

Minimally invasive interventions for pulmonary nodule biopsy: A systematic review protocol.

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Protocol

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Abstract

Background Lung cancer is the leading cause of cancer-related deaths worldwide, causing more than 1.6 million deaths annually, including 26,500 deaths in Brazil in 2015. The diagnosis of lung cancer in the early stages remains a challenge. Imaging tests are important for diagnostic suspicion and risk evaluation, but biopsy is needed to confirm malignancy. Minimally invasive methods for biopsy used include computed tomography-guided percutaneous biopsy (CTGB) and bronchoscopy transbronchial biopsy. The method of choice should have the best accuracy and the lowest complication rate. This systematic review is designed to map, critically evaluate and compare the effects (benefits and risks) of all lung nodule biopsy techniques.

Methods We will conduct a systematic review according to the Cochrane Handbook for Systematic Reviews of Interventions recommendations.

Discussion This study aims to compare the diagnostic yield and the safety of different techniques used for pulmonary nodule biopsy. We will include randomized clinical trials comparing tomography-guided percutaneous biopsy, nonguided transbronchial biopsy, fluoroscopy-guided transbronchial biopsy, transbronchial biopsy guided by endobronchial ultrasound with a radial probe and transbronchial biopsy guided by electromagnetic navigation. This study was approved by the research ethics committee of Universidade Federal de São Paulo (UNIFESP) (number 1344040918). The results of the completed protocol will be presented at any appropriate conference by the authors.

Systematic review registration The protocol for this review was prospectively registered in the PROSPERO database (CRD42018092367).

Background

Lung cancer is the leading cause of cancer-related deaths in the world, causing more than 1.6 million deaths annually, including 26,500 in Brazil in 2015 [Hirsch 2017, INCA 2018, Snoeckx 2017]. If diagnosed at an early stage, when it is still a solitary pulmonary nodule, the 5-year survival rate of lung cancer may reach 80-90%, a high rate when compared to the 5-year overall survival rate of 4-17% [Hirsch 2017]. Hence, interest in screening, diagnosing and treating lung malignancies is growing.

The etiological diagnosis of pulmonary nodules remains a challenge. Imaging tests are important for diagnostic suspicion and risk estimation, but biopsy is necessary to confirm malignancy [Melo 2012, Snoeckx 2017]. There are protocols and algorithms to estimate the probability of malignancy of lung nodules, and the American College of Chest Physicians (ACCP) guidelines suggest performing biopsies when this probability is above 60% [Dale 2012, Ito 2018, Swensen 1997, Wang 2018].

Several approaches to acquire tissue from these nodules are available, ranging from open surgery by thoracotomy to newer, less invasive techniques. The method of choice should have the best accuracy with the lowest possible complication rate [Wang 2018].

The minimally invasive methods currently used include computed tomography-guided percutaneous biopsy (CTGB) and bronchoscopy transbronchial biopsy [Dale 2012, Ito 2018, Wang 2018]. CTGB has an accuracy of 90%, especially in peripheral nodules, but with an overall rate of complications of 38.8% and major complications, such as pneumothorax, hemoptysis and pulmonary hemorrhage, it may reach 5.7% [Fielding 2012, Steinfert 2011, Wen 2015, Heerink 2016]. Non-guided transbronchial biopsy has a low diagnostic accuracy for peripheral nodules, which is approximately 34% for nodules smaller than 2 cm [Swensen 1997, Wen 2015]. To improve these rates, different methods have been developed to guide transbronchial biopsies: fluoroscopy (FGTB), endobronchial ultrasound with a radial probe (R-EBUSTB) and electromagnetic navigation (NBTB). [Dale 2012, Fielding 2012, Shankar 1998, Steinfert 2011, Wang 2018].

Rather than having good accuracy, it is expected that a suitable technique for pulmonary nodule biopsy should have a good diagnostic yield and acceptable safety. This systematic review was designed to map, critically evaluate and compare the effects (benefits and risks) of all lung nodule biopsy techniques.

Objectives

To compare the diagnostic yield and the safety of different techniques used for pulmonary nodule biopsy.

Methods

Venue

Evidence-Based Health Program e Discipline of Evidence-Based Medicine, Escola Paulista de Medicina (EPM), Universidade Federal de São Paulo (UNIFESP), São Paulo, Brazil.

Study Design

We will conduct a systematic review according to the Cochrane Handbook for Systematic Reviews of Interventions recommendations [Higgins 2011]. The protocol for this review was prospectively registered in the PROSPERO database (CRD42018092367, available from https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=92367). We developed this study in accordance with the recommendations of the PRISMA-P Statement [Moher 2015].

Criteria for Study Inclusion

- **Study Types**

Randomized clinical trials with parallel design, including those of the cluster type.

- **Types of participants**

Adults with malignancy-suspected peripheral pulmonary nodules, defined as pulmonary nodules between 8 mm and 30 mm, with characteristics such as spiculation, pleural retraction, notch sign, growing size and complex features. [Snoeckx 2017] It is important to mention that nodules with other characteristics but considered malignancy-suspected by the authors could be included as well.

