Study protocol

Effect of an artificial intelligence-assisted system on endoscopic diagnosis of superficial esophageal squamous cell carcinoma and precancerous lesions: A multicenter, tandem, randomized controlled study

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Protocol version	4.2
Version date	August 4, 2023
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Contents

1. Summary

Title	Effect of an artificial intelligence-assisted system on endoscopic diagnosis of superficial esophageal squamous cell carcinoma and precancerous lesions: A multicenter, tandem, randomized controlled study
Diseases	Superficial esophageal squamous cell carcinoma and precancerous lesions
Trail design	Multicenter, prospective, randomized, controlled, single-blind, tandem trial
	Multicenter: (1) West China Hospital, Sichuan University, (2) Nanchong Central Hospital, (3) Affiliated Hospital of North Sichuan Medical College, (4) Meishan People's Hospital, (5) Shimian People's Hospital, (6) Cangxi People's Hospital, (7) Nanbu People's Hospital, (8) Zigong Fourth People's Hospital, (9) Zizhong People's Hospital, (10) The First Veterans Hospital of Sichuan Province, (11) The Third People's Hospital of Yunnan Province, and (12) Huai'an First People's Hospital.
	Prospective: Consecutive patients were prospectively recruited from October 19, 2021.
	Randomized: Complete randomized.
	Controlled: Research group (AI-assisted gastroscopy first) and control group (routine gastroscopy first).
	Single-blind: Patients, pathologists, and statistical analysts were blinded. Endoscopists and research assistants were aware of the grouping.
	Tandem: A same day tandem gastroscopy was performed for each eligible patient by the same endoscopist.
Patients	Consecutive patients undergoing gastroscopy at the 12 hospitals from October 2021 to June 2022 were recruited.
Sample size	9,954 patients
Aims	To evaluate whether the AI system can reduce the miss rate of superficial esophageal squamous cell carcinoma and precancerous lesions and improve their detection rate in real clinical settings.
Fundings	(1) National Natural Science Foundation of China (Grant No: 82170675); (2) 1·3·5 project for disciplines of excellence, West China Hospital, Sichuan University (Grant No: ZYJC21011). (3) Chengdu Science and Technology Project (Grant No:2022-YF05-01722-SN

2. Introduction

Esophageal cancer is a common and serious disease worldwide. According to the World Health Organization data in 2020, esophageal cancer ranks eighth among the most common malignant tumors in terms of incidence and sixth in terms of mortality[1]. Esophageal cancer is mainly classified into esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma. Despite a recent decrease in the incidence of ESCC, it remains the predominant pathological type of esophageal cancer in Asia and parts of sub-Saharan Africa[1]. It has been reported that the 5-year survival rate of patients with advanced ESCC is less than 30%, while the 5-year survival rate of patients with superficial ESCC and precancerous lesions can reach more than 90%[2-4]. Therefore, early detection, diagnosis and treatment are crucial in reducing mortality and improving survival of patients with ESCC.

Endoscopy is the most commonly used method for screening and early diagnosis of ESCC. However, endoscopy cannot detect all lesions in the endoscopic field of vision, and several factors such as examinee cooperation, standardization of endoscopic operation, lesion recognition ability, examination time and visual fatigue can affect the lesion detection rate. Thus, different endoscopists may provide entirely different subjective results when judging lesions. It has been reported that certain superficial ESCC and precancerous lesions are missed during gastroscopy, with a miss rate ranging from 4·2% to 17·0%[5-10]. Hence, it is imperative to address this issue and find ways to reduce the miss rate and improve the detection rate of superficial ESCC and precancerous lesions.

