

Preoperative CT versus Intraoperative Hybrid DynaCT Imaging for Localization of Small Pulmonary Nodules: A Randomized Controlled Trial

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Method Article

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Abstract

Background

Small and/or deep pulmonary nodules have been traditionally localized using preoperative CT (POCT) imaging. However, the advent of hybrid operating rooms (ORs) has allowed intraoperative computed tomography (IOCT)-guided lesion localization. This single center, open-label, randomized, controlled clinical trial aims to compare the efficacy and safety of IOCT *versus* POCT.

Methods/design

The study sample will consist of patients presenting with small and/or deep pulmonary nodules who will be randomly allocated to either POCT or IOCT. The time required for identifying the lesion will be the primary efficacy outcome. The following parameters will serve as secondary endpoints: rate of successful targeting in the operating field, time at risk, complication (pneumothorax and hemorrhage) rates, and radiation exposure.

Discussion

Owing to the increased availability of HORs, our data will be crucial to clarify the feasibility and safety of IOCT *versus* the traditional POCT approach.

Background

With the implementation of lung cancer screening based on low-dose computed tomography (CT), the number of patients diagnosed with small and/or deeply located pulmonary nodules has markedly increase. The lesions detected during screening should be carefully evaluated and eventually removed (when their malignant nature is highly suspected) [1]. However, the use of video-assisted thoracoscopic surgery (VATS) for their excision may be challenging – particularly when such nodules are small (diameter: < 10 mm) and/or deeply located in the lung parenchyma (> 5 mm from the pleural surface). Under these circumstances, conversion from VATS to thoracotomy may be required in up to 63% of cases [2]. Efficient and safe tumor marking before embarking on VATS is paramount to circumvent this issue. To this aim, several approaches have been proposed, including percutaneous CT-guided [3-5], bronchoscopy-guided (grounded in segmental anatomy and virtual imaging) [6, 7], and electromagnetic navigation bronchoscopy (ENB)-guided [8-10] methods. The results of a randomized study have previously shown that preoperative lesion localization is superior to no localization in terms of increased number of successful VATS wedge resections, reduced surgical time, and less frequent use of staples [11]. Moreover, total costs did not increase appreciably.

The percutaneous approach for localization of lung nodules is generally based on preoperative CT (POCT) imaging, followed by their removal in an operating room (OR) [3]. However, this two-step

methodology requires a careful planning in order to avoid complications (e.g., pneumothorax, hemothorax, wire dislodgement, dye diffusion) – whose incidence increases in parallel with that of the time elapsed from localization to surgery.

The recent advent of hybrid ORs is triggering a paradigm shift in the treatment of pulmonary nodules, paving the way to intraoperative CT (IOCT)-guided VATS. Although numerous studies have already shown that IOCT is clinically feasible [12-15], the question as to whether this approach is superior to traditional POCT remains open. To address this issue, well-designed prospective randomized studies are eagerly awaited. Here, we describe the protocol of a single-center prospective study that aims to provide a direct head-to-head comparison of IOCT *versus* POCT for localizing pulmonary nodules. The two techniques will be investigated in relation to efficacy, accuracy, complications, and radiation exposure.

Methods

Study design

Figure 1 depicts the flow of this investigator-initiated, investigator-driven study, which was designed as a single-center, open-label, randomized controlled trial. Patients diagnosed with pulmonary nodules and scheduled to undergo tumor localization before VATS will be randomized (1:1 ratio) to either IOCT or POCT.

Study patients

Subjects aged at least 18 years will be considered eligible for the study in presence of a lung tumor requiring localization before VATS. Localization will be deemed necessary when one of the following criteria will be met: 1) presence of solid pulmonary nodules of less than 10 mm in size and/or with a distance from the visceral pleura of at least 10 mm, or 2) evidence of subpleural cavitory lesions/ground glass nodules (GGNs), independent of their size and/or depth.

Exclusion criteria will be as follows: 1) presence of more than one nodule requiring localization; 2) inability to provide written informed consent, and 3) unwillingness or inability to adhere to the proposed follow-up protocol.

Screening for inclusion

Potentially eligible patients will be approached about potential inclusion either during the prehospitalization visit or while being hospitalized (before scheduled surgery). Complete information about the study objectives will be provided to all candidates.

Randomization

Patients will be randomized to either IOCT or POCT (1:1 ratio) using a computerized randomization tool. We will implement a permuted-block randomization scheme with varying block sizes, while maintaining

both allocation and block sizes concealed to the study investigators. Owing to the obvious procedural differences between IOCT and POCT, blinding of surgeons and patients cannot be achieved. In order to ensure an objective evaluation of the endpoints, all of the study outcomes will be investigated by an independent assessor (blinded to the allocation of patients to either POCT or IOCT) through a careful review of clinical records. After randomization, patients will be excluded when tumor regression or progression will be evident on prelocalization images (ultimately abrogating the need of localization). Patients will be allowed to exit from the study at any time.

