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

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Study protocol

Abstract

Background Localization of small and/or deep pulmonary nodules before thoracoscopic exploration is paramount to minimize the likelihood of unplanned conversion to thoracotomy. As far as the percutaneous approach is concerned, the most common workflow consists of preoperative computed tomography (POCT) imaging-guided tumor marking (performed in an interventional CT suite) followed by their removal in an operating room (OR). However, the advent of hybrid 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 to complete lesion localization will be the primary efficacy outcome. The following parameters will serve as secondary endpoints: rate of successful targeting during localization and in the operating field, time at risk, operating time, length of time under anesthesia, global operating room utilization time, 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 increased. Lesions detected during screening should be carefully evaluated and eventually removed (when their malignant nature is highly suspected) [1]. However, their excision through video-assisted thoracoscopic surgery (VATS) may be challenging – particularly when such nodules are small (<10–15 mm in size) and/or deeply located (>5–10 mm from the pleural surface) in the lung parenchyma.[2,3] Efficient and safe tumor marking before embarking on VATS is paramount to avoid an unplanned conversion to thoracotomy.[4] To this aim, several approaches have been proposed, including percutaneous CT-guided [5-8], bronchoscopy-guided (grounded in segmental anatomy and virtual imaging) [9,10], and electromagnetic navigation bronchoscopy (ENB)-guided [11-13] 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 [3]. Moreover, total costs did not increase appreciably.

As far as the percutaneous approach is concerned, the most common workflow consists of preoperative computed tomography (POCT) imaging-guided tumor marking (performed in an interventional CT suite) followed by their removal in an operating room (OR).[5,8] However, this two-step methodology requires a careful planning in order to avoid complications (e.g., pneumothorax, hemorrhage, 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 [14-16], the question as to whether this approach is superior to traditional POCT remains open.[17] To address this issue, well-designed prospective randomized studies are eagerly awaited.[18] 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 to the edge of nodule of at least 10 mm, or 2) evidence of subpleural cavitary 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 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

All POCT-guided localization will be performed on a CT scanncer(GE BrightSpeed; GE healthcare, Milwaukee, WI, USA) (figure 2A) by a single team of interventional radiologists according to a previously described workflow.[8] Before implementing the procedure, case images will be reviewed to determine the most suitable needle trajectory. Sterile wraps will be positioned around the patient's chest, followed by injection of 1% lidocaine at the site of needle insertion in the chest. A scalpel will be subsequently 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). Under intermittent CT guidance, the needle will be positioned at the edge of the nodule of interest. 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-long spinal needle will be used to localize superficial lesions(figure 2B). 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 3A). 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.[19] 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 3B). CBCT will be

used to confirm an appropriate needle positioning , 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 [20].The correct lesion localization will be confirmed through a post-procedural CBCT scan.

Surgical treatment

Patients in both arms will undergo VATS wedge resection, with the resected specimen being submitted to frozen section examination. Cases with a confirmed diagnosis of primary lung cancer will undergo lobectomy. Patients unable to tolerate lobectomy because of an inadequate pulmonary function or with peripheral lung cancer of limited size (<2 cm) and adequate resection margins (either >2 cm or >tumor size) will be treated with a sublobar resection (wedge resection or segmentectomy).

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 investigation. 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 during localization (defined as the number of successful targeting procedures divided by the number of all localization procedures), 2) successful targeting rates in the operating field (defined as the number of successful targeting procedures minus the number of wire dislodgements or dye fading/spillage occurring in the

operation field divided by the number of all localization procedures), 3) time at risk (defined as the time elapsed between the completion of localization and skin incision), 4) other time parameters (including operating time, length of time under anesthesia, global operation room utilization time, and length oh hospital stay), 5) rate of conversion to thoracotomy, and 6) complication rates. The occurrence of complications (including pneumothorax and lung hemorrhage) will be recorded after the initial 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.[21] As far as radiation doses are concerned, we will quantify the radiation dose delivered to patients by determining the effective dose (ED). During POCT procedures, the radiation dose delivered by MDCT will be determined using the dose length product (DLP) and expressed as mGy/cm. The radiation dose will be converted to the ED using a suitable conversion factor (0.014, $mSvGy^{-1}cm^{-1}$).[22] During IOCT procedures, the radiation doses delivered by both CBCT and fluoroscopy will determined using the dose area product (DAP) and expressed as mGy/cm^2. Two appropriate conversion factors (0.146 and 0.12 $mSvGy^{-1}cm^{-2}$) will be used to calculate the ED for CBCT and fluoroscopy, respectively.[23, 24] Four sets of thermoluminescent dosimeters (TLDs, UD-802A; Panasonic, Osaka, Japan) will be also placed 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 4). 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.[25] Our original assumption was that the time required for tumor localization would be the same in the IOCT and POCT groups. Based on a two-sample t-test under an equality hypothesis, at least 24 patients per treatment arm will be required under the following conditions: alpha error, 0.05; power, 80%; and a balanced trial design. Under the assumption of a 10% total dropout rate, we are planning to enroll at least 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 ± 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.