In recent years, with the rapid development of artificial intelligence (AI), computer vision, intelligent media information processing and other computer fields, AI-assisted diagnosis based on deep learning has emerged to provide a new way to solve the abovementioned issues. This technology has powerful image recognition and data processing capabilities, allowing for the extraction of significant feature information from medical images. By simulating the human brain's feedback learning process, it can continuously improve the accuracy of image recognition and analysis. AI-assisted diagnosis can assist in lesion detection, regardless of subjective factors such as fatigue and stress, while improving diagnosis efficiency and accuracy. AI based on deep convolutional neural networks has rapidly developed in the field of gastrointestinal endoscopy, with several studies demonstrating that AI can accurately identify ESCC[11-13] and determine the invasion depth of lesions[14-17] or intraepithelial papillary capillary loops classification[18-20]. Despite these promising results on still images or video data, few clinical trials have been conducted to evaluate their performance in real clinical settings.

Our team has developed an AI system that can identify superficial ESCC and precancerous lesions in real time under common clinical endoscopic light modalities, including white light endoscopy (WLE) and nonmagnified narrow band imaging (NBI). This AI system differed from other systems that required a separate monitor. It

was directly connected to the endoscopy monitor used by endoscopists, allowing for single-screen use, and assisted endoscopists in lesion detection in real time during gastroscopy without requiring any changes in their operating habits, making it more suitable for clinical needs. Endoscopists could switch between the original endoscopic videos and the composite videos with the results of the AI system by using a button on the endoscopic monitor. The AI system represented suspicious lesions with polygons, along with the probability scores of suspicious lesions on the upper left of the endoscopic monitor. At present, clinical trials are needed to evaluate the auxiliary diagnostic performance of this AI system.

3. Aims

This study aimed to evaluate whether this AI system can reduce the miss rate of superficial ESCC and precancerous lesions and improve their detection rate in real clinical settings through a prospective tandem trial.

4. Study design

This was a prospective, multicenter, tandem, randomized controlled study conducted at 12 hospitals, including West China Hospital, Sichuan University (WCHSCU), Nanchong Central Hospital, Affiliated Hospital of North Sichuan Medical College, Meishan People's Hospital, Shimian People's Hospital, Cangxi People's Hospital, Nanbu People's Hospital, Zigong Fourth People's Hospital, Zizhong People's Hospital, The First Veterans Hospital of Sichuan Province, The Third People's Hospital of Yunnan Province, and Huai'an First People's Hospital. Among these hospitals, there were seven tertiary class A hospitals, three tertiary class B hospitals, and two secondary class A hospitals. Consecutive patients undergoing gastroscopy at the endoscopy center of twelve hospitals from October 2021 to June 2022 were recruited for this study. A total of 9,954 subjects were expected to be enrolled, with at least 146 lesions diagnosed as superficial ESCC and precancerous lesions. A same-day tandem gastroscopy was performed for each eligible patient by the same endoscopist. Patients received either AI-assisted or routine gastroscopy under WLE and nonmagnified NBI first, followed immediately by the other procedure.

5. Patients

Consecutive patients scheduled to undergo gastroscopy at the endoscopy center of twelve hospitals from October 2021 to June 2022 were recruited for this study. Gastroscopy was performed for screening, investigation of gastrointestinal symptoms, or surveillance (for patients who had undergone previous upper gastrointestinal endoscopic resection). Patients who met the inclusion criteria and did not meet any of the exclusion criteria and withdrawal criteria were included in the final statistical analysis.

5.1. Inclusion criteria

Patients who met both of the following criteria were invited to participate in this study.
(1) Patients aged 18 years or older;
(2) Patients who underwent sedated gastroscopy.

5.2. Exclusion criteria

Patients who met any of the following criteria were excluded from the final analysis of this study.
(1) Patients with advanced esophageal cancer (comprehensive diagnosis made by endoscopy, pathology, imaging, etc);
(2) Patients with a history of previous esophagectomy;
(3) Patients with contraindications to biopsy or those who refused biopsy;
(4) Patients with known active upper gastrointestinal bleeding or emergency endoscopy;
(5) Patients with esophageal strictures;
(6) Pregnant patients;
(7) Patients with duplicate registrations (those who were previously included in this study);
(8) Patients with serious underlying disease that the endoscopists deemed inappropriate for participation in this trial;
(9) Patients who refused to participate in the study.

