Study protocol

Official Title of the study: Research on New Intelligent Diagnosis and Treatment Technologies for Early Lung Cancer Based on Multimodal Imaging Bronchoscopy Navigation

Affiliation: Sir Run Run Shaw Hospital, Zhejiang University School of Medicine

Department: Department of Respiratory and Critical Care Medicine

Date of the document: May 20, 2024

Research on new intelligent diagnosis and treatment technologies for early lung cancer based on multimodal imaging bronchoscopy navigation

Background

Lung cancer is one of the malignant tumors with the highest incidence and mortality rates worldwide. From the 1970s to the present, the mortality rate of lung cancer in China has been climbing year by year, and currently lung cancer ranks first in China in terms of incidence rate and mortality rate. Meanwhile, data show that 75% of lung cancer patients are already in advanced stage when they are diagnosed. The 5-year survival rate of advanced lung cancer in China is only 16.1%, while the 5-year survival rate of early lung cancer patients can reach 73%. Therefore, improving the early diagnosis rate of lung cancer will greatly reduce the mortality rate of lung cancer.

Regular chest computed tomography (CT) in the population can detect a large number of nodular lung lesions, and data show that lung nodules are detected in approximately 25% of the population on routine screening, most of which (96.4%) are benign. Further examination of these high-risk lung nodules is effective in improving early lung cancer detection and reducing mortality by approximately 20%. CT-guided percutaneous lung puncture is the mainstay of conventional diagnosis of lung nodules, and the risk of complications is a major concern. Its complications include pneumothorax, hemoptysis, and needle tract metastasis, among which the incidence of pneumothorax is 12.3% and hemoptysis is 20%. In recent years, the use of navigational tracheoscopy for peripheral lung nodule biopsy has gradually increased in the clinic due to good safety and accuracy. 2020 CHEST published a meta-analysis on navigational tracheoscopy, the incidence of pneumothorax is only 2%, which is obviously advantageous compared with the traditional methods.

Even so, navigational bronchoscopy techniques have limitations in the management of peripheral lung nodules. Navigation bronchoscopy has limitations in the diagnosis and treatment of peripheral lung nodules. Data show that the overall diagnostic rate of navigation bronchoscopy for biopsy of peripheral lung nodules is

80%, which is lower than that of traditional CT-guided percutaneous lung puncture, especially for near-pleural foci and foci with a diameter of less than 1 cm. There are three reasons for this. First, the current mainstream navigation system based on CT images does not have enough ability to recognize airways smaller than 3 mm, and intraoperative blindness exists in some of the small airway areas, resulting in failure or inaccuracy of preoperative bronchoscopic path planning in some areas. Second, the current mainstream bronchoscopy equipment apex outer diameter is generally around 4-5mm, which cannot enter the finer distal small airways, and it is difficult to reach some peripheral lesions close to the subpleural area, which makes it difficult to increase the biopsy positivity rate of this part of the lesion. Third, the small airways around the lesions are in a collapsed state due to various reasons such as sputum stasis, insufficient inspiration or breath holding during the acquisition of CT images, so it is difficult for preoperative CT to truly reflect the situation of the patient's airway, which ultimately results in the difference between the real-time observation of the distribution of the airway and the pathway of the preoperative planning, and makes it impossible to realize the accurate guidance in the intraoperative period.

To improve the diagnostic rate of lung nodules by navigational bronchoscopy, this project has conducted a preliminary exploration to address the three main issues mentioned above. The preliminary research found that the mainstream whole-lung navigation systems on the market, including The SPiN Thoracic Navigation System magnetic navigation system from Veran, the virtual bronchoscopic navigation (VBN) System from Lungpro of Broncus, and the Super Dimension Electromagnetic Navigation System from Medtronic, are all similar, although there are differences in the operation process. Despite the differences in operation procedures, the core technology of computerized virtual bronchial tree imaging is similar, and all of them are suboptimal for the reconstruction of small airways less than 3 mm. The main reason is that for small airways less than 3 mm, the airway features are not obvious or missing, which are difficult to be extracted by the existing navigation algorithms. To address this problem, on the basis of the existing algorithms to recognize airway segments, deep learning technology is added to do super-resolution reconstruction of the original CT by super-

resolution convolutional neural network (SRCNN), so as to enhance the visual features of the airway smaller than 3mm, and link the 3D-VNET network model with its own attention mechanism to intelligently recognize more small airway segments smaller than 3mm.

Study purpose and design

To improve the problems of recognition, extraction, and three-dimensional reconstruction of 2-3mm small airways that have not been solved by mainstream navigation software on the market through deep learning methods based on the VBN navigation system, and evaluate the accuracy of the improved navigation system and the original navigation system in the diagnosis of peripheral pulmonary lesions (PPL) through a randomized controlled trial.