List Of Abbreviations

CBCT, cone-beam computed tomography

CRF, case record form

CT, computed tomography

ENB, electromagnetic navigation bronchoscopy

GCP, good clinical practice

GGNs, ground glass nodules

HORs, hybrid operating rooms

IOCT, intraoperative computed tomography

OR, operating room

POCT, preoperative CT

SPIRIT, Standard Protocol Items: Recommendations for Interventional Trials

TLDs, thermoluminescent dosimeters

VATS, video-assisted thoracoscopic surgery

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 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

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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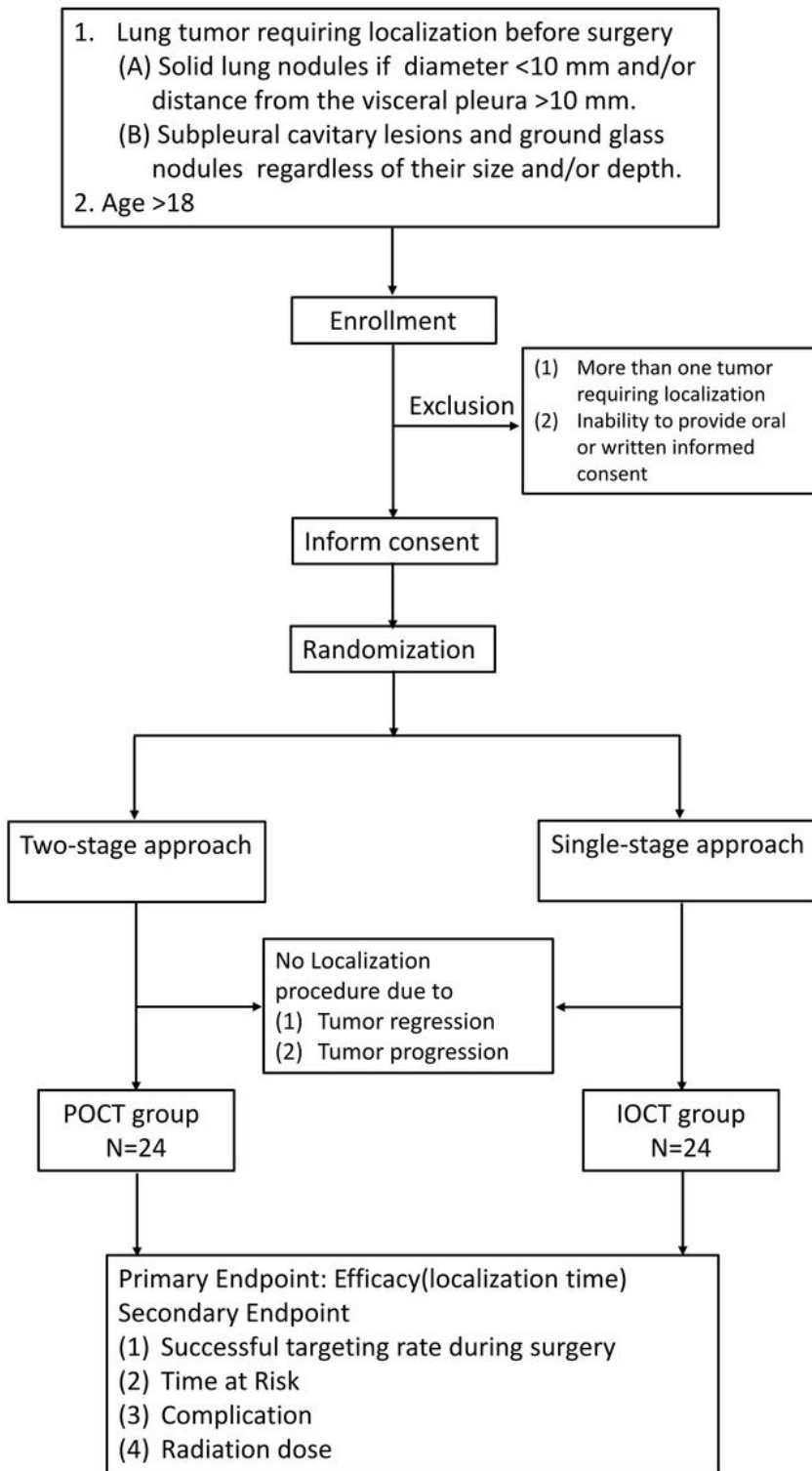
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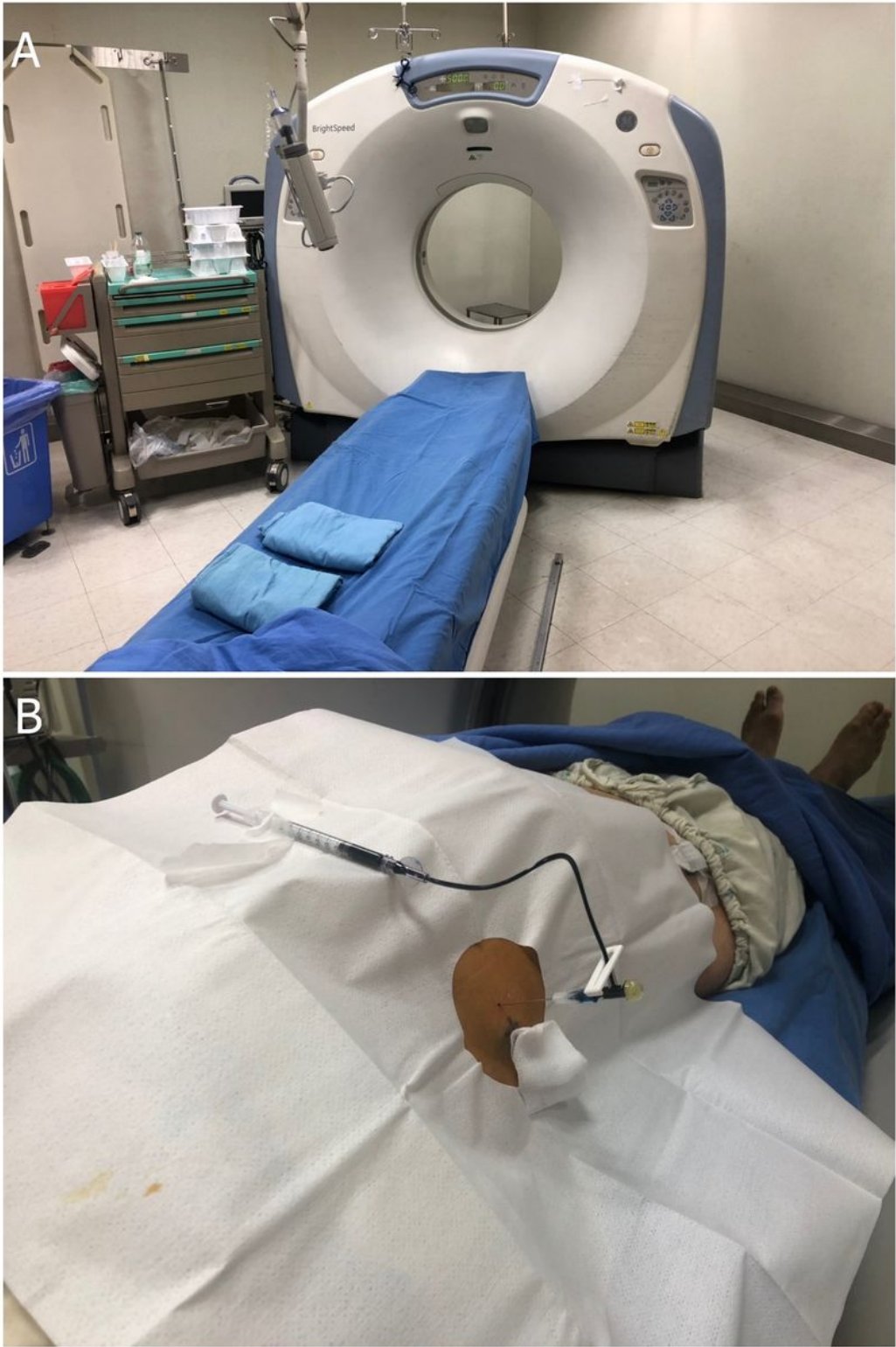
Figure 1

Flowchart of the study.

