STUDY PROTOCOL

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Pericancerous lymph node imaging with indocyanine green-guided near-infrared fluorescence in radical esophagectomy: Protocol for a single-center, prospective, randomized controlled clinical trial

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Abstract

Introduction: The incidence and mortality rates of esophageal carcinoma are higher than those of most malignancies in humans. Radical esophagectomy is the preferred treatment for early-stage esophageal cancer. However, the extent of lymphadenectomy during radical esophagectomy remains controversial. Indocyanine green (ICG) is the most commonly used imaging agent for the diagnosis of tumors and metastatic lymph nodes in clinical settings. Thus, the main aim of this study was to evaluate pericancerous lymph nodes imaging in video-assisted thoracoscopic surgery radical esophagectomy using a near-infrared (NIR) ICG imaging system and to improve the detection rate of sentinel lymph nodes (SLNs) and overall survival of patients with esophageal cancer.

Methods: This was a single-center, prospective, randomized controlled clinical trial (allocation rate = 1:1). Forty treatment-naive esophageal cancer patients were recruited and divided into two groups: the ICG and control groups. The inclusion criteria were age, absence of preoperative neoadjuvant therapy, elective surgery, and signed informed consent. Data of participants at four different time points (preoperation, intraoperation, postoperative 1 week and 3 months) were collected and recorded. The main endpoint of this study was to explore the accuracy and false-negative rate of lymphadenectomy using NIR-ICG fluorescence imaging and to identify the location of esophageal cancer SLN combined with postoperative pathological reports.

Discussion: This trial will provide more evidence on the extent of lymph node dissection for esophageal cancer and contribute to the development of treatment guidelines for esophageal cancer.

Trial registration number: NCT04615806.

KEYWORDS
esophageal cancer, indocyanine green, lymphadenectomy, randomized controlled trial, sentinel lymph node

INTRODUCTION

Esophageal carcinoma (ESCC) is one of the most frequently occurring malignant cancers in human, and is the leading cause of cancer-related death. Increasing numbers of patients with ESCC have been diagnosed with the evolution of new prognostic technologies. Currently, surgical resection remains the first-line treatment for patients with early-stage ESCC. However, there are two contrasting views regarding surgical extent: one is to minimize the extent of surgery, and the other is maximal surgical resection. Nevertheless, it is mostly agreed that the difference in survival and the incidence of postoperative complications has not been found to be statistically significant.

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Indocyanine green (ICG) is a water-soluble amphiphilic anionic fluorophore with a molecular weight of 776 Da. It has been the subject of many studies since it was authorized by the U.S. Food and Drug Administration and the European Medicine Agency. ICG is one of the most frequently used fluorescent groups in near-infrared (NIR) imaging technology because of its ability to absorb and emit NIR light. In addition, it has been proven that ICG plays a significant role in the diagnosis of tumor and lymph node metastasis.[1–4]

Sufficient and scientific lymph node dissection is critical for radical esophagectomy and the presence of lymph node metastasis plays a vital prognostic marker in esophageal cancer. Previous studies have indicated that widespread, even skipping lymph node metastases, has been found in early-phase esophageal cancer limited to the submucosal layer.[5,6]

Previous reports indicate that approximately 45.0%–85.0% of patients have occurred lymph node metastasis when symptoms are associated with eating obstruction.[7,8] Some clinical studies have reported that 80% of patients die of tumor recurrence after esophagectomy, of which lymph node metastasis accounts for over 40%.[9]

Substantial clinical experience of lymph node dissection indicated lymphatic reflux of the lower esophagus mainly involving the lymph nodes around both sides of the cardia, the left gastric artery and celiac artery, and lymphatic circulation of the upper and mid-esophagus drains to the cervical lymph nodes and upper mediastinal lymph nodes. However, esophageal cancer without distant metastasis is not a focal lesion of the cancer itself, but should be regarded as a regional lesion, including the neck, mediastinum as well as the upper abdomen. During radical esophagectomy, if the lymphoid tissues of the draining regions are completely cleared while removing tumor lesions, there is a greater chance of improving the patient survival rate.

