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Lipiodol lOcalization for Ground-glass opacity mInimal Surgery: Rationale and design of the LOGIS trial

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ABSTRACT

Objectives: The diagnosis and treatment of ground-glass opacity (GGO) lesions have become important issues because subsolid nodules including GGO are known to frequently represent the histologic spectrum of lung adenocarcinoma. Because small GGO lesions cannot usually be palpated or visualized during surgery, several marking techniques have been reported for localization during thoracoscopic surgery, such as lipiodol and hook-wire localization. This study is designed to demonstrate the usefulness and safety of the lipiodol localization technique for individuals undergoing GGO VATS resection compared to the hook-wire localization technique.
Methods: Two hundred fifty participants will be prospectively enrolled in a 1:1 manner to the lipiodol or hook-wire group according to the inclusion criteria. All study participants will undergo preoperative lung localization using either the lipiodol or hook-wire method. Thoracoscopic surgery will be performed by experienced thoracoscopic surgeons within several hours after marking under general anesthesia. The primary endpoint is the procedure success rate, and the secondary endpoints are the procedure complication rate, procedure time, surgery time and the margin from the lesion in the resected specimen.
Results: Patient enrollment will be completed within 2 years. We will analyze the procedure success rate and the presence of complications with regard to the CT results. In addition, the procedure and surgery times, and the safety margin will be also compared between the 2 techniques.
Conclusion: If the aims of this study are achieved, then the use of lipiodol localization technique will be widespread in the localization of non-palpable pulmonary lesions that are indicated for surgical resection. (ClinicalTrials.gov: NCT02180568)

1. Introduction

The growing popularity and efficacy of computed tomography (CT) has led to an increase in the identification rate of ground-glass opacity (GGO) pulmonary lesions. Recently, the diagnosis and treatment of GGO lesions have become important issues because GGO is currently known to frequently represent the histologic spectrum of lung adenocarcinoma [1]. Although GGO lesions were traditionally regarded as areas of inflammation, hemorrhage, or fibrosis, GGO lesions on CT have been reported to comprise a wide range of diagnoses, from preinvasive lesions, such as atypical adenomatous hyperplasia (AAH) or adenocarcinoma in situ (AIS), to invasive lesions, such as minimally invasive adenocarcinoma or invasive adenocarcinoma [2–4]. Moreover, some reports suggested that focal GGO lesions with solid components (part-solid GGO) are more likely to be associated with malignancy [2,5]. The management of GGO lesions depends on their persistency, size, solid portion, and multiplicity. Current guidelines recommend biopsy or surgical resection for persistent GGO lesions with solid components at least 5 mm in size or lesions that enlarge and/or increase attenuation [6]. Although, CT-guided percutaneous needle aspiration biopsy (NAB) of the lungs is commonly used for the diagnosis of pulmonary lesions [7], a percutaneous biopsy of GGO lesions is often difficult, and the diagnostic yield of CT-guided NAB for GGO lesions has been reported to be

Abbreviations: AAH, atypical adenomatous hyperplasia; AIS, adenocarcinoma in situ; CT, computed tomography; MDCT, multi-detector computed tomography; GGO, ground-glass opacity; LOGIS, Lipiodol lOcalization for Ground-glass opacity mInimal Surgery; NAB, needle aspiration biopsy; VATS, video-assisted thoracic surgery.

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significantly lower than that of solid lesions because of the low cellularity in GGO lesions [3,8]. Therefore, current guidelines do not recommend percutaneous transthoracic NAB for GGO lesions [6]. Video-assisted thoracic surgery (VATS) offers a minimally invasive method for diagnosing and treating these lesions. However, the localization of lesions for VATS can be problematic [9], because GGO lesions on CT cannot be palpated or visualized frequently. Several marking techniques have been developed to localize lesions during thoracoscopic surgery using a dye, lipiodol, or hook-wire [10–13]. Currently, hook-wire localization is most commonly performed for patients with solitary pulmonary nodules [14]. However, this technique can result in complications, such as pneumothorax, hemorrhage, and air embolism. Furthermore, wires are easily dislodged when the lungs collapse [10]. Clinically, there is a need for a less invasive, safer method for localizing GGO lesions. Preoperative localization of GGO lesions with lipiodol would provide several advantages, including easy handling, prevention of over-resection of normal lung tissue around the nodules, long-term persistency, and the lack of an effect on pathologic findings [15]. However, the usefulness and safety of the lipiodol localization technique for GGO lesions compared to the hook-wire localization technique is not well established. Therefore, a comparative trial is needed to compare these methods in terms of success rates and safety for GGO pulmonary lesions.

