CLINICAL TRIAL PROTOCOL

Project Title: Effectiveness and Safety of Septum-guided Segmentectomy in Solid-dominant, Deep-seated Early-stage Non-small Cell Lung Cancer (≤2 cm): A Single-center, Prospective, Single-arm Clinical Trial (SGS2512)

Protocol Number: SGS2512

Version: V1.4 (Sample Size Specification)

Sponsor: Shanghai Chest Hospital

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NCT Number: Pending

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This document includes both the Study Protocol and the Statistical Analysis Plan.

1. PROTOCOL SUMMARY

1.1 Overview

- **Study Title:** Effectiveness and safety of septum-guided segmentectomy in solid-dominant, deep-seated early-stage non-small cell lung cancer (NSCLC) with a tumor diameter ⩽2 cm.
- **Study Design:** Single-center, prospective, single-arm clinical trial.
- **Study Population:** Patients with clinical stage IA (cT1a-bN0M0) NSCLC, tumor diameter ⩽2 cm, solid-dominant (CTR > 0.5), located in the deep lung parenchyma (inner 2/3).
- **Intervention:** Septum-guided segmentectomy (utilizing intersegmental veins and septa as anatomical boundaries).
- **Primary Endpoint:** 3-year recurrence-free survival (RFS).
- **Sample Size:** 89 cases.
- **Study Period:** 2 years for enrollment, 3 years for follow-up.

1.2 Visit Flowchart

- **Screening Period (Day -14 to Day 0):** Sign informed consent; complete baseline assessments (CT, PET-CT, pulmonary function).
- **Treatment Period (Surgery Day):**
    - Initiation of anesthesia and surgery.
    - **Intraoperative Second Registration** (confirming pathology and lymph node status).
    - Implementation of septum-guided segmentectomy.
- **Postoperative Hospitalization:** Monitor complications, extubation, and discharge.
- **Follow-up Period:**
    - **1 Month Post-surgery:** Outpatient follow-up.
    - **6, 12, 18, 24, 30, and 36 Months Post-surgery:** Chest CT, tumor markers, pulmonary function tests; PET-CT or brain MRI as needed.
    - **Years 4–5 Post-surgery:** Annual follow-up.

2. INTRODUCTION

2.1 Background

The treatment of early-stage NSCLC primarily relies on surgical resection, with lobectomy long considered the standard. However, lobectomy can lead to significant loss of pulmonary function. Studies like JCOG0802 have shown segmentectomy is comparable for peripheral tumors ⩽2 cm, but its use for deep-seated tumors (inner 2/3) remains controversial due to complex anatomy.

We propose **Septum-guided Segmentectomy (SGS)**, which uses the intersegmental veins and their sheaths as natural anatomical boundaries. Our previous retrospective study of 492 cases showed that SGS achieved comparable 3-year RFS and OS to lobectomy in deep-seated lesions. Notably, nearly half of the cases did not meet the NCCN margin criteria (>2 cm or tumor diameter), yet no local recurrence was observed, suggesting the intersegmental septum provides superior oncological protection. This prospective study aims to validate these findings.

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3. STUDY OBJECTIVES

- **Primary Objective:** To evaluate the 3-year RFS of SGS for deep early-stage NSCLC.
- **Secondary Objectives:** Perioperative safety (Clavien-Dindo), pulmonary function (FEV1 changes), technical success (R0 rate), and local recurrence rate.

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4. STUDY DESIGN

Single-center, prospective, single-arm, open-label trial. All eligible subjects receive SGS; historical data and JCOG0802 results serve as the reference benchmark.

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5. STUDY POPULATION

5.1 Inclusion Criteria

1. Age: 18–80 years.
2. Clinical Stage: IA (cT1a-bN0M0), tumor diameter ⩽ 2 cm.
3. Pathology: Solid-dominant (CTR > 0.5).
4. **Tumor Location:** Deep-seated lung parenchyma (inner 2/3), defined as the

tumor center being located in the **inner 2/3** region of the lung field on axial, coronal, and sagittal CT views.

5. ECOG PS: 0–1.
6. Pulmonary Function: FEV1 ⩾ 60% predicted, DLCO SB ⩾ 60% predicted.
7. Voluntary signed informed consent.

5.2 Exclusion Criteria

1. Multiple nodules or distant metastasis.
2. Intraoperative confirmation of lymph node metastasis (N1/N2) or pleural dissemination.
3. Prior ipsilateral lung surgery.
4. Other malignancies within the past 5 years.
5. Severe cardiovascular/cerebrovascular diseases.
6. Pregnancy or breastfeeding.

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6. STUDY TREATMENT AND MANAGEMENT

6.1 Intraoperative Second Registration

A critical quality control step:

- **Timing:** After surgery starts, before resection/after frozen pathology results.
- **Criteria:** Confirmed NSCLC, no pleural dissemination, negative lymph node pathology, and anatomy suitable for SGS.
- **Decision:** If criteria are met, proceed with SGS; if not, convert to lobectomy (excluded from primary efficacy analysis).

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9. STATISTICAL ANALYSIS PLAN (SAP)

9.1 Statistical Hypothesis

This is a Phase II study using the **A'Hern single-stage exact binomial design**.

- **Null Hypothesis (H0):$p \leq 0.81$**.
- **Alternative Hypothesis (H1):** $p \geqslant 0.91$.

- **Parameters:** α = 0.05 (one-sided), Power (1-β) = 0.80$.

9.2 Sample Size Calculation

Based on the A'Hern design with P0=0.81 and P1=0.91:

- **Required Evaluable Subjects (n):** 80.
- **Decision Rule:** If ⩾71 out of 80 subjects achieve 3-year RFS, the surgical technique is considered to have acceptable oncological safety.
- **Planned Enrollment:** Adjusted to **89 cases** to account for a 10% attrition/conversion rate.

9.3 Statistical Software

Analysis will be completed using **R software (version 4.0 or above)** and SPSS (version 26.0 or above).

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11. ETHICS AND DATA PROTECTION

The study follows the Declaration of Helsinki and Chinese GCP. All subjects' identities will be coded to ensure strict confidentiality. Approved by the Ethics Committee of Shanghai Chest Hospital.