Study population

Subjects for this single-center randomized controlled trial were recruited from August 2023 to December 2024 at the Sir Run Run Shaw Hospital, Zhejiang University School of Medicine.

Inclusion and exclusion criteria

Inclusion criteria: (1) aged 18 years or above; (2) patients with one or more peripheral lung nodules suspected to be lung cancer or poorly absorbing lesions on conventional anti-infective therapy; (3) patients with nodule diameters ≤30 mm (diameters mentioned in the text are the average of the maximum and minimum diameters; (4) the nodules were pure ground glass nodules, partially solid nodules, or solid nodules; (5) the nodule is surrounded by lung parenchyma and is not visible in the bronchial lumen above the segment.

Exclusion criteria: (1) preoperative judgment that it is difficult for the patient to benefit from bronchoscopic biopsy (e.g., high risk of bleeding due to perivascular encasement of the lesion, difficulty in reaching the airway adjacent to the lesion due to previous lung surgery, etc.); (2) those with incomplete clinical data; (3) those with missing visits

after biopsy.

Interventions

After stratification according to the size of the lesion and the proportion of solid components in the lesion (≥50%, <50%), the eligible subjects were randomized into the new navigation system group (experimental group) and the old navigation system group (control group) in a 1:1 ratio. All included subjects underwent transnavigation-guided bronchoscopic lung biopsy at the respiratory endoscopy center. For pre-biopsy navigation path planning, the small airway reconstruction system-pro (SARS-pro) (self-developed by our team) was used in the experimental group and the conventional VBN system (LungPro; Bronchus Corporation) in the control group. The SARS-pro navigation system is an augmented reality optical navigation system based on VBN, which upgrades the small airway tree reconstruction navigation system through deep learning and multiple trainings.

Outcomes

The primary outcome was the diagnostic positive yield of the different navigation systems for PPL. The second outcome was the adverse events (hemoptysis, pneumothorax, and mediastinal emphysema) of the subjects.

Ethical approval and informed consent statement

The trial was approved by the Ethics Committee of the Sir Run Run Shaw Hospital, Zhejiang University School of Medicine (approval number: 2024-1000) (See the attachment "Ethics Approval Document"). For statistical analysis, subject identities were expressed as codes, which did not involve disclosure of subjects' privacy and personal information, and the study did not involve commercial interests, so informed consent was waived by the Ethics Committee (See the attachment " Informed consent form").

Statistical analysis plan

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Research on New Intelligent Diagnosis and Treatment Technologies for Early Lung Cancer Based on Multimodal Imaging Bronchoscopy Navigation

Statistical analysis

For sample size calculation, a study reported a deep learning-based airway segmentation algorithm based on 40 CT images. Based on the benefit of a larger sample size in deep learning, the sample size in this study was set to 100. For subject characteristics, the quantitative data were tested for normality using the skewness and kurtosis methods, and the homogeneity of variance was tested using the Levene test. Normal distribution measurement data were described as mean and standard deviation [Mean (±SD)], and t test or t' test was utilized for comparison between groups. Non-normal data were summarized as median and interquartile range [M (Q_1, Q_3)], and group comparisons were made using the Wilcoxon rank sum test. Count data were reported as the number of cases and composition ratio [n (%)], and the chi-square test or the Fisher exact test was utilized for comparison between groups. Data cleaning was accomplished using Python 3.9.12 (Python Software Foundation, Delaware, USA), and the difference comparison was completed by R version 4.3.3 (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was set to $P<0.05$.

Data management and confidentiality

(1) The data is stored in the hospital's server with strict security protection and is not accessible to external networks; (2) All information related to the identity of the CT's patients is kept confidential, and the relevant information is not disclosed to the public outside of the scope permitted by relevant laws and/or regulations.

