STUDY PROTOCOL COVER PAGE

Official Title: Indocyanine Green-Guided Omental Shield Anastomosis (ICG-OSA) for Cervical Esophagogastric Anastomosis in Minimally Invasive McKeown Esophagectomy: A Single-Center, Single-Arm, Open-Label Clinical Study

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Sponsor: Daping Hospital, Army Medical Center, Chongqing, China

TABLE OF CONTENTS

## 1.STUDY SYNOPSIS

Study Design : This is a single-center, single-arm, open-label clinical study to evaluate the safety and efficacy of Indocyanine Green-Guided Omental Shield Anastomosis (ICG-OSA) in minimally invasive McKeown esophagectomy.

Study Population : 73 subjects with middle/lower thoracic esophageal squamous cell carcinoma (ESCC) undergoing minimally invasive McKeown esophagectomy.

Primary Endpoint : Anastomotic leakage rate within 30 days postoperatively.

Secondary Endpoints:Subclinical anastomotic leakage rate,postoperative anastomotic stenosis rate,anastomotic leakage-related complications, health economic indicators.

Study Duration : December 2025 to March 2027

Primary Completion Date : December 2026

## 2.BACKGROUND AND RATIONALE

Esophageal cancer is a high-incidence malignancy in China, with over 90% being esophageal squamous cell carcinoma (ESCC). Minimally invasive McKeown esophagectomy (MIE) has become the standard surgical approach for middle and lower thoracic ESCC. However, cervical esophagogastric anastomotic leakage remains a severe postoperative complication with incidence rates of 5-30%. Our center's historical data shows a 14.8% leakage rate following conventional MIE.

Indocyanine green (ICG) fluorescence angiography enables real-time assessment of gastric conduit perfusion, with meta-analyses demonstrating a 42% relative risk reduction in anastomotic leakage. However, existing ICG applications face limitations including subjective interpretation, lack of standardized thresholds, and failure to integrate with mechanical reinforcement strategies.

The pedicled omental flap serves as a "biological shield" that mechanically protects the anastomosis and promotes healing, but current techniques lack precise perfusion assessment and standardized fixation methods. Linear stapled side-to-side anastomosis reduces tension and may decrease stenosis, but carries risks of staple line ischemia.

This study innovatively integrates ICG fluorescence navigation, pedicled omental shield protection, and T-shaped stapled anastomosis into a unified ICG-OSA technique, creating a "perfusion assessment-biological protection-mechanical optimization" triad strategy. Preliminary application in 20 cases demonstrated no anastomotic leakage, warranting formal clinical validation.

## 3. STUDY OBJECTIVES

Primary Objective： Anastomotic leakage rate：to evaluate whether the anastomotic leakage rate within 30 days postoperatively with ICG-OSA technology is superior to the historical control data (14.8%), verifying the superiority of this technique in reducing cervical anastomotic leakage.

Secondary Objectives:

Subclinical anastomotic leakage rate： to observe the incidence of subclinical anastomotic leakage within 30 days postoperatively.

Postoperative anastomotic stenosis rate：to assess the incidence of anastomotic stenosis at 6 months postoperatively.

Anastomotic leakage-related complication rate： to evaluate the incidence and severity of anastomotic leakage-related complications (pulmonary infection, empyema, mediastinal infection, etc.).

Health economic indicators： to analyze health economic indicators (length of hospital stay, hospitalization costs)

## 4.STUDY DESIGN

Study Type : Single-center, single-arm, open-label, interventional clinical study Blinding : No blinding (open-label)

Randomization : No randomization (single-arm)

Follow-up Duration : 6 months primary follow-up.