Nevertheless, so far, no clear evidence has indicated that the extent of lymph node dissection and location of the sentinel lymph node (SLN) during radical esophagectomy. Therefore, the present study aimed to explore whether the application of the NIR-ICG imaging system can accurately evaluate the mapping of pericancerous lymph nodes during esophagectomy for esophageal cancer via combined thoracoscopy-laparoscopy to increase the detection rate of SLN and postoperative survival rate of esophageal cancer patients.

METHODS

Study design and setting

This was a single-center, prospective, randomized controlled clinical trial (allocation rate = 1:1). One of the researchers informed the participants about the risks and benefits of the trial, both orally and in writing. The estimated enrollment rate was 40 patients. All treatment-naive esophageal cancer patients with stage $T_{1-3}N_{1-2}M_0$ who met the inclusion criteria, did not meet the exclusion criteria and provided informed consent were randomly divided into two groups: the ICG group and the traditional surgery group (control group). The participants were allowed to withdraw from the study at any time and for any reason. Additionally, the researcher could also withdraw the subjects from the study for emergency medical reasons.

All participants were recruited from the Department of Thoracic Surgery at Fujian Medical University Union Hospital, from January 2021 to December 2022. The ethical committees of Fujian Medical University Union Hospital approved this trial (no. 2020YF025-01) and the trial protocol has been registered on NIH ClinicalTrials database (www.clinicaltrials.gov/ct2/home, NCT04615806). Figure 1 illustrates the study design.

Inclusion criteria

(1) Male or female aged 18–75 years with a confirmed diagnosis, (2) esophageal cancer was diagnosed through preoperative pathological biopsy,

(3) none of participants had received neoadjuvant chemotherapy or radiotherapy before surgery, (4) all participants received elective radical esophagectomy and intraoperative anastomosis, (5) major organ function (such as the heart, lung, liver and kidney) of patients able to tolerate the surgical procedure, and (6) patients and their families consented to participate in this study and signed a written informed consent form.
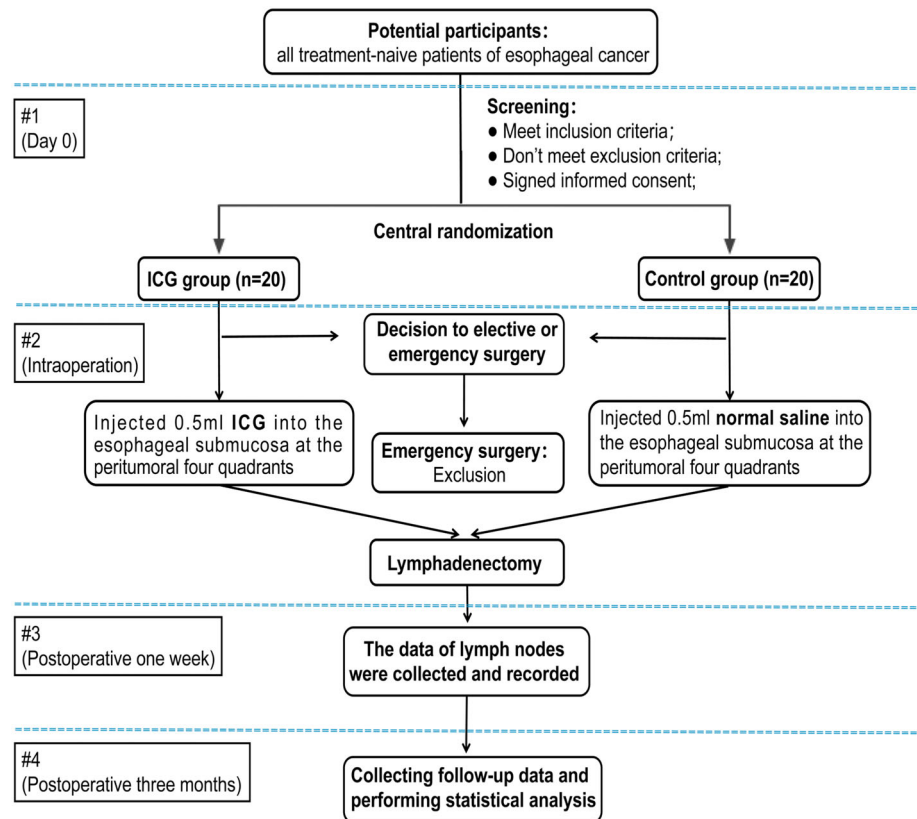
Exclusion criteria