Patients with a prior history of advanced esophageal cancer were excluded. If the patient has a history of superficial ESCC and precancerous lesions, but has already undergone endoscopic resection. The indication for this gastroscopy was surveillance, and these patients were still be included in the study.

5.3. Withdrawal criteria

Patients who met any of the following criteria were excluded from the final analysis of this study.
(1) Observation of the whole esophagus was compromised due to a large amount of food retention;
(2) The second esophageal examination was not completed.

6. Sample size calculation

We estimated a 15% miss rate of SESCC and precancerous lesions in the control group and a 2% miss rate in the research group based on previous studies and our experience[5,6,21,22]. The detection rate of SESCC and precancerous lesions in Asia was estimated to be approximately 0.8%. We anticipated that the detection rate would increase to over 1·4% with the aid of the AI system. To achieve statistically

significant differences in both the miss rate and detection rate with 80% power and a two-sided α level of 0·05, accounting for a 5% dropout rate, we calculated that at least 73 SESCC and precancerous lesions and 4,977 patients were required in each group. Therefore, a total of 146 cases and 9,954 patients were necessary for this study.

7. Randomization and blinding

A simple randomization method was adopted in this study. A research assistant from WCHSCU, the study leader, first used a computer to generate 12,000 cells in an Excel sheet with random numbers ranging from 0 to 1. These cells were then divided into two groups, the research group (AI-assisted gastroscopy first group) and the control group (routine gastroscopy first group), at a ratio of 1:1.

The Excel sheet contained information such as the random number, grouping, hospital, identification number of the enrolled patients, and date of patient enrollment. The randomization grouping form (excel sheet) was uploaded to an online system (https://www.kdocs.cn), which was accessible by research assistants at the twelve participating hospitals using mobile phones or laptops. Before eligible patients underwent gastroscopy, the research assistants opened the randomization grouping form and filled in the blank cells for the hospital, the identification number of the enrolled patients and the date of inclusion of the patients in the corresponding numbered column. They then informed the endoscopists of the grouping. To ensure that no duplicate cells were filled in under a single number, the online system indicated to the other research assistants that the cell corresponding to that number was being edited. Research assistants were required to fill in the cells in order from smallest to largest number and were not allowed to fill in cells across numbers.

This study employed blinding procedures to reduce the risk of bias. Patients, pathologists, and statistical analysts were blinded to the group allocations. Endoscopists were unaware of the trial design and study purpose, but were informed of the group allocations to determine whether to use the AI system when conducting the esophageal examinations. Research assistants and data collectors were also aware of the group allocations. Unblinded researchers were instructed to avoid discussing group allocations with patients, pathologists, and statistical analysts during and after the examinations to prevent inadvertent unblinding.

8. Endpoints

8.1. Primary endpoint

The primary endpoint was the miss rate of SESCC and precancerous lesions. A missed lesion was defined as a lesion that was not detected in the first examination but was detected in the second examination.

(1) Per-lesion miss rate=the number of newly detected SESCC and precancerous lesions in the second examination/the total number of SESCC and precancerous lesions detected in both examinations.

(2) Per-patient miss rate=the number of patients newly diagnosed with SESCC or precancerous lesions in the second examination/the total number of patients diagnosed with SESCC or precancerous lesions in both examinations.

8.2. Secondary endpoints

The secondary endpoints included the detection rate of SESCC and precancerous lesions, the biopsy rate, the number of SESCC and precancerous lesions per-patient, consistent false detection by the AI system, inspection time, and adverse events.
(1) The detection rate=the number of patients diagnosed with SESCC or precancerous lesions in the first examination/the total number of patients.
(2) The biopsy rate=the number of patients biopsied in the first examination/the total number of patients.
(3) The number of SESCC and precancerous lesions per-patient=the total number of SESCC and precancerous lesions detected in both examinations/the total number of patients.
(4) Consistent false detection by the AI system: lesions were consistently detected by the AI system but were confirmed by the endoscopist or histopathology to not be SESCC or precancerous lesions and were not found to be cancerous at the end of the study.
(5) Inspection time: the time required to examine the esophagus, excluding the time for biopsy.
(6) Adverse events: the AI system was a medical software and hardware, which was not indirect contact with the human body. There was no difference between the experimental examination and the routine examination. The expected adverse events were essentially the same as gastroscopy-related complications.