POCT-guided localization

CT-guided localization will be performed by experienced board-certified interventional radiologists. Patients will be positioned in the CT scanner (GE HiSpeed, Milwaukee, WI, USA) in order to minimize the path between the skin and the pulmonary lesion (using a vertical direct needle trajectory whenever possible). The thickness of lesion images will be 2.5 mm. The skin at the puncture site will be carefully cleansed. A scalpel will be used to create a small skin incision followed by the insertion through the chest wall of a 10.7-cm-long, 20-gauge cannula needle containing a double-thorn hookwire (length: 20 cm; DuaLok®, Bard Peripheral Vascular Inc., Tempe, AZ, USA). All maneuvers will be guided by sequential CT with the patient under local anesthesia. An attempt to pierce the lung lesion with the cannula needle will be performed in all patients. As soon as the needle tip will be close or will reach the lesion, the hookwire will be advanced through the cannula. PBV dye (0.5 mL, patent blue V 2.5%; Guerbet, Aulnay-sous-Bois, France) injected through a 22-gauge, 8.9-cm-long spinal needle will be used to localize superficial lesions. The proper reciprocal positioning of the lesion and hookwire will be investigated through an immediate follow-up CT scan. Upon completion of localization, patients will be moved to a general ward before undergoing the scheduled resection.

IOCT-guided localization

Patients in the IOCT group will undergo lesion localization in a hybrid OR equipped with C-arm cone-beam computed tomography (CBCT; ARTIS zeego; Siemens Healthcare GmbH, Erlangen, Germany) and a Magnus surgical table (Maquet Medical Systems, Wayne, NJ, USA) (Figure 2A). The nodules will be localized and subsequently removed in a unique section by a single team of thoracic surgeons according to a previously described workflow [16]. After induction of general anesthesia, patients will be positioned in the lateral decubitus. A 6-sec protocol (6s DynaCT Body) will be used to acquire an initial scan for surgical planning (with the patient under end-inspiratory breathhold). We will model the needle entry path in the isotropic data set under the syngo Needle Guidance provided with the syngo X-Workplace (Siemens Healthcare GmbH). The needle trajectory will be initially identified by marking the entry and target points. A laser-target cross will be projected onto the patient's surface to visualize the needle entry point and angulation. An 18-gauge marker needle will be deployed into the patient's thorax during end-inspiratory breathhold under three-dimensional laser-guidance and guided fluoroscopy (Figure 2B). CBCT will be used to confirm an appropriate needle positioning (Figure 2C), and the lesion will be subsequently localized using either a hookwire (DuaLok®; Bard Peripheral Vascular Inc.) or a microcoil (Cook Medical,

Bloomington, IN, USA). Superficial lesions will be identified through the injection of either PBV (0.3-0.5 mL, patent blue V 2.5%; Guerbet, Villepinte, France) or near-infrared dye as previously described [17]. In selected cases, the correct lesion localization will be confirmed through a post-procedural CBCT scan. Patients in both arms will undergo VATS wedge resection, with the resected specimen being submitted to frozen section examination. Because their impact on the study results is likely to be noninfluential, other surgical variables – including the number of ports, the field of lymph node dissection, and the positioning of a chest tube – will be left to the surgeon’s discretion.

Data collection and management

Each participant will be unequivocally identified through a personal code (accessible to the principal investigator and the study coordinators only) assigned at inclusion. Digital case record forms (CRF) compliant to good clinical practice standards will be used for data collection and managed by the study coordinators and/or research nurses. Paper records will be stored in secured cabinets located at the data coordinating centers, with access being granted to the principal investigator and other researchers (nurses and physicians). Request for consultation of raw data (upon completion of the study) should be directed to the principal investigator. In order to ensure that the primary and secondary study outcomes will be accurately reported, all CRFs will be thoroughly cross-checked with the original sources. Clinical data will be stored in an anonymized fashion in keeping with local privacy laws.

Primary outcome measure

The time required for lesion localization will be the primary outcome measure. In the POCT group, it will be defined as the time elapsed from the beginning of preprocedural CT imaging to the end of postprocedural CT scan. In the IOCT group, it will be calculated from the docking of the C-arm to the end of the procedure (i.e., retraction of the C-arm from the table to the park position).