(1) Iodine or ICG allergy, (2) patients needed emergency surgery, (3) combined resection of adjacent organs involving the tumor was performed in patients, (4) with tumor recurrence or distant metastasis, (5) patients had participated in any other clinical trials during the previous 4 weeks, (6) patients with a history of severe mental illness, (7) Pregnant or women who were breast feeding were excluded, and (8) patients with certain conditions were not considered suitable to participate in the trial by the investigators.

Recruitment strategies

Medical history and physical examinations were performed after the patients were admitted to the hospital. The patients subsequently underwent contrast-enhanced computed tomography (CT) of the chest and gastroscopy. The CT results suggested a high possibility of esophageal cancer. Pathological reports of gastroscopic biopsy identified an ESCC. All patients underwent color doppler ultrasound of the whole abdomen, bone scan, and magnetic resonance imaging (MRI) of the brain (positron-emission tomography [PET-CT] was performed when necessary) to evaluate local invasion or distant metastasis. Patients with stage $T_{1-3}N_{1-2}M_0$ who met the inclusion

FIGURE 1 Trial design. ICG, indocyanine green

Intervention

All patients underwent surgery within 2 weeks(including day 14) after enrollment. After enrollment, the decision to proceed with elective surgery was made on a case-by-case basis by an attending surgeon. Patients will be excluded if they require emergency surgery or cancel the surgery. The study protocol did not stipulate the requirement before anesthesia, such as preoperative fasting and water prohibition duration, which was performed according to the routine anesthesia procedure of each research center. Perioperative preventive measures have been suggested for high-risk patients with advanced age, smoking, diabetes, obesity, and chronic cardiovascular and cerebrovascular diseases. Prophylactic antibiotics were recommended before surgery. As for other potential high-risk complications, preventive measures were taken by the surgeon or medical center preference. All operations were performed under general anesthesia with double-lumen endotracheal intubation.

ICG group

After general anesthesia, intraoperative gastroscopy was used to explore esophageal cancer location and inject 0.5 ml ICG (Yichuang Pharmaceutical) into the esophageal submucosa at the four quadrants around the tumor. During surgery, NIR fluorescence imaging and video recording were started and consistently maintained.

criteria and did not meet the exclusion criteria were defined as potentially eligible participants. Potential subjects will be informed about the entire study procedure and screened based on the inclusion and exclusion criteria. All eligible participants were informed in detail about the guiding evidence of current treatment outcomes, study objectives and procedures, risks and potential benefits, baseline and follow-up time, crossover and exit procedure, clinical significance, funding as well as provided with the contact details of researchers. Each thoracic surgeon and researcher who participated in the trial was trained to provide standard verbal and written trial information and facilitate communication between patients and physicians during the recruitment process. Patients and their families were advised to consider or discuss at least 24 h before deciding whether to participate in this trial. Informed written consent was obtained from all eligible participants, which were saved separately by the two researchers.

Randomization and blinding

After informed consent was obtained, patients were randomly 1:1 assigned to the ICG group (intervention group) or the traditional treatment group (control group) using a computer-generated randomization scheme with permuted block size maintained by a centralized randomization system. Randomization will be conducted one day prior to surgery. The randomized protocol was managed by external study administrators to prevent selection bias.

Thoracic surgeons preferentially dissected the lymph nodes that emitted fluorescence within the thoracic cavity. The location and number of lymph nodes were recorded by the researchers. To ensure compliance with oncology principles, all ICG group patients underwent standard surgical procedures for radical esophagectomy plus systematic nodal dissection.