- **Types of intervention:**

- Computed tomography-guided percutaneous biopsy.
- Fluoroscopy-guided transbronchial biopsy.
- Transbronchial biopsy guided by endobronchial ultrasound with a radial probe.
- Transbronchial biopsy guided by electromagnetic navigation.

Studies comparing different sizes of bronchoscopes or studies comparing different nodule localization techniques will not be considered.

- **Comparison**

All methods will be compared with each other; however, the main comparison will be between CTGB and bronchoscopic methods. Studies involving the combination of these diagnostic methods will not be considered.

Outcomes

- **Primary:**

- Diagnostic yield, measured as the proportion of biopsies in which it was possible to define the histological diagnosis of the pulmonary nodule.
- Major adverse events including procedure complications such as pneumothorax complications (symptomatic and/or requiring drainage), hemothorax complications (symptomatic and/or requiring drainage), and death.
- Need of approach by another technique.

- **Secondary:**

- Nonserious adverse events, including pain (frequency and intensity).
- Time of procedure.

We will consider any time point reported in the included studies. However, we plan to pool only similar time points: short-term period (up to six months) or long-term period (more than six months). Whenever a study reports outcomes at multiple time points within the same period (as listed above), we will use the last measurement.

We will consider studies regardless of whether they report an outcome of interest for this review. In this case, we will contact the authors to confirm whether at least one of the outcomes planned in the

systematic review was assessed (but not reported until the date).

Searching for studies

- **Electronic search**

We will carry out comprehensive searches in the following electronic databases: CENTRAL (Cochrane Controlled Register of Trials, via Wiley), EMBASE (Excerpta Medica database, via Elsevier), and MEDLINE (Medical Literature Analysis and Retrieval System Online, via PubMed). All databases will be searched from inception to the date of the search, with no restrictions on language or publication status. The search strategy for MEDLINE is detailed in **Table 1**. For other electronic databases, we will develop search strategies based on the search strategy for MEDLINE by making adjustments in accordance with the syntax and controlled vocabulary, both specific for each database.

We will look for ongoing trials in ClinicalTrials.gov (www.clinicaltrials.gov) and the World Health Organization (WHO) International Clinical Trials Registry Platform (WHO-ICTRO, apps.who.int/trialsearch). Additionally, we will search the gray literature on Open Grey (<http://www.opengrey.eu/>).

- **Hand search**

We will scrutinize the reference lists of the included studies and of narrative reviews to identify additional studies. We will contact experts in the area, requesting information about ongoing or unpublished trials.

Study selection

First, we will select studies based on the titles and abstracts of the retrieved records. Second, we will assess the full-texts of eligible studies and then classify them as included or excluded. The entire selection process will be conducted independently by two authors. Any disagreements between them will be resolved by a third author. The selection process will be performed through the **rayyan** platform (<http://rayyan.qcri.org>) [Ouzzanni 2016]. The full process of selection will be detailed in a PRISMA flow diagram.

Data extraction and management

Data will be extracted and combined in a standard form. Data extraction will be performed independently by two authors. Any disagreements will be resolved by a third author. The following data will be considered: study design, follow-up, number of study centers, setting, date of study (start-end), sample size, mean age and sex of the participants, nodule characteristics, interventions, comparison, primary and secondary outcomes reported, time point measures, funding sources and conflicts of interest.

Assessment of the risk of bias of the included studies

We will evaluate the risk of bias with the use of the Cochrane Risk of Bias (RoB) table [Higgins 2011]. Two authors will independently apply the seven domains of the RoB table: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective reporting of outcomes, and other potential sources of bias. For the blinding of participants and personnel, blinding of outcome assessors and incomplete outcome data domains, we will perform the assessment at the outcome level. We will present the reasons for each judgment.

Heterogeneity assessment

First, we will assess the heterogeneity based on the clinical and methodological diversity of the included studies. Clinical diversity will be assessed by comparing the PICO elements of the included studies. Inconsistencies (statistical heterogeneity) will be evaluated by the Chi² test ($p < 0.1$ as indicative of statistical heterogeneity), and the extent of the inconsistencies will be evaluated by the I² test ($I^2 > 50$ as indicative of significant inconsistency) [Higgins 2011]. Whenever possible, we will investigate the reasons for heterogeneity by additional analysis.

Measuring the treatment effect and data synthesis

When two or more trials assessing the same outcome exist and are homogeneous, we will perform quantitative synthesis. We will estimate treatment effects with a 95% confidence interval, calculating the risk ratio (RR) for dichotomous outcomes and the mean difference (MD) for continuous outcomes. We will summarize the data using random effects model meta-analysis in Review Manager 5.3 software [Higgins 2011]. When quantitative synthesis is not possible due to clinical and/or methodological diversity, we will present the results through a narrative approach.

Additional analysis

We plan to perform subgroup analysis for all primary outcomes considering the anatomic region of nodules (central or peripheral), since we expect different diagnostic yields for each technique; bronchoscopic methods tend to have better results for central lesions, and the transthoracic approach tends to show better yields in peripheral lesions. We also plan to carry out sensitivity analyses by excluding studies with an unclear or high risk of bias for at least one domain of the RoB Table.

