

## LOGIS (L0calization of Ground-glass-opacity and pulmonary lesions for mInimal Surgery) registry: Design and Rationale



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### ABSTRACT

**Background and purpose:** An optimal pulmonary localization technique for video-assisted thoracic surgery (VATS) of small lung nodules has not yet been established. The L0calization of Ground-glass-opacity and pulmonary lesions for mInimal Surgery (LOGIS) registry aims to establish a multicenter database and investigate the usefulness and safety of localization techniques for small pulmonary lesions in individuals undergoing VATS.

**Methods/Design:** The LOGIS registry is a large-scale, multicenter cohort study, aiming to enroll 825 patients at 10 institutions. Based on the inclusion and exclusion criteria, all study participants with pulmonary lesions indicated for VATS will be screened and enrolled at each site. All study participants will undergo preoperative lesion localization by the hook-wire or lipiodol localization methods according to site-specific methods. Within a few hours of marking, thorascopic surgery will be done under general anesthesia by experienced thorascopic surgeons. The primary endpoints are the success and complication rates of the two localization techniques. Secondary endpoints include procedure duration, recurrence rate, and all-cause mortality. Study participant enrollment will be completed within 2 years. Procedure success rates and incidence of complications will be analyzed based on computed tomography findings. Procedure duration, recurrence rate, and all-cause mortality will be compared between the two techniques. The study will require 5 years for completion, including 6 months of preparation, 3.5 years for recruitment, and 1 year of follow-up endpoint assessment.

**Discussion:** The LOGIS registry, once complete, will provide objective comparative results regarding the usefulness and safety of the lipiodol and hook-wire localization techniques.

### 1. Introduction

The diagnosis rate of small pulmonary lung nodules has been increasing with the increasing use of computed tomography (CT) in lung cancer screening and daily practice [1–3]. While malignancy rates of small pulmonary lesions depend on nodule size and characteristics, they

are not negligible upon with subsolid nodules as well as solid nodules [4,5]. Therefore, proper management of small pulmonary nodules is an important issue [6]. Because of its safety and minimal invasiveness, video-assisted thorascopic surgery (VATS) is widely used for diagnosis and treatment of small pulmonary nodules [7]. However, if the targeted pulmonary lesion is too small or too deeply located to be

**Abbreviations:** CT, computed tomography; eCRF, electronic case report form; GGO, ground-glass opacity; LOGIS, L0calization for Ground-glass opacity and pulmonary lesions for mInimal Surgery; NAB, needle aspiration biopsy; VATS, video-assisted thoracic surgery

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visible or palpable, pre-VATS localization is mandatory for successful minimally invasive surgery without open thoracotomy conversion [8–10].

Pulmonary localization techniques for small lung nodules vary greatly and employ various materials or methods [11–14]. However, an optimal pulmonary lesion localization method that is effective and safe for VATS has not yet been established. Currently, CT-guided hook-wire localization is the most widely used method for pre-VATS localization [15]. However, a previous meta-analysis reported that CT-guided hook-wire localization exhibited a lower success rate and higher complication rate than microcoil and lipiodol localization [16]. Lipiodol localization for small lung nodules prior to VATS has been reported to be accurate and safe, with high success rates and low complication rates [13,17,18]. Pulmonary lesion localization using lipiodol has been consistently reported as exhibiting a success rate of over 90% [16]. The ongoing Localization of Ground-glass-opacity for mInimal Surgery (LOGIS) trial involves comparison of effectiveness and post-procedural complications between the hook-wire and lipiodol localization methods for VATS resection of ground-glass opacity (GGO) lesions [15]. However, depending on nodule characteristics and operator experience, there could be variations in results. Therefore, it is necessary that multi-institutional cohorts of a larger scale be established to comparatively evaluate the safety and effectiveness of various pulmonary lesion localization techniques.

## 2. Materials and methods

### 2.1. Overall study design

The Localization of Ground-glass-opacity and pulmonary lesions for mInimal Surgery (LOGIS) registry is a retrospective and prospective multicenter registry of patients who have undergone or will undergo pulmonary lesion localization by the hook-wire or lipiodol method prior to pulmonary VATS (Fig. 1).