Figure 2

(A) Interventional Radiology Suite equipped with a 16-slice CT scanner(GE BrightSpeed; GE healthcare, Milwaukee, WI, USA) (B) PBV dye injection following needle localization.
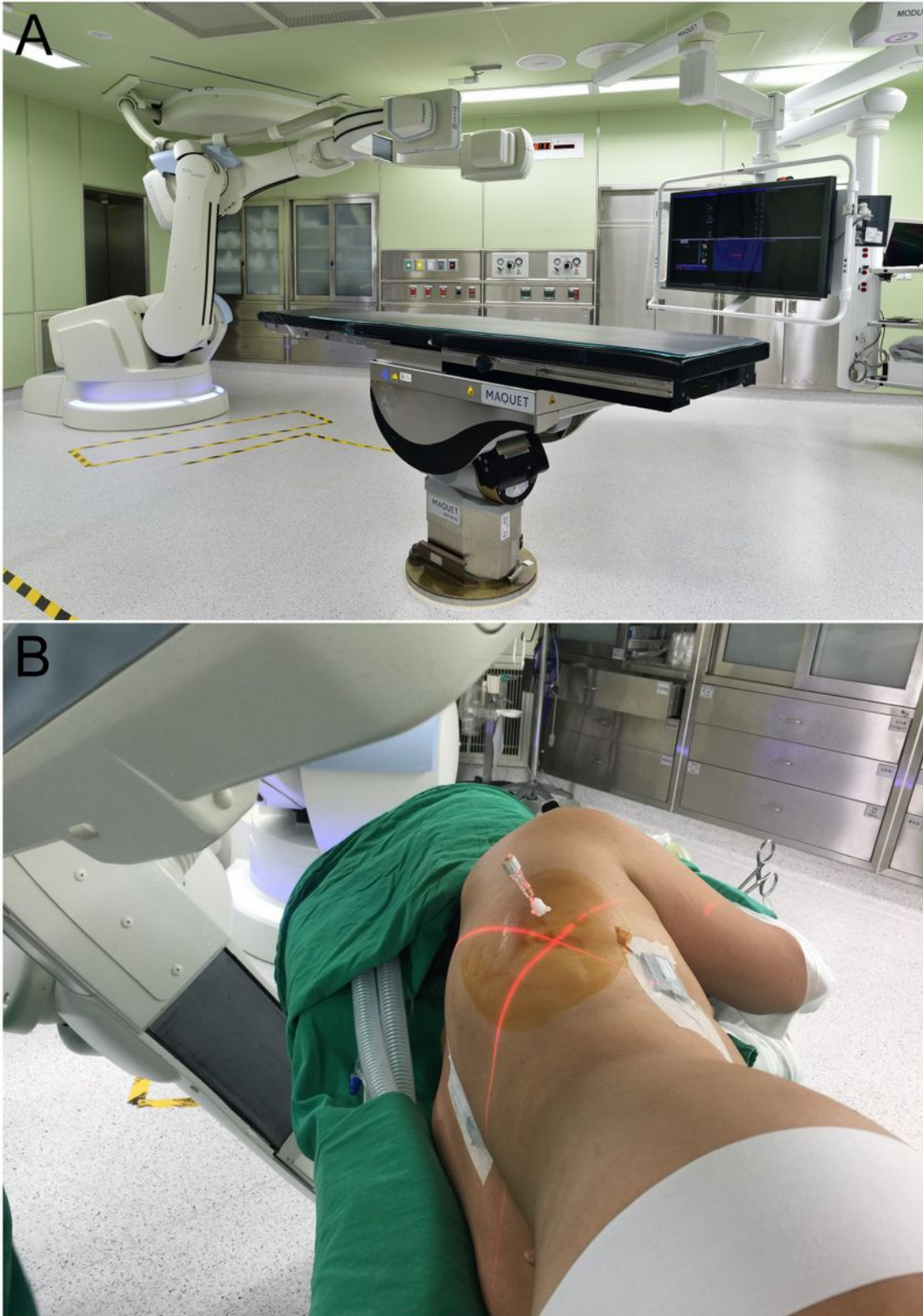
Figure 3

(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.

Time point	Enrolment and allocation	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 4

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

Supplementary Files

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