Ethics Committee Approval (Original Chinese version)

Official Title of the study: Research on New Intelligent Diagnosis and Treatment Technologies for Early Lung Cancer Based on Multimodal Imaging Bronchoscopy Navigation

Affiliation: Sir Run Run Shaw Hospital, Zhejiang University School of Medicine

Department: Department of Respiratory and Critical Care Medicine

Date of the document: June 6, 2024

浙江大学医学院附属邵逸夫医院伦理审查批件

Ethics Committee Approval Letter of Sir Run Run Shaw Hospital, Zhejiang University School of Medicine

批件号 Approval NO.：邵逸夫医院伦审 2024 研第 1000 号

项目名称 Study Title	呼吸疾病诊治新技术研究-基于多模态影像支气管镜导航的早期肺癌智能诊疗新技术的研究		
申办方 Sponsor	无		
受理号 Acceptance Number	2024-2289-01		
主要研究者 Principal Investigator	陈恩国	承担科室 Responsible Department	呼吸内科
审查类别 Category of Review	初始审查	审查方式 Type of Review	快速审查
审查日期 Date of Review	2024.06.06	审查地点 Location of Review	/
审查文件清单 Items Reviewed	见附件		
审评意见 Evaluation	本伦理委员会认为递交的审查材料符合伦理规范，同意开展临床研究。		
审查决定 Decision	委员会对该项目的审查决定为： 同意		
主任/副主任委员签字 Chair Signature			
签发日期 Date of issue	2024.6.6		
伦理审查委员会 Stamp of EC	伦理审查委员会盖章		
批件有效期 Period of Validity	自本伦理审查委员会初始审查批准之日起一年内，本临床研究应在本院启动。		
年度/定期跟踪审查 Continue Review	审查频率为该研究批准之日起每 12 个月一次，首次 2025 年 06 月 05 日，请于批件到期前 1 个月递交研究进展报告。 伦理审查委员会有根据实际进展情况改变跟踪审查频率的权利。		
声明 Statement	本伦理审查委员会的职责、人员组成、操作程序及记录遵循《涉及人的生物医学研究伦理审查办法》、《涉及人的健康相关研究国际伦理准则》、《赫尔辛基宣言》、GCP 和 ICH-GCP 等国际伦理指南和国内相关法律法规。		
注意事项：			

1. 请遵循我国相关法律、法规和规章中的伦理原则。
2. 请遵循经本伦理审查委员会批准的临床研究方案、知情同意书、招募材料等开展本研究，保护受试者的健康与权利。对研究方案、知情同意书和招募材料等的任何修改，均须得到本伦理审查委员会审查同意后方可实施。
3. 在本院发生的 SAE/SUSAR 以及研发期间安全性更新报告须按照 NMPA/GCP 最新要求及时递交本伦理审查委员会，国内外其它中心发生的 SAE/SUSAR 需定期汇总、评估后递交本伦理审查委员会。
4. 根据报告情况，本伦理审查委员会有权对其评估做出新的决定。
5. 无论研究开始与否，请在跟踪审查日到期前 1 个月提交研究进展报告。
6. 申办方应当向组长单位伦理审查委员会提交中心研究进展报告汇总；当出现任何可能显著影响研究进行或增加受试者危险的情况时，请申请人及时向本伦理审查委员会提交书面报告。
7. 研究纳入了不符合纳入标准或符合排除标准的受试者，符合中止研究规定而未让受试者退出研究，给予错误治疗或剂量，给予方案禁止的合并用药等没有遵从方案开展研究的情况；或可能对受试者的权益或健康以及研究的科学性造成不良影响等违背 GCP 原则的情况，请申办方、监查员或研究者提交违背方案报告。
8. 申请人暂停或提前终止临床研究，请及时提交暂停或终止研究报告。
9. 完成临床研究，请申请人提交结题报告。
10. 凡涉及中国人类遗传资源采集标本、收集数据等研究项目，必须获得中国人类遗传资源管理办公室批准后方可在本中心开展研究。
11. 凡经本伦理审查委员会批准的研究项目在实施前，申请人应按相关规定在国家卫健委、药审中心等的临床研究登记备案信息系统平台登记研究项目相关信息。

附件：

1.初始审查申请表（科研专用）

2.主要研究者责任声明

3.主要研究者履历

4.研究方案（V1.0；2024.05.20）

5.免除 / 免签知情同意书申请表

6.浙江省科技计划项目 项目编号:2022C03086

Ethics Committee Approval (English translation version)

Official Title of the study: Research on New Intelligent Diagnosis and Treatment Technologies for Early Lung Cancer Based on Multimodal Imaging Bronchoscopy Navigation

Affiliation: Sir Run Run Shaw Hospital, Zhejiang University School of Medicine

Department: Department of Respiratory and Critical Care Medicine

Date of the document: June 6, 2024

Ethics Committee Approval Letter of Sir Run Run Shaw Hospital, Zhejiang University School of Medicine

Approval No: Sir Run Run Shaw Hospital Ethical Review 2024 Study No. 1000 (Abbreviation: 2024-1000)