Publication bias

We plan to investigate publication bias by the use of funnel plots if 10 or more studies are pooled into a meta-analysis [Higgins 2011].

Certainty of the body of evidence

To evaluate the certainty of the body of evidence, we will use the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach, which comprises five criteria: risk of bias,

inconsistency, imprecision, indirectness and publication bias [Guyatt 2011]. We will develop a summary of findings (SoF) table in GRADEpro GDT considering all outcomes for each pairwise comparison. We will report reasons to downgrade the evidence for each outcome.

Protocol Amendments

Our group recognizes the importance of documenting protocol amendments. Any relevant change in the protocol will be registered and described in the final review article.

Discussion

The importance of this article is to evaluate and compare minimally invasive lung nodule biopsy methods. Many resources have been spent on developing new technologies to bring more security and accuracy to invasive procedures, but the differences in the results of existing methods are questionable [Dale 2012]. This protocol is the initial step in a systematic review to evaluate such differences and compare methods in an effort to understand the best method (percutaneous or bronchoscopic) for peripheral pulmonary nodule biopsy.

One of the difficulties of the study is the comparison of different methods from heterogeneous studies. To address this issue, however, an assessment of heterogeneity will be performed seeking a correct comparison. Another point to consider is that this systematic review will not compare all interventions at the same time but will compare studies with approximately 2 or more methods at a time. Moreover, comparisons will not be made between combined methods; in other words, only patients undergoing one type of biopsy will be compared for one intervention at a time, which will bring greater clarity to the advantage of each method.

Declarations

Author Statement

Authors contributed for this study as the following:

AM: Development of the protocol, drafting the manuscript, search strategy. Main author and guarantor of the review.

JAJ: Development of the protocol, drafting the manuscript.

RLP: Development of the protocol, drafting the manuscript, search strategy.

COCL: Drafting the manuscript, search strategy.

RR: Development of the protocol, drafting the manuscript, search strategy.

Ethics approval and consent to participate

This study was approved by the research ethics committee of Universidade Federal de São Paulo (UNIFESP) with the number 1344040918. The results of the completed protocol will be presented at any appropriate conference by the authors.

This study will not involve the use of any animal or human data or tissue.

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Conflict of interest: None.

Data Statement

Technical appendix, statistical code, and dataset available from the Dryad repository, DOI:10.5061/dryad.t5b1s9d.

Abbreviations

ACCP American College of Chest Physicians

CENTRAL Cochrane Controlled Register of Trials

CTGB Tomography-guided percutaneous biopsy

EMBASE Excerpta Medica database

EPM Paulista Medicine School

FGTB Fluoroscopy-guided transbronchial biopsy

GRADE Grading of Recommendations, Assessment, Development and Evaluations

GRADEpro GDT GRADE software

INCA National Cancer Institute (Rio de Janeiro - Brazil)

MD Mean difference

MEDLINE Medical Literature Analysis and Retrieval System Online

NBTB Electromagnetic navigation transbronchial biopsy

PICO Patient, intervention, comparison, outcome

PRISMA-P Preferred Reporting Items of Systematic reviews and Meta-Analyses protocols

PROSPERO International prospective register of systematic reviews

R-EBUSTB Endobronchial ultrasound with radial probe transbronchial biopsy

RoB Cochrane Risk of Bias

RR Risk ratios

SP Sao Paulo (City in Brazil)

SoF Summary of Findings table

UNIFESP Federal University of Sao Paulo

WHO World Health Organization

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Table

Table 1. Search strategy for MEDLINE

Base	Search strategy
Medline via Pubmed	<p>#1 "Multiple Pulmonary Nodules"[Mesh] OR (Multiple Pulmonary Nodules) OR (Multiple Pulmonary Nodule) OR (Pulmonary Nodule, Multiple) OR (Pulmonary Nodules, Multiple) OR (Lung Nodules) OR (Lung Nodule)</p> <p>#2 "Solitary Pulmonary Nodule"[Mesh] OR (Solitary Pulmonary Nodule) OR (Pulmonary Nodule, Solitary) OR (Nodule, Solitary Pulmonary) OR (Solitary Pulmonary Nodules) OR (Nodules, Solitary Pulmonary) OR (Pulmonary Nodules, Solitary) OR (Pulmonary Coin Lesion) OR (Lesion, Pulmonary Coin) OR (Lesions, Pulmonary Coin) OR (Coin Lesions, Pulmonary) OR (Pulmonary Coin Lesions) OR (Coin Lesion, Pulmonary) OR (Pulmonary Nodules) OR (Pulmonary Nodule)</p> <p>#3 (Pulmonary lesion*) OR (Lung lesion*)</p> <p>#4 #1 OR #2 OR #3</p> <p>#5 "Biopsy"[Mesh] OR Biopsy OR Biopsies</p> <p>#6 #3 AND #4</p> <p>#7 ((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials as topic[MeSH Terms] OR clinical trial[Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading])</p> <p>#8 #6 AND #7</p>

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