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Annals of Medicine and Surgery

# Conformity of Fine Needle Aspiration Biopsy (FNAB) and Core Needle Biopsy (CNB) in Peripheral Lung Tumor Patients: A Cross-Sectional Study

--Manuscript Draft--

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| **Manuscript Number:** | AMSU-D-21-01394R1 |
| **Article Type:** | Cross-sectional Study |
| **Keywords:** | core needle biopsy; fine-needle aspiration biopsy; lung tumor |
| **Corresponding Author:** | Isnin Anang Marhana<br>Universitas Airlangga Fakultas Kedokteran<br>Surabaya, Jawa Timur INDONESIA |
| **First Author:** | Isnin Anang Marhana |
| **Order of Authors:** | Isnin Anang Marhana |
| | Kadek Widianiti |
| | Etty Hary Kusumastuti |
| **Abstract:** | Background: The problem of establishing lung tumor diagnostics is a challenge for clinicians, especially pulmonologists, in determining a definitive diagnosis of a lung tumor. Objective: Analyzing the conformity of anatomical pathology results between core needle biopsy (CNB) and fine-needle aspiration biopsy (FNAB) materials in peripheral lung tumors. Methods: A cross-sectional study was conducted from July 2019 to December 2020 with 66 participants. Participants were examined for CNB and FNAB, in which the results of these examinations were compared for conformity. Statistical analysis used the Kappa test with $p < 0.05$. Result: Most participants' tumor size was >70 mm, with FNAB results showing malignant category (39.5%), non-malignant (40.0%), and undiagnosed (38.9%; $p = 0.757$). Meanwhile, CNB examination showed a tumor size of >70 mm that was categorized into malignant (40.4%) and non-malignant (33.3%; $p = 0.510$). Most tumors were located in the right superior lobe that had FNAB results in the malignant (39.5%), non-malignant (30.0%) and undiagnosed (27.8%; $p = 0.306$) categories. The CNB examination also showed that most tumors were located in the right superior lobe, which had resulted in the category of malignant (34.4%), non-malignant (26.7%), and undiagnosed (75.0%; $p = 0.240$). Conformity of anatomical pathology results from FNAB and CNB subject such as malignancy category of 35 participants (74.5%), non-malignancy of 7 participants (53.8%) and undiagnosed of 4 participants (16.7%) with an accuracy of 69.69% ($K = 0.43$; $p = 0.001$). Conclusion: There is a conformity between the anatomical pathology results from FNAB and CNB materials for the diagnosis of lung tumors. CNB showed better results in the detection of anatomical malignancy and specimen adequacy. |
| **Suggested Reviewers:** | Emanuela Capalbo<br>emanuelacapalbo@tiscalinet.it |
| | Helmut Schoellnast<br>helmut.schoellnast@medunigraz.at |
| | M M Gomes<br>mgomes@toh.on.ca |
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| The authors declare that they have no conflict of interest. |

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| Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request. |

**Author contribution**

Please specify the contribution of each author to the paper, e.g. study concept or design, data collection, data analysis or interpretation, writing the paper, others, who have contributed in other ways should be listed as contributors.

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| All authors contributed toward data analysis, drafting and revising the paper, gave final approval of the version to be published and agree to be accountable for all aspects of the work. |

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Isnin Anang Marhana.

To,

Covering Letter

The Editor

Sub: Submission of Manuscript for publication

Dear sir,

We intend to publish an article entitled "**Conformity of Fine Needle Aspiration Biopsy (FNAB) and Core Needle Biopsy (CNB) in Peripheral Lung Tumor Patients: A Cross-Sectional Study**" in your esteemed journal as an Original Article.

On behalf of all the contributors I will act and guarantor and will correspond with the journal from this point onward.

In this paper, I/ww report on conformity of fine needle aspiration biopsy and core needle biopsy in lung cancer diagnosis. This is significant because as the number of lung cancer diagnosis is getting increase, we have to consider which tools that have the better diagnostic parameter. The paper should be of interest to readers in the areas of pulmonologist, pathology anatomy expert, and clinical oncology.

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

All authors have approved the manuscript and agree with its submission to Annals of Medicine and Surgery.

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Thanking you,

Yours' sincerely,

Isnin Anang Marhana
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Reviewer 2:

ABSTRACT AND RESULTS ARE CONFUSED. IT HAS TO BE CLEARLY SPECIFY THE LOCALIZATION OF THE LUNG TUMOR AND THE RESULTS FROM CNB AND FNAB ACCORDING TO THE TUMOR LOCALIZATION

**Author response:** we have revised it in our manuscript.

## Highlights

1. There is a conformity between the results of FNAB and CNB assisted by ultrasound.
2. FNAB and CNB results in lung cancer are similar >70%.
3. The use of FNAB followed by CNB minimizes misdiagnosis.

