prior to completion of the final report. The sponsor has final authority over manuscripts and publications.

11.6 Human Genetic Resources

The collection, acquisition, trade, export, or cross-border transfer of human genetic resources shall comply with the Interim Measures for the Administration of Human Genetic Resources (Guo Ban Fa [1998] No. 36).

12. Research-Related Ethics

12.1 Ethics Committee

Before study initiation, investigators must submit the investigator's brochure (if applicable), study protocol, request for waiver of informed consent, and any other participant-related information to the ethics committee for review and approval. Any protocol amendments must be approved again by the ethics committee.

12.2 Informed Consent

Qualified investigators must explain the nature and purpose of the study, procedures, expected duration, potential risks and benefits, and any possible discomfort to each participant as part of the informed consent process. Each participant must understand that participation is voluntary and that they may withdraw from the study at any time without affecting subsequent treatment or the relationship with their treating physician.

The informed consent form should follow a standard format and use non-technical language as much as possible. Each informed consent form must include the above content and a statement of voluntariness, and must be submitted to the ethics committee for approval.

A waiver of informed consent will be requested because study samples and information are derived from medical records and specimens collected during routine clinical care; the study poses no more than minimal risk; the waiver will not adversely affect participants' rights or welfare; and obtaining consent would make the study impracticable. Participant privacy and personal identifiers will be protected.

12.3 Other

None.

13. References

1. Kida M, Kawaguchi Y, Miyata E, Hasegawa R, Kaneko T, Yamauchi H, Koizumi S, Okuwaki K, Miyazawa S, Iwai T, Kikuchi H, Watanabe M, Imaizumi H, Koizumi W. Endoscopic ultrasonography diagnosis of subepithelial lesions. Dig Endosc 2017; 29 (4): 431-443. doi: 10.1111/den.12854.

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3. Surgery Group of the Chinese Society of Digestive Endoscopy, Chinese Society of Digestive Endoscopy; NOTES Group of the Chinese Society of Digestive Endoscopy; Digestive Endoscopy Professional Committee of the Endoscopist Branch of the Chinese Medical Doctor Association; Gastrointestinal Surgery Group of the Surgery Branch of the Chinese Medical Association. Chinese expert consensus on endoscopic diagnosis and treatment of gastrointestinal submucosal tumors (2023 edition). *Chin J Dig Endosc.* 2023;40(4):253–263. doi:10.3760/cma.j.cn321463-20230310-00039