### 2.2. Study objectives

This study aims to establish a multicenter registry of pulmonary-lesion localization techniques and investigate the usefulness and safety of two different localization methods for small pulmonary lesions in individuals undergoing VATS.

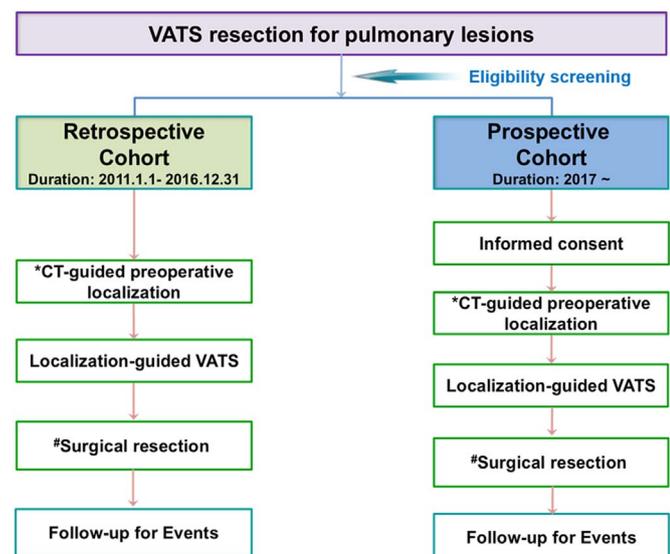


Fig. 1. Overall study design of the LOGIS registry.

### 2.3. Ethical considerations

The institutional review board of each participating institution reviewed and approved the study protocol. Informed patient consent will be obtained for the prospective cohort, and its requirement will be waived for the retrospective cohort. Patient records and data will be anonymized and de-identified prior to analysis.

### 2.4. Funding

The LOGIS registry is a physician-initiated registry, sponsored by Guerbet. Therefore, the authors are solely responsible for the design and conduct of this study, analysis of all study data, and drafting and editing of the manuscript, as well as its final contents.

### 2.5. Targeted population

Based on the inclusion and exclusion criteria, all subjects with pulmonary lesions indicated for VATS, including solid and GGO nodules, will be screened and enrolled at each site.

The inclusion criteria are as follows: consenting adults who is equal or older than 19 years of age; pulmonary lesions (solid nodules or GGO nodules) indicated for VATS; no contraindications for surgery; and willingness to sign the informed consent form.

The exclusion criteria are: contraindication for surgery; uncooperative behavior; severe neurologic or physiologic problems; unwillingness or inability to provide informed consent; and pregnancy.

### 2.6. Study endpoints

The primary endpoints of the LOGIS registry are the procedure success rates and complication rates of the lipiodol and hook-wire localization methods. Secondary endpoints include procedure duration, recurrence rate, and all-cause mortality. Procedure duration is defined as the period from the start of pre-localization CT to the end of pulmonary-lesion localization. The end of localization is defined as the time at which the needle leaves the lungs after lipiodol administration or the time at which the hook-wire is anchored onto the lesion. Recurrence is defined by the discovery and diagnosis of new lesions through histological examination or medical imaging during the follow-up period. All-cause mortality includes death from any reason.

### 2.7. Participating sites and eligibility criteria for participation

The requirements for participating sites to contribute to the LOGIS registry are same as those stipulated for the LOGIS trial [15].

Minimum requirements for participating sites include:

- (1) Experienced radiologists who have at least 1 year of experience with at least 30 cases of lipiodol or hook-wire localization for pulmonary nodules
- (2) Experienced thoracic surgeon who has at least 3 years of experience with at least 100 cases of VATS
- (3) Multi-detector CT scanner ( $\geq 16$ -slice) for localization

Overall ten university hospitals are participating in this multicenter registry. The lipiodol-guided localization group is consisted of five hospitals and the hook-wire-guided localization group is composed of the remaining five hospitals, based on their routine localization practices at each site.