Study Schema :Screening Period: Admission to preoperative (Day -7 to Day 0)；

Treatment Period: Surgery to postoperative day 14；Follow-up Period: Postoperative day 15 to month 6

5.STUDY POPULATION

Inclusion Criteria:

a. Age 18-80 years, both sexes.

b. Histologically confirmed esophageal squamous cell carcinoma by biopsy.

c. Clinical stage cT1-4aN0-3M0 (AJCC 8th edition), evaluated as eligible for radical McKeown esophagectomy.

d. Performance status ECOG 0-1.

e. No contraindications for chemotherapy/immunotherapy or surgery based on major organ function assessment.

f. Able to understand and comply with study requirements and follow-up.

g. Signed informed consent form.

Exclusion Criteria:

a. History of allergy to ICG, iodides, or iodinated contrast agents.

b. Severe hepatic or renal dysfunction (Child-Pugh Class C or eGFR<30 mL/min/1.73m² ).

c. Tumor location in cervical or upper thoracic esophagus (<25 cm from incisors).

d. Prior esophageal, gastric, or mediastinal surgery.

e. Concurrent active malignant tumors in other sites.

f. Pregnancy, lactation, or planned pregnancy during study period.

g. Severe psychiatric illness, cognitive impairment, or substance abuse.

h. Participation in other interventional clinical trials.

i. Investigator judgment of unsuitability.

Withdrawal Criteria:

a. Withdrawal of informed consent.

b. Loss to follow-up (3 failed contact attempts over 2 months).

c. Major protocol violation (failure to receive core ICG-OSA intervention)

d. Safety concerns requiring termination

e. Intraoperative findings precluding R0 resection

f. Poor compliance with postoperative assessments

6.INTERVENTION DESCRIPTION

Intervention Name : Indocyanine Green-Guided Omental Shield Anastomosis (ICG-OSA)

Procedure Details :

Step 1: ICG Fluorescence-Guided Gastric Conduit Preparation.

a. Extend subxiphoid incision to 5cm and exteriorize esophagus and stomach.

b. Ligate and divide the right gastric artery at its 3rd branch.

c. Administer ICG 3ml (0.25mg/kg) via central venous catheter.

d. Switch to near-infrared fluorescence mode using fluorescence laparoscopy system.

e. Evaluate: (1) Vascular arcade visualization and Koskas classification, (2) Perfusion zone determination (red=good, blue=poor).

f. Mark anastomotic site on greater curvature with optimal fluorescence intensity.

g. Optimize gastric conduit tailoring using linear staplers based on fluorescence imaging

Step 2: T-Shaped Stapled Anastomosis.

a. Create ~1cm opening on posterior wall of greater curvature at marked site.

b. Ensure anastomotic site is located in optimal perfusion zone confirmed by ICG.

c. Perform side-to-side anastomosis between posterior esophageal wall and greater curvature using linear stapler (T-shaped design).

d. Close common opening with linear stapler and reinforce anterior/posterior walls with absorbable sutures.

Step 3: Omental Shield Construction

a. Mobilize pedicled omentum with good blood supply under fluorescence guidance

b. Perform 360-degree "sleeve-like" wrapping of anastomosis and surrounding 2cm area

c. Fix with 4-6 interrupted absorbable sutures to gastric wall above and below anastomosis

d. Ensure tight apposition without tension or torsion

Concomitant Therapy : All perioperative management follows thoracic surgery standards; no additional interventions required beyond ICG-OSA technique

7.STUDY PROCEDURES AND TIMELINE

Screening Period (Day -7 to Day 0):

a. Informed consent process

b. Baseline assessments: demographics, tumor staging (CT, EUS, pathology), ECOG score

c. ICG allergy screening

d. Laboratory tests: CBC, liver/kidney function, coagulation, infectious disease panel, tumor markers, CRP

e. Diagnostic tests: ECG, chest/abdominal CT, echocardiography, pulmonary function test, endoscopic ultrasound

Treatment Period (Surgery Day to POD 14):

a. Intraoperative ICG injection and fluorescence imaging

b. Performance of ICG-OSA technique

c. Video recording of entire procedure (ICG injection to omental fixation)

d. Surgical parameter documentation: operative time, anastomosis time, blood loss, transfusion volume