# Conformity of Fine Needle Aspiration Biopsy (FNAB) and Core Needle Biopsy (CNB)in Peripheral Lung Tumor Patients: A Cross-Sectional Study

Running head: FNAB and CNB in Lung Cancer

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# Conformity ~~Comparison~~ of ~~Core Needle Biopsy (CNB) and~~ Fine Needle Aspiration Biopsy (FNAB) and Core Needle Biopsy (CNB) in Peripheral Lung Tumor Patients: A Cross-Sectional Study

## Abstract

**Background:** The problem of establishing lung tumor diagnostics is a challenge for clinicians, especially pulmonologists, in determining a definitive diagnosis of a lung tumor. **Objective:** Analyzing the conformity of anatomical pathology results between core needle biopsy (CNB) and fine-needle aspiration biopsy (FNAB) materials in peripheral lung tumors. **Methods:** A cross-sectional study was conducted from July 2019 to December 2020 with 66 participants. Participants were examined for CNB and FNAB, in which the results of these examinations were compared for conformity. Statistical analysis used the Kappa test with $p$ <0.05. **Result:** Most participants' tumor size was >70 mm, with FNAB results showing malignant category (39.5%), non-malignant (40.0%), and undiagnosed (38.9%; $p$ = 0.757). Meanwhile, CNB examination showed a tumor size of >70 mm that was categorized into malignant (40.4%) and non-malignant (33.3%; $p$ = 0.510). Most tumors were located in the right superior lobe that had FNAB results in the malignant (39.5%), non-malignant (30.0%) and undiagnosed (27.8%; $p$ = 0.306) categories. The CNB examination also showed that most tumors were located in the right superior lobe, which had resulted in the category of malignant (34.4%), non-malignant (26.7%), and undiagnosed (75.0%; $p$ = 0.240). Conformity~~comparison~~ of anatomical pathology results from FNAB and CNB subject~~material~~ such as ~~for~~ malignancy category ~~as many as~~of 35 participants (74.5%), non-malignancy of 7 participants (53.8%) and undiagnosed ~~as many as~~of 4 participants (16.7%) with an accuracy of 69.69% ($K$ = 0.43; $p$ = 0.001~~–~~). **Conclusion:** There is a conformity between the anatomical pathology results from FNAB and CNB materials for the diagnosis of

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lung tumors. CNB showed better results in the detection of anatomical malignancy and specimen adequacy.

**Keywords:** core needle biopsy, fine-needle aspiration biopsy, lung tumor

## Introduction

The problem of establishing lung tumor diagnostics is a challenge for clinicians, especially pulmonologists, in determining the diagnosis of lung tumors. Generally, patients are admitted to hospitals with advanced stage and physical limitations to carry out invasive diagnostic procedures. Even though the patient is willing to undergo a diagnostic procedure, there are limited diagnostic specimens for lung tumor material. Diagnostic modalities of peripheral lung lesions include traditional and advanced techniques. Traditional diagnostic techniques consist of percutaneous biopsy with transthoracic needle aspiration (TTNA) known as fine-needle aspiration biopsy (FNAB) and bronchoscopy, while advanced techniques include endobronchial ultrasound (EBUS) and electromagnetic navigation bronchoscopy (ENB) [1].

Fine needle aspiration biopsy is recognized as an initial diagnostic tool for all body lesions, whether suspected to be benign or malignant. In some cases, there are limitations and shortcomings where the cytological sample of FNAB material is not sufficient to determine lung tumor diagnosis. Therefore, the patient must undergo other diagnostic procedures by performing a repeat biopsy procedure using a larger needle (core needle biopsy-/-CNB) or an open biopsy [2]. This procedure does not rule out the possibility of causing the patient to become uncomfortable, prolonging the treatment period that leads to a higher cost of treatment [3, 4].

In several hospitals, concurrent FNAB and CNB procedures have been applied and show several advantages when these biopsies are combined at one time, which includes: (a)

time efficiency since patients come in one visit and receive both procedures; (b) the specimens obtained by both procedures are more adequate, representative and complementary to enable the anatomical pathologist to obtain an accurate diagnosis; (c) cost-effective since it is expected to eliminate second diagnostic procedure that is potentially more invasive [4, 5].

A thoracic ultrasonography (USG)-guided biopsy facilitates the process of determining the area of peripheral thoracic lesions, thereby increasing the success of sampling required for diagnosis [6]. Based on the description above, we are interested in analyzing the comparison between CNB and FNAB results with the help of thoracic ultrasound in peripheral lung tumors.

## Methods and Materials

### Participants

Participants in this study were lung tumor patients who met the inclusion and exclusion criteria. Participants included in this study were patients with peripheral lung tumors based on chest X-ray, ultrasound, and CT scan [7-9] and those who could perform a percutaneous biopsy using thoracic ultrasound guidance. Meanwhile, exclusion criteria were patients with a performance score of <50 or hemodynamically unstable, massive untreated pleural effusion, mediastinal tumor, central lung tumor, coexisting lung disease conditions, impaired hemostatic function, and anatomical pathology results from either biopsy or FNAB or CNB that didn't come out.