Secondary endpoints

The following secondary endpoints will be examined: 1) successful targeting rates, 2) time at risk, 3) complication rates, and 4) radiation doses. The rate of successful targeting will be calculated as the number of procedures characterized by successful targeting minus the number of cases with wire dislodgement/microcoil migration or dye diffusion/spillage divided by the total number of localization procedures. The time at risk will be defined as the time elapsed between the completion of localization and skin incision. The occurrence of complications (including pneumothorax and lung hemorrhage) will be recorded after the first follow-up CT scan following localization. According to the 2010 British Thoracic Society guidelines, large or small pneumothorax will be defined by a distance between the lung margin and chest wall greater or less than 2 cm, respectively.[18] The radiation dose delivered to patients will be quantified by placing four sets of thermoluminescent dosimeters (TLDs, UD-802A; Panasonic, Osaka, Japan) around the patient’s chest wall (in proximity to the lesion of interest). The radiation dose absorbed by each TLD will be measured using a TLD reader (UD-716AGL TLD reader; Panasonic, Tokyo, Japan) and mean values will be used for analysis.

Follow-up schedule

The start of the study will be set at randomization. Follow-up will be performed until 3 months after surgery according to a predetermined schedule (Figure 3). Within one week of the operation, we will assess the primary study endpoint. The following variables will be collected: postoperative complications, readmission rates, and deaths occurring within 30 and 90 postoperative days. Postoperative visits will be scheduled at 3–4 weeks after surgery and at 3 postoperative months.

Sample size calculation

The sample size was established according to a retrospective study previously designed by our group [19]. The original assumption was that the time required for tumor localization would be similar in the IOCT and POCT groups. Each treatment arm will require enrolment of 24 patients under the following conditions: alpha error, 0.05; power, 80%; and balanced trial design. Under the hypothesis of a total 10% dropout rate, we aim to enrol 27 patients in each arm.

Timeline

The clinical trial will last two years – a time span that includes prearrangement and statistical analysis. Recruitment has begun on October 8, 2018, with a planned 2-year duration. Data analysis is scheduled to start upon discharge of the last randomized patient.

Data analysis

Both intention-to-treat (i.e., in all of the randomized patients) and per-protocol (i.e., only in patients who will have their pulmonary lesion localized according to the method assigned on randomization and with complete follow-up data) analyses will be conducted. Categorical variables will be expressed as frequencies and compared with the chi-squared test or the Fisher's exact test, as appropriate. Continuous data will be summarized as means \pm standard deviations (for Gaussian variables) or medians and interquartile ranges (for skewed parameters). The Mann-Whitney *U* test and the Student's *t*-test will be used to compare normally distributed and skewed continuous variables, respectively. Two software packages – SAS (version 9.3; SAS Institute Inc., Cary, NC, USA) and SPSS (version 20.0; SPSS Inc., Chicago, IL, USA) – will be used for statistical calculations. A *P* value <0.05 (two-tailed) will be considered statistically significant.

Discussion

Currently, two major techniques can be implemented for performing CT-guided VATS removal of pulmonary nodules. The first is a two-stage approach based on preoperative lesion localization in a CT suite followed by its excision in an operating room, whereas the second consists in single-stage localization and removal in a hybrid OR.

It is a common assumption that IOCT-guided VATS performed in a hybrid OR may ultimately reduce the time at risk between localization and the subsequent excision when compared to POCT – ultimately resulting in a more patient-centered approach. The current randomized clinical trial will be the first to test the hypothesis that – besides reducing the time at risk – IOCT-guided VATS could also be as effective as the conventional two-stage POCT-guided approach for localizing pulmonary nodules. In particular, we will focus on the time required for localization when each approach will be used (a variable which will serve as the primary study endpoint). In addition, we will compare the successful targeting rates during surgery. In terms of safety, a point that will merit consideration is the radiation exposure delivered to patients. Because CBCT and MDCT differ significantly in terms of radiation dynamics, direct use of scanner-estimated doses will be suboptimal for comparison purposes. In order to circumvent this issue, patients in the IOCT arm will be requested to apply TLDs. This approach will allow obtaining direct measures of individual surface radiation exposure.

Finally, we are aware that the utilization of the the IOCT-guided approach in a hybrid OR may potentially increase the procedural costs (owing to a longer time under anesthesia and a higher global OR utilization time). The question as to whether IOCT will be cost-effective compared with POCT will be assessed separately.

Trial status

The trial commenced on October 8, 2018 and the recruitment period is projected to last two years. Data analysis will be started upon discharge of the last randomized patient.