Study Title	Research on new intelligent diagnosis and treatment technologies for early lung cancer based on multimodal imaging bronchoscopy navigation		
Sponsor	No		
Acceptance Number	2024-2289-01		
Principal Investigator	Enguo Chen	**Responsible Department**	Department of Respiratory Medicine
Category of Review	Initial review	**Type of Review**	Quick review
Date of Review	2024.06.06	**Location of Review**	/
Items Reviewed	See the attachment		
Evaluation	This ethics committee believes that the submitted review materials comply with ethical norms and agrees to conduct clinical research.		
Decision	The committee's review resolution on the project is: Consent		
Chair signature			
Date of issue			
Stamp of EC	Stamped by the Ethics Review committee.		
Period of Validity	This clinical study shall be initiated in our hospital within one year from the date of the initial review and approval by this ethics review committee.		
Continue Review	The review frequency is once every 12 months from the date of approval of this research. The first time is on June 5, 2025. Please submit the research progress report one month before the expiration of the approval document. The Ethics Review committee has the right to change the frequency of follow-up reviews according to the actual progress.		
Statement	The responsibilities, composition of personnel, operating procedures and records of this ethics review committee comply with the "Ethical Review		

	Measures for Biomedical Research Involving Humans", the "International Ethical Guidelines for Research Related to Human Health", the "Declaration of Helsinki", international ethical guidelines such as GCP and ICH-GCP, and relevant domestic laws and regulations.

Precautions

l. Please follow the ethical principles in the relevant laws, regulations and rules of China.

2. Please conduct the study in accordance with the clinical research protocol, informed consent form and recruitment materials approved by the Ethics Review Committee to protect the health and rights of the subjects. Any modification of the study protocol, informed consent form, recruitment materials, etc. must be reviewed and approved by the Ethics Review Committee before implementation.

3. SAE/SUSARs occurring in this institution and safety update reports during the research and development period shall be submitted to the Ethics Review Committee in a timely manner in accordance with the latest requirements of NMPNGCP, and SAE/SUSARs occurring in other centers in China and abroad shall be summarized and evaluated periodically and then submitted to the Ethics Review Committee.

4. The Ethics Review Committee has the right to make a new decision on the evaluation based on the reports.

5. Regardless of whether the study is started or not, please submit the study progress report 1 month before the due date of the follow-up review.

6. The sponsor should submit a summary of the center's research progress report to the Ethics Review Committee of the group leader. The applicant is requested to submit a written report to this Ethics Review Committee in a timely manner when any situation arises that may significantly affect the conduct of the study or increase the risk to the subjects.

7. When the study enrolls subjects who do not meet the inclusion criteria or meet the exclusion criteria, withdraws subjects from the study in accordance with the rules for discontinuation of the study, administers incorrect treatments or dosages, or administers combinations of medications prohibited by the protocol, etc., and conducts the study without complying with the protocol, or violates the principles of GCP by potentially adversely affecting the rights and interests of subjects or their health as well as the scientific validity of the study, the applicant, the Supervisory Reviewer, or the

investigator shall submit a report on the violation of the protocol. investigator to submit a report on the violation of the protocol.

8. If the applicant suspends or prematurely terminates the clinical study, the applicant is requested to submit a report on the suspension or termination of the study in a timely manner.

9. Upon completion of the clinical study, the applicant is requested to submit a completion report.

10. All research projects involving the collection of specimens and data from Chinese human genetic resources must be approved by the China Human Genetic Resources Management Office before the research can be carried out in the Center. 11.

11. Before the implementation of any research project approved by the Ethics Review Committee, the applicant shall register the relevant information of the research project on the clinical research registration information system platform of the National Health and Keystone Commission and the Center for Drug Control and Prevention in accordance with relevant regulations.

Attachments:

1. Application form for initial review (for scientific research)

2. Principal Investigator's Responsibility Statement

3. Principal Investigator's Curriculum Vitae

4. Study protocol (V1.0; 2024.05.20)

5.Application for exemption/waiver of informed consent form

6. Science and Technology Program of Zhejiang Province Project No.: 2022C03086.

Informed Consent Form (Original Chinese version)

Official Title of the study: Research on New Intelligent Diagnosis and Treatment Technologies for Early Lung Cancer Based on Multimodal Imaging Bronchoscopy Navigation

Affiliation: Sir Run Run Shaw Hospital, Zhejiang University School of Medicine

Department: Department of Respiratory and Critical Care Medicine

Date of the document: May 28, 2024

免除/免签知情同意书申请表

项目名称	呼吸疾病诊治新技术研究-基于多模态影像支气管镜导航的早期肺癌智能诊疗新技术的研究		
临床研究类别	☐申办方发起的非注册性临床研究 ☑研究者发起的临床研究		
申办方	无		
主要研究者	陈恩国	承担科室	呼吸内科