### Ethical Approval

This research has been submitted for ethical approval with registration research based on the Declaration of Helsinki at the Health Research Ethics Committee in the Hospital. All participants first filled out the informed consent form before the research was carried out.

**Study Design**

A cross-sectional study was carried out at Hospital, from September 2019 to December 2020. The number of participants in this study was 66 participants with consecutive sampling. This study compared the results of sampling using FNAB and CNB techniques assisted by ultrasound. This research report used Strengthening the Reporting of Cohort Studies in Surgery (STROCSS) 2021~~9~~ guidelines ~~[~~10, 11] [10].

**Fine Needle Aspiration Biopsy Procedure**

Fine needle aspiration biopsy is a diagnostic procedure in the form of a percutaneous biopsy of the thoracic region using a 25-gauge fine needle. The FNAB sampling technique is to lay the patient on the operating table, determine the biopsy site, disinfect the skin in the biopsy area with 10% povidone-iodine followed by 70% alcohol, install a sterile drape, perform 2% lidocaine infiltration (1-2 cc) at the biopsy site, intracutaneously, subcutaneously until it reaches the parietal pleura, perform a vertical spinal needle puncture until it reaches the lesion. The stylet is taken, the needle is connected to a 20 cc syringe, the suction is pulled firmly, the needle is moved up and down along 0.5-1 cm several times. The suction is slowly returned to its original position, the needle is removed. The aspirated biopsy material is removed onto a slide, a flat smear is made immediately, fixed, and then dried. If necessary, this procedure can be repeated a second or third time according to the initial assessment by an anatomical pathologist in assessing the adequacy of the specimen [8, 9, 11].

**Core Needle Biopsy Procedure**

Core needle biopsy is a diagnostic procedure in the form of a percutaneous biopsy of the thoracic region using a 14-gauge core needle with the tip of the needle functioning as a cutter. The CNB sampling technique is carried out by inserting the core needle at the same location at the previous FNAB needlepoint until it reaches the lesion according to the depth of the thoracic ultrasound. Biopsy material that has been cut through the core is removed onto a slide, immediately a flat smear is made, fixed, and then dried. If necessary, this procedure can be repeated a second or third time according to the initial assessment by the anatomical pathologist in assessing the adequacy of the specimen. Post-biopsy observations are conducted for inpatients while in the room. For outpatients, observation is carried out for 2 hours in the operating room, if there are no complications, the participant is allowed to go home with advice to return immediately if symptoms of shortness of breath or coughing up blood are found [12, 13].

**Statistical analysis**

The measured data were analyzed by univariate and bivariate analysis, in which univariate data was displayed in the form of a frequency distribution or mean ± standard deviation (SD). Measurement data were analyzed using IBM SPSS Statistics software version 21.0 (IBM Corp., Armonk, NY, USA). Statistical analysis in this study used the Kruskal Wallis, Fisher Exact, and Kappa test with $p < 0.05$ was considered significant.

**Results**

**Characteristics of Participants**

Most participants were male (81.8%), aged >50 years (77.3%), with most respiratory symptoms being chronic cough (63.6%). Most tumors were located in the right lung (62.1%)

and most were in the right superior lobe (34.8%). Most participants had a needle inserted in the anterior (66.7%). Most tumors sized >70 mm as much as 39.4%, and the majority of participants did not experience post-FNAB and CNB complications (95.5%; Table 1).

Most participants had two punctures in each technique (FNAB = 93.9% and~~,~~ CNB = 63.6%). In both groups, the results of anatomical malignancy were found, ~~in~~ which FNAB ~~was~~ of 57.6% and CNB ~~was~~ of 71.2%. Materials in both groups were declared adequate, ~~where~~ which FNAB ~~was~~ of 72.7% and CNB ~~was~~ of 89.4% (Table 2).

**Correlation between Tumor Size, Age, and Number of Punctures with Post-FNAB and CNB Complications**

Most participants had tumor size >70 mm in diameter, 23 participants (36.5%) had no complications, but 3.8% had hemoptysis and 7.7% had pneumothorax ($p$ = 0.857). Most uncomplicated participants were aged >50 years as much as 96%, but there were still participants who had hemoptysis (2%) and pneumothorax (2%) who were also >50 years old ($p$ = 0.198). Most FNAB participants did not experience complications on 2 punctures as much as 95.2% ($p$ = 1.000) and CNB participants did not experience complications on more than 2 punctures as much as 87.5%, but there were still occurrences of pneumothorax and hemoptysis on more than 2 punctures ($p$ = 0.040; Table 3).