2. Objectives

The primary objective of the LOGIS trial is to demonstrate the usefulness and safety of the lipiodol localization technique for individuals undergoing GGO VATS resection compared to the hook-wire localization technique. The specific aims include the following: 1) to compare the procedure success rates of the lipiodol and hook-wire localization techniques; 2) to compare the complication rates of the 2 techniques; 3) to compare the procedure times of the 2 techniques; 4) to compare the surgical times during VATS resection after the 2 techniques; and 5) to compare the margins from the lesion in the resected specimens of the 2 techniques.

3. Primary hypothesis

The hypothesis of the LOGIS trial is that the preoperative localization of GGO with lipiodol will not be inferior to that using the hook-wire technique in terms of the procedure success and complication rates. In the absence of prior controlled trial experience, this hypothesis is supported by the following considerations:

(1) The success rate of the hook-wire technique varies from 58 to 97.6% [10,16–20].
(2) The failure rate of the hook-wire technique is as high as 47% as a result of wire dislodgement [10,21,22].
(3) In the hook-wire technique, the pneumothorax rates are 24.4–49% [12,13,20].
(4) The success rate of the lipiodol technique is relatively high at more than 90% [23,24].
(5) In the lipiodol technique, the pneumothorax rates range is 17–31% [11,15,24].
(6) There is no report of fatal complications associated with lipiodol-guided localization.

4. Methods

4.1. Funding

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

4.2. Overall study design

LOGIS is a prospective multicenter, controlled, comparative Phase III trial comparing procedure success and complication rates between the lipiodol and hook-wire localization techniques for individuals undergoing minimally invasive lung surgery for GGO lesions. The study will consist of 8 qualifying university teaching hospitals in Korea and will aim to enroll 250 study participants in a 1:1 manner to the lipiodol or hook-wire group according to the inclusion criteria. All study participants will undergo preoperative lung localization using either lipiodol (lipiodol-guided group) or hook-wire (hook-wire-guided group). At 4 sites, 125 participants will be enrolled to undergo preoperative lung localization using lipiodol, whereas the remaining 125 participants will be enrolled to undergo preoperative lung localization using hook-wire at the other 4 sites. After the localization procedures, thoracoscopic surgery (wedge resection) will be performed by experienced thoracoscopic surgeons within several hours after localization (Fig. 1).

4.3. Study population

All study participants with GGO lesions indicated for surgical resection under VATS will be screened and enrolled at the sites according to the inclusion criteria. Subjects considered for enrollment into LOGIS are patients with proven persistent GGO lung lesions whose physician had determined that the lesions required surgical resection. GGO is defined as an area of increased attenuation without obscuration of the underlying vessels or bronchi. All lesions must be examined by thin-section CT (slice thickness ≤3 mm), and they must exhibit persistence in a follow-up examination performed after 3 months. The inclusion criteria are 1) age of ≥20 years, 2) pulmonary lesion with a GGO component of more than 50%, 3) a lesion size of less than 3 cm, 4) persistence or growth of the established lesion at the 3-month follow-up examination, 5) no contraindication to surgery, and 6) a willingness to sign the informed consent form. The exclusion criteria include the following: 1) unwilling or unable to give consent; 2) multiple GGO lesions; 3) solid pulmonary lesion (GGO component of less than 50%); 4) contraindication for surgery; 5) uncooperative behavior; 6) concomitant participation in another clinical trial in which the subject is subject to an investigational drug or device; and 7) pregnancy (Table 1).

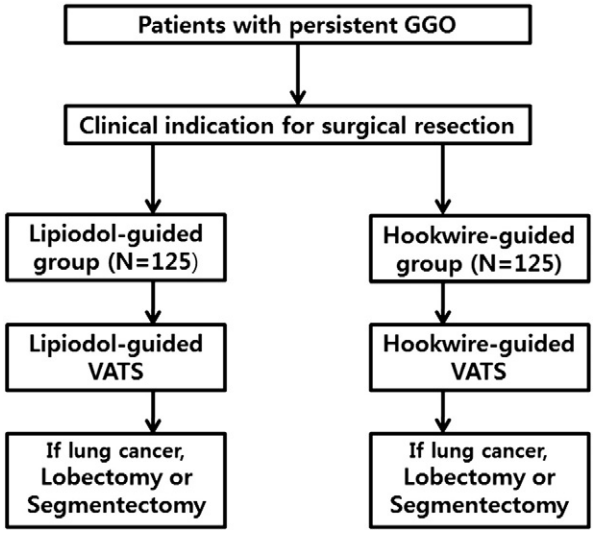

Fig. 1. Overall study design of LOGIS trial. GGO, ground glass opacity; VATS, video-assisted thoracic surgery.