During the endoscopic examinations, when the AI system detected a lesion, the endoscopists conducted a thorough examination of the indicated area. If the AI indication was brief, lasting generally less than 1 second, the endoscopists might choose to disregard it based on their own judgment. However, for obvious and consistent indications, research assistants recorded these results, and they were subsequently confirmed by the endoscopists or histopathological examination to determine if they were false positive detection.

9. Devices

(1) Standard endoscopes and video processors (Olympus Co, Tokyo, Japan).
(2) An AI system: This AI system could identify superficial ESCC and precancerous lesions in real time under common clinical endoscopic light modalities, including white light endoscopy (WLE) and nonmagnified narrow band imaging (NBI). This AI system differed from other systems that required a separate monitor. It was directly connected to the endoscopy monitor used by endoscopists, allowing for single-screen use, and assisted endoscopists in lesion detection in real time during gastroscopy

without changing their operating habits, making it more suitable for clinical needs. Endoscopists could switch between the original endoscopic videos and the composite videos with the results of the AI system by using a button on the endoscopic monitor. The AI system indicated suspicious lesions with polygons and simultaneously displayed the probability scores of suspicious lesions on the upper left of the endoscopic monitor.
(3) Digital video recorders (Smart HD Capture Box, Shenzhen JiuShi Technology Co., Ltd, Shenzhen, China).

10. Study process

10.1. Summary of study process

Prior to the commencement of the trial, the randomization grouping form and the case report form (CRF) were uploaded to an online system by a research assistant from WCHSCU. All researchers involved in this study were briefed on the study protocol, the utilization of the AI system and the online system, and the data collection requirements.
During the trial, eligible patients were invited to participate and were required to provide informed consent before undergoing gastroscopy. Patients who met the inclusion criteria and did not meet any of the exclusion criteria were included in the study. Subsequently, patients were randomized to undergo gastroscopy and postoperative follow-up, after which the CRF was updated. Follow-up assessments were carried out until the end of the study. Patient confidentiality and privacy were upheld throughout the study.

10.2. Patient selection

Patients undergoing gastroscopy at the endoscopy center of 12 hospitals from October 2021 were recruited. Eligible patients were screened according to the inclusion and exclusion criteria.
Patients who met the inclusion criteria were enrolled, and their screening information, including screening date, hospital, identification number, patient information, screening results, and reasons for exclusion, were recorded in the CRF. To ensure unique identification, patients were assigned a fixed 6-digit identification number, with each hospital having a designated center number. For instance, WCHSCU's center number was 01, and the first and second patients meeting the inclusion criteria were assigned identification numbers 010001 and 010002, respectively. Once an identification number was assigned, it could not be reused.

10.3. Gastroscopy

10.3.1. Preprocedural preparation

The preprocedural preparation for gastroscopy included the following steps:

(1) Fasting for 8 hours and water deprivation for 4 hours before the examination;
(2) Cessation of long-term anticoagulants as appropriate for the patient's condition;
(3) Provision of psychological preparation to patients;
(4) Assessment of the need for anaesthesia for patients undergoing sedated gastroscopy;
(5) Acquisition of informed consent from patients for participation in the study;
(6) Randomization of patients into either the research group or control group.