Postoperative Hospitalization (POD 1-14):

a. Daily ward assessments: vital signs, wound condition, drain characteristics

b. Critical assessment at POD 7 $\pm$ 1: Chest CT + endoscopy/contrast study for

anastomotic leakage diagnosis

c. Complication recording: timing, clinical manifestations, management, outcomes

d. Hospital cost data extraction from HIS system

Follow-up Period (POD 15 to Month 6):

a. 30-day follow-up : Outpatient review (symptom inquiry, complication confirmation)

b. 6-month follow-up : Gastroscopy for stenosis evaluation, CT for tumor recurrence, quality of life assessment (EORTC QLQ-OES18)

c. Extended follow-up : Every 6 months recording oncological outcomes and survival (up to 24

8.OUTCOME MEASURES Primary Endpoint:

Anastomotic Leakage Rate within 30 Days Postoperatively

Definition: Anastomotic leakage rate assessed by clinical evaluation, computed tomography (CT) scan with oral contrast, and endoscopy according to ECCG criteria.

Confirmation: Independent interpretation by two senior thoracic surgeons.

Grading: Type I (conservative management), Type II (interventional drainage), Type III (surgical intervention).

Time Frame: Up to 30 days postoperatively (critical assessment window: postoperative day 7±1）.

Secondary Endpoints:

1. Subclinical Anastomotic Leakage Rate (30 days)

Definition: Turbid mediastinal drainage fluid with positive bacterial culture, but requiring no intervention (i.e., no puncture drainage, stent placement, or surgery); daily recording of drainage fluid characteristics, with positive culture results confirmed by laboratory reports.

Time Frame: Daily through postoperative day 30.

2. Postoperative anastomotic stenosis rate(6 months )

Description: Anastomotic stricture rate diagnosed by endoscopy and dysphagia symptoms.

Time Frame: 6 months postoperatively.

3. Anastomotic leakage-related complication rate

Description: Complications directly related to anastomotic leakage, including pulmonary infection, empyema, mediastinal infection, and sepsis. Complications will be graded using the Clavien-Dindo classification system. Diagnosis will be confirmed by clinical symptoms (fever, leukocytosis), microbiological cultures, and imaging findings (CT scan showing fluid collections or air-fluid levels). Each complication will be documented with onset date, severity grade, and required interventions.

Time Frame: Up to 30 days postoperatively

4. Health economic indicators

Description: Total medical costs from hospital admission to discharge, including operation fees, anesthesia, medication, laboratory tests, imaging studies, hospital bed, and other related expenses. Data will be extracted from the hospital information system (HIS) at discharge and recorded in the case report form.Number of days from the date of surgery to hospital discharge, calculated as (discharge date minus surgery date + 1 day).

Time Frame: From hospital admission through hospital discharge, an average of 10 days

9.SAMPLE SIZE AND STATISTICAL ANALYSIS

Sample Size Calculation:

1. Historical Control Rate ( $\pi_0$ ) : 14.8% (from center's retrospective database, n=386).
2. Expected Rate ( $\pi_1$ ) : 5.0% (based on preliminary 20-case study showing 0% leakage).
3. Parameters : One-sided $\alpha$ =0.05, power=80%, dropout rate=15%.
4. Software : PASS 25.0.
5. Result : Required sample size=62; Final planned enrollment=73 subjects.

Statistical Analysis:

Primary Analysis : Exact binomial test on Full Analysis Set (FAS) to compare observed leakage rate vs. historical control (14.8%). Superiority declared if upper limit of 95% CI <14.8% or one-sided p<0.025..

Sensitivity Analysis : Per-Protocol (PP) set analysis to confirm robustness

Secondary Analyses :

1. Descriptive statistics for complication rates with exact binomial 95% CIs.
2. Kaplan-Meier method for anastomotic stenosis cumulative incidence.
3. Spearman correlation for ICG parameters vs. healing quality.
4. Breslow-Day test for heterogeneity across stratification factors.