Declarations

Ethics approval and consent to participate

The study was granted ethics approval by the Institutional Review Board of the Chang Gung Memorial Hospital on October 1, 2016 (CGMHIRB: 201600671A3). The study will be follow the tenets of the Helsinki Declaration, and written informed consent will be obtained for all participants. The study protocol (version 3, 20171108) has been redacted in compliance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist (Additional File 1).

Consent for publication

Not applicable.

Availability of data and materials

Raw data will be available from the corresponding author upon reasonable request. Transfer of clinical data will require approval from the Institutional Review Board.

Competing interests

The authors declare that they have no competing interests.

Funding

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Authors' contributions

YKC designed and promoted the trial in collaboration with HYF and CTW. YKC contributed to the first draft of the manuscript, applied for funding, established collaborations, and is responsible for logistics, patient recruitment, data collection and coordination of the trial. All authors contributed to the methodological design of trial, as well as to data analysis and manuscript writing. All authors revised the manuscript for important intellectual content and approved the submission of the study protocol in its current form.

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Figures

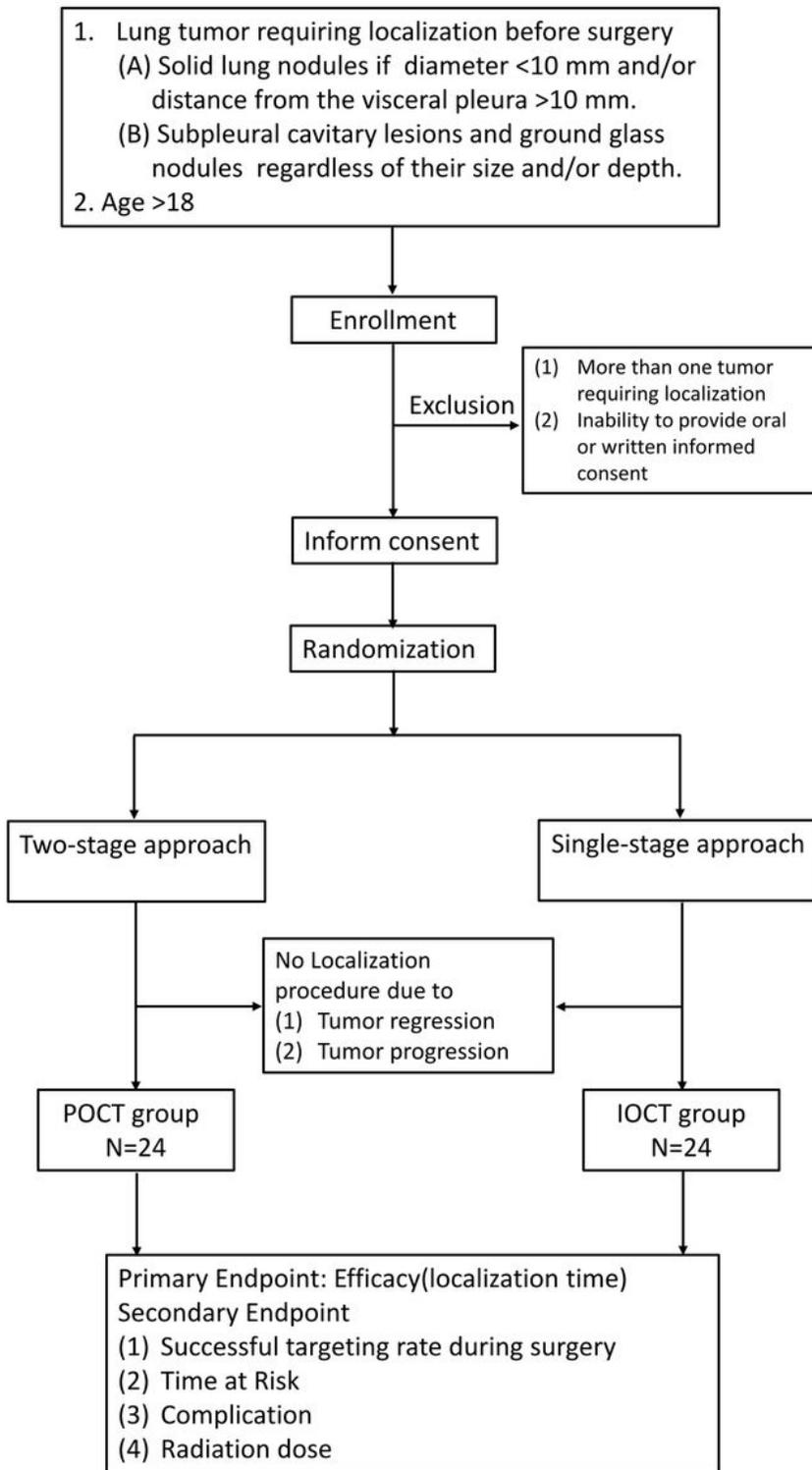


Figure 1

Flowchart of the study.