Traditional surgery group (control group)

Intraoperative gastroscopy was utilized to explore tumor location and normal saline (0.5 ml) injected into the esophageal submucosa at the four quadrants around the tumor after patients received general anesthesia. Similarly, intraoperative video recording was performed. According to the standard surgical protocol, surgeons dissected lymph nodes, the number and location of which were recorded by the researchers. Clinicians in our center judged whether the patient needed to undergo three-field lymphadenectomy according to two points: first, without group 1 lymph node and supraclavicular lymph node metastasis on PET-CT or neck ultrasonography; second, intraoperative frozen-section report revealed that anyone of the bilateral recurrent laryngeal nerve lymph node was positive. If any of the above two conditions are met, we will perform three-field lymphadenectomy. All patients in the control group underwent radical esophagectomy and two or three-field lymphadenectomy. Patients received standard postoperative care and treatment in both groups.

Safety assessment

Any unfavorable medical occurrence in a participant that was judged as related to a trial procedure was defined as an adverse event (AE), irrespective of whether the events were related to the study intervention. All potential AEs were monitored under the supervision of Ethical Review Committee of Fujian Medical University Union Hospital during the entire trial. Subjects could withdraw from the trial at any time if they could not tolerate treatment. AEs were recorded in all the subjects. The severity of side effects in the participants was evaluated by investigators to determine whether the subjects aborted the trial.

Outcomes

Primary outcomes

The primary objective of the trial was to explore the accuracy and false-negative rate of lymph node dissection using NIR-ICG fluorescence guidance. Simultaneously, we sought to determine the location of the SLN for esophageal cancer based on postoperative pathological reports.

Secondary outcomes

These outcomes were also evaluated in the present study. First, the development rate of the pericancerous lymph nodes was observed and recorded during esophagectomy at 3–5 min after injection of ICG. Second, the negative predictive value of lymph node dissection was explored using NIR-ICG fluorescence imaging. Third, the occurrence rate of complications was counted after esophagectomy. Finally, the five-year overall survival, recurrence and mortality rates of postoperative patients were followed-up and recorded

Data collection and management

Research data were collected, recorded and managed by two researchers based on Good Clinical Practice guidelines. Clinical data of participants from four time points were collected: first, baseline data, including age, sex, height, weight and so on, were extracted before the first surgery; second, intraoperative data, including the timing and duration of general anesthesia, operating time, surgical approach, pattern of lymphadenectomy, sites of metastatic lymph nodes and intraoperative complications were collected during the first operation; third, postoperative data, including postoperative pathological stages, histological grade, lymph node metastasis, drainage volume, urine volume and early postoperative complications, were gathered 1 week after surgery; and forth, follow-up data, including the condition of recurrence or metastasis, postoperative adjuvant therapy, reports of esophagography and routine blood tests, arterial blood gas analysis as well as tumor biomarkers (such as CEA, CA125 and CA199) were recorded 3 months post-surgery.

Statistical analysis

According to written informed consent, the medical data of participants were viewed and checked by researchers at any time, to collect and record the relative data. Data analyses based on the study endpoints were performed using the SPSS version 22.0 software (IBM Corp). Descriptive statistics (mean and 95% confidence interval) were calculated for data from the four time points. In the two groups, continuous data was presented as mean $\pm$ SD and categorical data as percentages. Stratified analysis was performed after all patients were enrolled. Comparisons of the former data were performed using the paired t-test, whereas those of the latter were conducted using the Chi-square test. Statistical significance was set at $p < 0.05$.

DISCUSSION

This was a single-center, prospective, randomized controlled trial. The difference in postoperative pathological results between the ICG and control groups was analyzed to

explore the esophageal cancer SLN, which may guide surgeons to perform surgery more precisely and reduce trauma.

ICG has excellent NIR optical absorption and fluorescence, which plays important roles in the diagnosis of tumors and metastatic lymph nodes.[10–12] Guo et al.[13] reported that ICG has a higher detection rate when exploring SLN in breast cancer. Chen et al.[14] found that ICG could assist surgeons perform lymphadenectomy in laparoscopic-assisted radical gastrectomy. Compared to traditional gastrectomy, there were no significant differences in operative time and complications. However, the use of ICG for exploring SLN in esophageal cancer remains controversial. Thus, we would like to contribute to the development of treatment guidelines for esophageal cancer through a randomized controlled trial.

In addition, we are conducting a single center prospective study and expect to gain a preliminary result. If the preliminary data show that the trial is meaningful, we will conduct a follow-up multicenter study.

CONFLICT OF INTEREST
None declared.

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