Analysis Sets :

1. FAS : All subjects receiving ICG injection and completing anastomosis (primary endpoint)
2. PP : Subjects completing all three core technique steps without major violations
3. SS : All subjects receiving ICG injection and surgical intervention (safety endpoints)

10.SAFETY EVALUATION

Adverse Event (AE) Definition : Any unfavorable medical event occurring after ICG-OSA intervention, regardless of causality.

Serious Adverse Event (SAE) : Events resulting in death, life-threatening condition, permanent disability, or requiring prolonged hospitalization.

AE Severity : Graded per CTCAE 5.0 criteria ICG-Specific Risks :

Allergic Reaction (0.01-0.05% incidence): Screening for iodine/seafood/contrast allergy, emergency equipment (epinephrine, dexamethasone) on standby, 5-minute vital sign monitoring post-injection.

Omental Complications : Ischemic necrosis (1-2%), impaired gastric emptying. Managed by fluorescence assessment during mobilization and postoperative CT monitoring.

Reporting Timeframes :

Non-serious AEs: Documented in CRF within 24 hours

SAEs: Reported to PI and clinical research office within 2 hours, to ethics committee within 24 hours

Death Events: Immediate reporting with investigation coordination

Causality Assessment : Investigator-rated as definite, probable, possible, unlikely, or unassessable; SAEs require dual senior physician confirmation

## 11. DATA MANAGEMENT

Data Collection Method : Hybrid system combining paper Case Report Forms (CRF) and Electronic Data Capture (EDC)

Paper CRFs : Source documents completed in real-time by investigators during screening, surgery, and follow-up; stored in Thoracic Surgery Laboratory

EDC System : Dedicated research data system in Thoracic Surgery Laboratory; data entry by independent data manager within 48 hours of CRF completion

Data Recording Standards :

1. Timeliness: ⩽24 hours from event occurrence.
2. Accuracy: Numerical values to one decimal place.
3. Completeness: No blanks; "NA" with justification for non-applicable items.
4. Traceability: All data linked to source documents; images retain metadata (date, equipment).

Quality Control :

1. Investigator cross-check every 10 cases
2. Independent data manager audits for logical errors
3. Database lock after final subject completes 6-month follow-up and blinded review

Privacy Protection :

1. De-identified study IDs (format: ICG-OSA-2025-001 to 073)
2. Identity-linking file encrypted and stored separately by PI
3. Identity information destroyed after 5 years

## 12.ETHICAL CONSIDERATIONS

Ethics Review : Protocol, informed consent, and investigator documents submitted to

Daping Hospital Ethics Committee for initial approval prior to study initiation.

Informed Consent Process :

1. Conducted by PI (Prof. Wei Guo) or designated deputy chief physician
2. Minimum 30-minute explanation using simplified language and diagrams for low-literacy subjects
3. Family member co-signature required for elderly subjects (⩾80 years)
4. Independent witness for vulnerable populations (e.g., low education, solitary elderly)

Participant Rights :

1. Voluntary participation with right to withdraw at any time without penalty
2. Privacy protection through de-identification and data encryption
3. Continued medical care guaranteed even if study participation terminates

Study termination

if overall leakage rate ⩾25% significantly exceeds historical control.

Vulnerable Populations :Elderly (⩾80) : Stricter inclusion (ECOG 0-1, 6-minute walk test ⩾300m), mandatory family co-consent, ICU monitoring extended to 48 hours;

Excluded : Minors (<18), pregnant/lactating women, severe cognitive impairment

Conflict of Interest : No commercial funding; ICG is standard clinical drug; equipment is hospital property; no manufacturer involvement in design, data collection, or interpretation.

13.REFERENCES


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Protocol Approval : This protocol must be approved by the Daping Hospital Ethics Committee prior to any study-related procedures. All amendments require ethics committee approval and participant re-consent if applicable.

END OF PROTOCOL