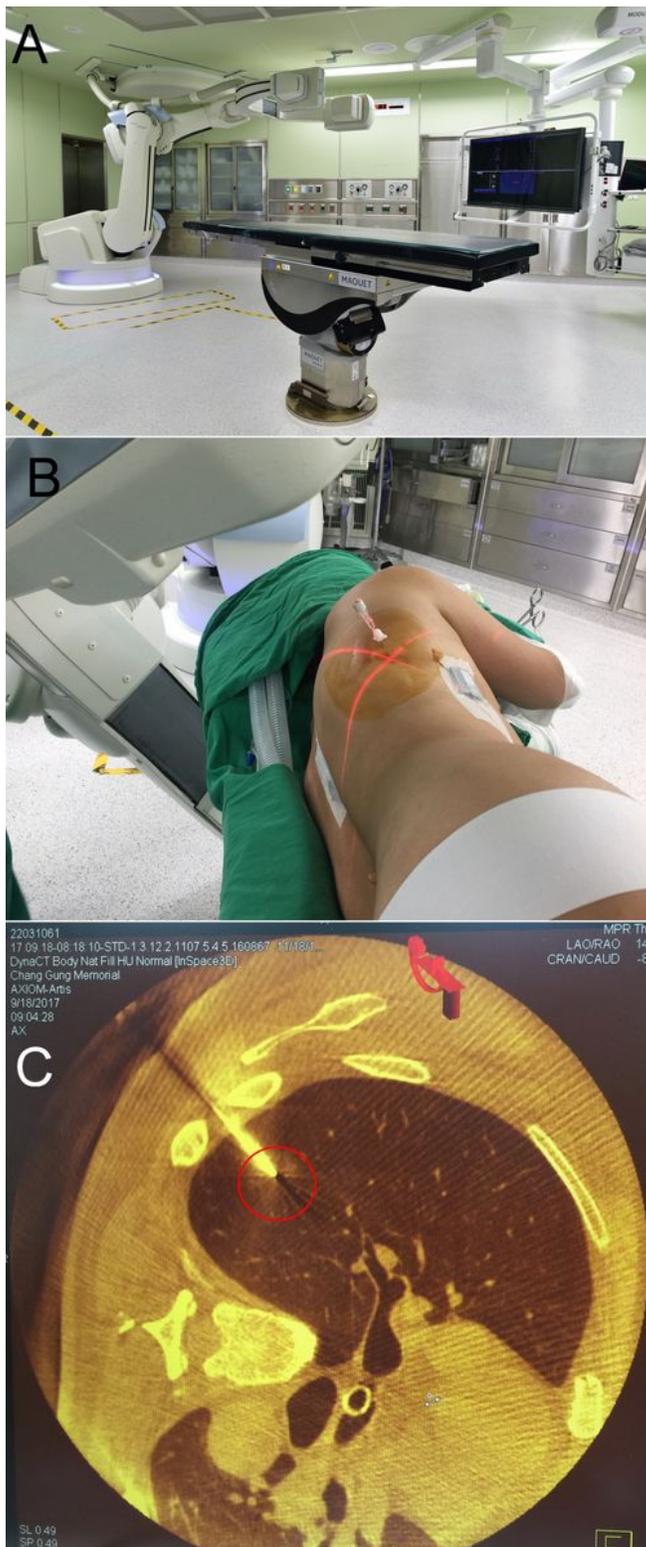


Figure 2

(A) Hybrid operating room equipped with a cone-beam CT apparatus (ARTIS zeego; Siemens Healthcare GmbH, Erlangen, Germany) and a Magnus surgical table (Maquet Medical Systems, Wayne, NJ, USA). (B) The needle entry point and angulation were visualized by projecting a laser-targeting cross onto the patient's surface. (C) CBCT image obtained after needle puncture. The needle was positioned within a ground-glass opacity (red circle).

Time point	Study period				
	Enrolment and allocation	Post-allocation			
Time point		Inpatient phase		Outpatient phase	
		1 day	1 week	4 weeks	12 weeks
Enrolment:					
Eligibility screen	X				
Informed consent	X				
Allocation	X				
Interventions:					
POCT approach		X			
IOCT approach		X			
Assessments:					
Baseline patient characteristics	X				
Baseline tumor characteristics	X				
Localization outcome parameter		X	X		
Perioperative outcome	X		X	X	X
Pathology data				X	

Figure 3

Schedule of patient enrolment, interventions, and assessments; Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)

Supplementary Files

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