10.3.2. Intraoperative procedures

All eligible patients underwent tandem gastroscopy on the same day, performed by the same endoscopists. In the AI-assisted first group, the AI system was activated and assisted the endoscopists in observing the esophagus from the upper esophagus to the cardia under WLE. Subsequently, the endoscopists conducted routine observations of the stomach and duodenum. Afterward, the endoscope was withdrawn from the cardia to the upper esophagus using nonmagnified NBI. Following completion of the first examination, the second esophageal examination began immediately with the AI system turned off, and the esophagus was reobserved using the same examination method. In cases where the AI system alerted the endoscopist to areas of concern, the endoscopist carefully examined and assessed these areas according to their clinical experience. In the routine first group, the first examination was a standard gastroscopy, and the second esophageal examination was assisted by the AI system.
The duration of the two examinations was not strictly limited. Biopsies were taken from all suspected lesions only after the completion of two sequential examinations to prevent biopsy manipulation from interfering with subsequent observations. Research assistants recorded the endoscopists' findings of suspected superficial ESCC and precancerous lesions during the first examination and any new findings of suspected superficial ESCC and precancerous lesions during the second examination. The recorded information included the number of lesions, the endoscopic mode of detection for each lesion (e.g., NBI only or both WLE and NBI), and the location, size, and macroscopic type of each lesion. Moreover, the research assistant used a stopwatch to record the time taken by the endoscopist to complete the first and second esophageal examinations, as well as any consistent false detection by the AI system and adverse events associated with the examination process.
All gastroscopy videos of the patients enrolled in this study were digitally recorded. Patients consented to video capture, and the captured videos could be used for data verification.

10.3.3. Patient withdrawal

Patients who signed the informed consent but later withdrew from the study, patients whose esophageal observation was compromised by massive food retention, and patients who did not undergo or complete a second esophageal examination were considered withdrawal cases. Their data from these cases were not included in the final statistical analysis.

10.3.4. Postoperative management

Postprocedural evaluation of patients was conducted on the day after the examination to assess for any adverse events related to gastroscopy. The study anticipated potential adverse events such as mechanical injury, bleeding, perforation, and other complications that may arise during the procedure. Adverse events, if any, were recorded in detail in the CRF and managed appropriately.

For mild cases of mechanical injury or perforation, endoscopic clips were applied under endoscopy, while in severe cases, gastrointestinal decompression tubes were placed under gastroscopic surveillance or surgery was performed. Minor bleeding was treated with wound flushing during the examination, and if necessary, endoscopic clips were used to treat the bleeding, while significant bleeding was referred to surgical hemostasis. Follow-up was arranged for patients with mild adverse events, whereas those with severe complications were promptly admitted to the hospital and monitored until their condition stabilized.

Following the examination, patients were promptly followed up for biopsy pathological results.

(1) In cases where patients were pathologically diagnosed with ESCC or precancerous lesions, treatment options were determined based on their overall conditions.

(2) Patients with pathology indicating noncancerous lesions or uncertain diagnosis of cancer or heterogeneous hyperplasia were followed up by phone every three months. If necessary, gastroscopy was performed to evaluate the lesions for any potential malignancy.

10.4. Data collection

The data collected for this study included the following:

(1) Screening information, which included the date of screening, the hospital where the screening was conducted, patient identification number, and reasons for exclusion.

(2) Information on the hospitals that participated in the study, which included the name and grade.

(3) Information on the endoscopists, which included sex, age, years of experience conducting independent gastroscopy, and the number of cases of independent gastroscopy.

(4) Information on the patients, which included their identification number, sex, date of birth, group assignment, source, indications for examination, history of smoking, history of alcohol consumption, history of malignancy in linear relatives, and any comorbidity.

(5) Information on the lesions, which included the endoscopic mode of detection, location, macroscopic type, circumference, size, pathological diagnosis method, and pathological diagnosis results.

(6) Other information, such as the type of endoscope used, whether iodine staining was conducted during the examination, inspection time, consistent false detection by the AI system, and any adverse events related to the gastroscopy examination.