一、免除知情同意（不适用请跳过）

☐ **利用以往临床诊疗、疾病监测或临床研究中获得的数据或标本进行的研究，且潜在受试者已签署知情同意书允许该数据或标本用于其它临床研究的（不适用请跳过）**

1	请提供原知情同意书所对应的伦理批件号或已签署的知情同意书
2	本研究是否超出原知情同意书许可的范围，请说明
3	受试者隐私和个人身份信息是否得到保护，请说明
4	后续是否需要随访或再次向受试者获取信息，请说明

☑ **利用以往临床诊疗、疾病监测或临床研究中获得的数据或标本进行的研究，且潜在受试者未签署知情同意书允许该数据或标本用于其它临床研究（不适用请跳过）**

1	所使用的数据或标本为以往临床诊疗、疾病监测或临床研究中获得的，请说明 是
2	是否使用受试者明确拒绝利用的数据或标本，请说明 否
3	若规定需获取知情同意，研究将无法进行（受试者有权知道其数据或标本可能用于研究，其拒绝或不同意参加研究，不是研究无法实施、免除知情同意的证据）
4	受试者隐私和个人身份信息是否得到保护，请说明 是
5	后续是否需要随访或再次向受试者获取信息，请说明 否

二、申请免除知情同意书签字（不适用请跳过）

☐ **签了字的知情同意书会对受试者的隐私构成不正当的威胁，联系受试者真实身份和研究的唯一记录是知情同意文件，主要风险就来自于受试者身份或个人隐私的泄露，请说明**

☐ **其它情况，比如通过邮件、微信、钉钉或电话等方式进行问卷调研，已向受试者或监护人提供书面知情同意或获得受试者或监护人的口头知情同意，请说明**

主要研究者签名	陈恩国	日期	2024.5.28

Informed Consent Form (English translation version)

Official Title of the study: Research on New Intelligent Diagnosis and Treatment Technologies for Early Lung Cancer Based on Multimodal Imaging Bronchoscopy Navigation

Affiliation: Sir Run Run Shaw Hospital, Zhejiang University School of Medicine

Department: Department of Respiratory and Critical Care Medicine

Date of the document: May 28, 2024

Application Form for Exemption/Signature of Informed Consent Form

Project Name	Research on new intelligent diagnosis and treatment technologies for early lung cancer based on multimodal imaging bronchoscopy navigation		
Clinical research category	□ Sponsor-initiated non-registered clinical studies √ Investigator-initiated clinical studies		
Sponsor	No		
Principal Investigator	Enguo Chen	**Responsible Department**	Department of Respiratory Medicine
1. Exemption from informed consent (skip if not applicable)			
□ **Research conducted using data or specimens obtained from previous clinical diagnosis and treatment, disease surveillance or clinical studies, and where potential subjects have signed informed consent forms allowing such data or specimens to be used in other clinical studies (not applicable, please skip)**			
1	Please provide the ethics approval number corresponding to the original informed consent form or the signed informed consent form.		
2	Please explain whether this study exceeds the scope permitted by the original informed consent letter.		
3	Please explain whether the privacy and personal identity information of the subjects are protected.		
4	Please specify whether follow-up or obtaining information from the subjects again is needed in the future		
√ Research conducted using data or specimens obtained from previous clinical diagnosis and treatment, disease surveillance or clinical studies, and where potential subjects have not signed the informed consent form allowing such data or specimens to be used in other clinical studies (If not applicable, please skip).			
1	Please explain if the data or specimens used are obtained from previous clinical diagnosis and treatment, disease surveillance or clinical		

	research. (Yes)
2	Please specify whether to use data or specimens that the subjects explicitly refused to utilize. (No)
3	If informed consent is required as stipulated, the study cannot be conducted. (The subjects have the right to know that their data or specimens may be used for the study. Their refusal or non-consent to participate in the study is not evidence that the study cannot be carried out or that informed consent is waived).
4	Please explain whether the privacy and personal identity information of the subjects are protected. (Yes)
5	Whether follow-up is needed in the future or to obtain information from the subjects again. (No)

2. Application for exemption from signing of informed consent Form (Skip if not applicable)			
□The signed informed consent form poses an improper threat to the privacy of the subjects. The only record that links the true identity of the subjects and the research is the informed consent document. The main risk comes from the leakage of the subjects' identities or personal privacy， please explain.			
□In other cases, such as when conducting questionnaire surveys through email, wechat, DingTalk or phone calls, if written informed consent has been provided to the subjects or their guardians or oral informed consent has been obtained from them, please explain.			
Signature of the principal researcher		Date	