### 2.8. Patient recruitment and evaluation

The LOGIS registry includes patients who have undergone or will undergo VATS for lung lesions after localization by the lipiodol or hook-wire methods. Following surgery, patient demographic characteristics,

targeted medical history, and CT findings will be recorded using online electronic case report forms (eCRFs). Eligible patients treated between January 1, 2011, and December 31, 2016, will be retrospectively reviewed and enrolled in a retrospective cohort. From 2017, eligible participants will be screened and enrolled prospectively in a prospective cohort. All prospectively enrolled subjects will be required to sign consent forms voluntarily; only those patients whose consent forms have been received by the institution will be allowed to participate in the clinical study. Before gathering informed consent, the participants will be explained the study details, including (1) study purpose; (2) autonomy of participation; (3) compensation for participation; (4) potential danger and benefits; and (5) ways to contact the researchers. Each enrolled patient is designated a baseline number (patient study ID), which is recorded in the corresponding case report form and retained until the end of the clinical study. Clinical trial institutions will monitor each patient through master files.

## 2.9. CT-guided lung localization and thoracoscopic surgery

All subjects will undergo preoperative lung localization at their respective sites according to site-specific methods. They will be transferred to the operating room immediately after localization. Within a few hours of marking, thoracoscopic surgery will be performed under general anesthesia. Patients with primary lung cancer will further receive thoracoscopic lobectomy or segmentectomy with lymph-node dissection.

## 2.10. eCRF and data management

After surgery, participants will be assessed every 3–6 months for a year. Each participating site will provide the data of enrolled patients, including eligibility criteria, baseline characteristics, pre-localization and localization CT characteristics, surgical characteristics, pathologic findings, and follow-up outcomes, through eCRFs. Baseline characteristics will include sex, age, height, weight, body mass index, and previous/current medical findings (hypertension, diabetes, cancer, surgery, heart diseases, lung diseases, alcohol, smoking, allergy, and medication). Pre-localization CT data will include imaging protocol (equipment, contrast material, tube voltage, reconstruction method, and radiation dose) and findings (number, size, location, type, and multiplicity of lesions, lymph node metastasis, pleural effusion, and metastasis). Localization CT data will include imaging protocol (equipment, radiation dose, and method), lesion characteristics (lesion size, location, and type), operator experience, and procedural characteristics (position, puncture time, pleura-to-nodule distance, start time, outcome, and complications).

Pathologic findings will include diagnosis (granuloma, atypical adenomatous hyperplasia, adenocarcinoma in situ, minimally invasive and invasive adenocarcinomas, metastasis, and others), gene mutation findings, and cancer stage. Follow-up outcome data will record recurrence and death. Each LOGIS investigator will get an ID and a password for accessing the eCRFs. After the eCRFs are entered by the participating sites, a dedicated biostatistician at the data coordinating center will check the data for possible errors, after which, the eCRF will be locked until data analysis. Severance hospital will serve as the data coordinating center for this study.

## 2.11. Statistical methods

### 2.11.1. Sample size and power calculation

The primary endpoint of the LOGIS registry is comparison of success rates between CT-guided lipiodol and hook-wire localization for lung-nodule VATS. In a previous meta-analysis [16], the mean success rates of lipiodol and hook-wire localization for pulmonary nodules were found to be 99% and 94%, respectively. Based on previous results, we performed sample size calculation by two independent proportions

power analysis, with a significance level of 0.05 and 90% statistical power. In a 1:2 ratio, we will enroll 220 and 440 patients, respectively, in the lipiodol and hook-wire localization groups. Assuming a 20% drop-out rate, we will enroll a total of 825 subjects. Sample size calculation was performed with the PASS software (ver. 12, power analysis and sample-size package, NCSS statistical software).

### 2.11.2. Primary statistical analysis

Categorical baseline characteristics will be expressed as number and percentage, and continuous variables will be expressed as mean and standard deviation. For the primary endpoints, procedure success rates and incidence of post-procedural complications, both evaluated based on CT findings will be analyzed by Student's t-test or chi-square test. If the results of this study demonstrate substantial variation among the participating sites, linear mixed model or generalized linear mixed model analysis will be performed to account for the clustering effect according to site. For the secondary endpoints, the procedure duration will be analyzed by Student's t-test. Cumulative survival rate or recurrence rate will be presented by a Kaplan–Meier curve and compared by an intergroup log-rank test. Hazard ratios for all-cause mortality, along with 95% confidence intervals, will be calculated by Cox proportional hazard regression or competing risk analysis. P-values < 0.05 will be considered statistically significant. All statistical analyses will be performed with the SPSS software (version 23.0; Statistical Package for the Social Sciences, Chicago, IL, USA).