11. Risk and benefit analysis

11.1. Risk analysis

The AI system used in this study was medical software and hardware that has no direct contact with the human body. The gastroscopy examination in this study followed the conventional approach with the addition of an extraesophageal examination for each patient. During gastroscopy, the AI system identified the suspected areas of superficial ESCC and precancerous lesions and displayed the corresponding probability values. The endoscopists then further examined these areas prompted by the AI system and decided on whether to perform a biopsy or any other required procedures. The AI system acted as an auxiliary tool and did not directly influence the judgment and treatment of the endoscopists or pose any increased risks to the patients. It should be noted that the first esophageal examination did not require the endoscope to be withdrawn from the esophagus. Therefore, the second examination did not involve a second insertion of the endoscope and hence did not significantly increase the operation time or risk of gastroscopy. However, it should be noted that gastroscopy-related adverse events such as mechanical injury, bleeding, and perforation may still occur.

11.2. Benefit analysis

With the assistance of the AI system, the detection rate of superficial ESCC and precancerous lesions may be improved.

12. Quality control of the study

All researchers participating in this study were trained on the study protocol, the use of the AI system and the online system, and the data collection specifications. A research assistant from WCHSCU was appointed to contact each subcenter monthly to ensure adherence to the standard operating procedures and maintain data quality control. After data collection, doctoral students from WCHSCU were responsible for organizing and extracting the data. The data analysis was conducted by doctoral students under the guidance of statistical experts.

13. Statistical analysis

13.1. Specifications for data processing

(1) Missing values were not filled.
(2) Outliers were not discussed and decided upon at the data review meeting.
(3) Calculations were performed using the original data, and rounding was only performed on the final data. The minimum, maximum, mean, median, standard deviation, variance, interquartile range, and confidence interval retained at least three

significant digits or one decimal, and percentages retained one decimal.

13.2. Statistical methods

13.2.1. General principles

In this study, all statistical analyses were conducted using SAS 9·4. The variables were classified into two categories: continuous and categorical variables. Continuous variables were presented as the mean, standard deviation, median, interquartile, minimum and maximum values, and 95% confidence interval according to their distribution. Group differences for continuous variables were compared using Student's t test or Wilcoxon rank-sum test. Categorical variables were presented as frequencies or percentages, and group differences were compared using the chi-square test or Fisher's exact test. A p value $< 0{\cdot}05$ was deemed statistically significant.

13.2.2. Patient enrollment analysis

The total number of patients who were invited to participate in this trial, as well as the number of patients who deviated or violated the study protocol, were recorded. A flow chart was drawn to illustrate the distribution of patients, and the number of patients excluded from the trial and the reasons for their exclusion are explained in the flow chart.

13.2.3. Demographics and baseline Analysis

Demographics and baseline analysis included age, sex, source of recruitment, history of smoking, history of alcohol consumption, history of malignancy in linear relatives, comorbidities, indications for gastroscopy, hospital grade, endoscopist experience, endoscope type, and weather iodine staining was performed.
All analysis items were described and presented statistically according to general principles. Continuous variables that followed a normal distribution were expressed as the mean ± standard deviation. Continuous variables that did not follow a normal distribution, they were expressed as median (interquartile range). Categorical variables were presented as frequencies or percentages.

13.2.4. Analysis of clinical characteristics of lesions

The clinical characteristics of lesions evaluated in this study included the endoscopic mode used to detect lesions, location, macroscopic type, circumference, size, pathological diagnosis method, and pathological diagnosis result. The number of lesions detected in the first examination and the second examination were recorded, and the percentage of the total number of lesions in each group was calculated.

13.2.5. Analysis of endpoints

Endpoints in this study included the miss rate of SESCC and precancerous lesions, the

detection rate of SESCC and precancerous lesions, the biopsy rate, the number of SESCC and precancerous lesions per-patient, consistent false detection by the AI system, inspection time, and adverse events.

Descriptive variables were presented as frequencies or percentages. Risk ratios and their corresponding 95% confidence intervals for each endpoint between the two groups were analysed. Group differences for continuous variables were compared using Student's t test or Wilcoxon rank-sum test. Group differences for categorical variables were compared using the Chi-square test or Fisher's exact test.

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