## 3. Discussion

The LOGIS registry is a multicenter cohort study for comparison of success and complication rates between hook-wire and lipiodol localization for VATS for small pulmonary lesions, including GGO and solid nodules.

Owing to recent technological advances in CT as well as the increasing number of lung cancer screening tests, the rate of diagnosis of small lung nodules has been increasing [5,19]. Nevertheless, it is still challenging to differentiate between benign and malignant lesions based solely on CT findings [20,21]. Solid nodules and persistent GGO lesions pose a risk of cancer [5,13]. However, percutaneous lung biopsy has been known to lack diagnostic accuracy for small nodules and GGO lesions [22].

With recent advances in surgical techniques, the use of VATS for diagnosis and treatment of small nodules has been increasing because of its safety and minimal invasiveness [7,23]. However, conversion to thoracotomy because of VATS failure is not rare [9,11]. It is because small pulmonary nodules and GGO lesions are not easily recognizable by palpation or inspection. Therefore, accurate and safe localization method for lung lesions prior to VATS is necessary [24].

There are various preoperative localization methods for identifying small lung lesions to reduce the thoracotomy conversion rate of VATS. These localization techniques involve ultrasonography, hook wire, microcoil, methylene blue, indocyanine green, radionuclides, lipiodol, barium, and iodine contrast agents [11–14,24,25]. Although CT-guided hook-wire localization is the most widely used localization technique and is considered both safe and effective for VATS, the risk of dislodgement or migration of the hook-wire after localization is a major limitation of this technique and has resulted in wide variation of its reported success rates [16]. In contrast, lipiodol localization has been reported as constantly exhibiting success rates of over 90% [16]. Several studies have reported on the simplicity and usefulness of preoperative lipiodol localization for identification of small or deeply located pulmonary nodules for thoracoscopic surgery [13,14,26]. Lipiodol localization has the advantages of being stable and easy to handle; additionally, it does not induce inflammatory responses, which can affect the pathologic findings of lesions [27,28]. Moreover, there has been no report of air embolism after lipiodol localization [16]. However, post-lipiodol localization surgery requires fluoroscopy, which

is a major drawback of this technique [13]. Despite the availability of various localization methods, the optimal method for preoperative localization of pulmonary nodules has not been established, which has limited the success rate of VATS for small lung lesions [24]. Furthermore, hook-wire localization, the most widely used pre-VATS localization method, suffers from inconsistent success rates relative to other localization methods [16].

The ongoing LOGIS trial is a prospective multicenter, controlled, comparative phase III trial designed to demonstrate the comparative usefulness and safety of lipiodol and hook-wire localization for GGO lung lesions [15]. Although the LOGIS trial is expected to provide valuable information, its non-randomized controlled study design renders it prone to selection and assessment bias. Furthermore, the small sample size (125 subjects per group) might nullify attempts to overcome any differences in experience, skill, and preference among radiologists and surgeons. To overcome these limitations, we intend to establish the LOGIS registry, a larger scale of multicenter registry, to compare the success rates and complication rates of localization techniques in individuals undergoing VATS for small pulmonary lesions. The LOGIS registry has several advantages over the LOGIS trial. First, the LOGIS registry is a large-scale, multicenter cohort study, aiming to enroll over 800 patients. For this reason, the LOGIS registry has broader inclusion criteria than the LOGIS trial, which will enable us to enroll patients with solid or GGO nodules. Second, the number of participating sites has been increased from 8 institutions in the LOGIS trial to 10 institutions in this registry. Third, detailed information regarding patient characteristics, procedures, surgical characteristics, and outcomes will be collected using the convenient eCRF system, which will ensure efficient and prompt data collection.

The LOGIS registry is the first large-scale cohort study for comparison of pulmonary lesion localization methods. Upon completion, the LOGIS registry will provide objective comparative results regarding the usefulness and safety of the lipiodol and hook-wire localization techniques.

### Competing interests

The authors declare that they have no competing interests.

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