**Correlation between Lung Tumor Size and Location with FNAB and CNB on Anatomic Pathology Findings**

Most participants' tumor size was >70 mm which had FNAB results in the malignant category (39.5%), non-malignant (40.0%), and undiagnosed (38.9%) with $p$ ~~-value~~ = 0.757. Meanwhile, the results of CNB categories were malignant (40.4%), non-malignant (33.3%) and undiagnosed (7.6%) with $p$ ~~-value~~ = 0.510. Most tumors were located in the right superior

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lobe, which ith FNAB results in thewere malignant (39.5%), non-malignant (30.0%) and undiagnosed (27.8%) categories with; *p* value = 0.306). Meanwhile, in CNB, most tumors were located in the right superior lobe, with CNB results were in the category of malignant (34.4%), non-malignant (26.7%), and undiagnosed (75.0%; ) with *p* value = 0.240). The level of conformity (not a comparative study but a conformity test) level of anatomical pathology results from FNAB and CNB material subject werefor the malignant category was of 35 participants (92.1%), non-malignancy was of 7 participants (70%) and undiagnosed were of 4 participants (11.2%;) with *K* = 0.43; *p* = 0.001; (Table 4). The accuracy value of the suitability of the results of anatomical pathology of the two techniques was 69.69%.

**Discussion**

Several factors can increase the diagnostic value of transthoracic biopsy and prove the safety of thoracic ultrasound in guiding CNB in peripheral lung tumors, chest wall tumors, anterior mediastinal lesions. The size of the lesion does not appear to affect the diagnostic accuracy with thoracic ultrasound as a guide, but it is reported that the diagnostic rate is decreased in lesions located close to the ribs and influenced by the patient's respiratory movement and there are no serious complications from the procedure [14].

Core needle biopsy is significantly higher adequate material preparation than FNAB. Adequate material from the FNAB is found to correlate with tumor size. The addition of the number of needles passed in the FNAB technique is reported to increase the material to be more adequate. The operator's experience in the univariate analysis is reported to play a role in providing adequate material. FNAB specimens at a lesion size of 35 mm are reported to be adequate to obtain specimens to be used for further molecular testing. On the other hand, direct assessment by an on-site anatomic pathologist may be the best way to ensure sample adequacy [15].

The diagnostic accuracy of transthoracic biopsy material is significantly affected by the lesion size. Accuracy will decrease in lesions smaller than 20 mm and accuracy will increase in lesions measuring 50 mm. The larger the lesion, the greater the chance that the tissue or tumor cells will undergo necrosis, so that the more likely the specimen is inadequate to make a definitive diagnosis. Thoracic ultrasound cannot identify the incidence of necrosis of a tumor lesion, so the strategy in sampling large lesions is to target the biopsy area at the periphery to avoid the central area of lung mass which has a high probability of necrosis area. The rates of necrosis in lesions measuring 20 mm, 21-49 mm, and 50 mm were 3.9%, 11.7%, and 28.8%, respectively [16].

The diagnostic accuracy of transthoracic biopsy decreases with lung tumor size. If the lesion is small, it may move during the respiratory phase so that the needle falls to accurately target the lesion throughout the patient's respiratory cycle. [8, 15, 17]. The location and size of the tumor lesion will affect FNAB accuracy. A good location for the FNAB technique is when the tumor lesion is located in the periphery with large size. Lung tumor located in the superior lobe is more easily accessible by the biopsy needle with a straight needle angle, as this position makes it easier for the needle to collect material without changing the pleural space [18]. The location of the mass attached to the pleura will also cause less movement during respiration to increase accuracy [18, 19].

This study found no correlation between age, lesion size, and the number of FNAB needle passes on the incidence of complications. A study conducted by Capalbo reported age as a factor that affects complications, with the incidence of pneumothorax due to CNB reported to be the majority in young patients, parenchymal bleeding in the elderly, and complications occurring more in the right lung. Fifty percent of pneumothorax cases occur in the superior lobe of the lung on the CNB technique, 40% of parenchymal hemorrhages in the inferior lobe on FNAB. In terms of size, the CNB technique is more complicated than the

FNAB in lesions sized less than 3.5 cm. However, unlike our research, Capalbo's study was not performed at the same time as a biopsy so there was no detail provided regarding the incidence of complications of each technique. Parameters associated with complications were needle access, lesion size, age, needle diameter, and the number of needle passes. Concerning age, pulmonary parenchymal bleeding and hemoptysis complications occur more frequently in the elderly who undergo CNB, possibly because they usually use anticoagulant therapy due to comorbid disease. There was no significant correlation between the number of needles passed with complications and diagnostic accuracy because the average success with only 1 pass, in contrast to other studies that reported pneumothorax will occur more often in those who undergo many needles passes because this can cause a lot of trauma to the pleura or so that coaxial needle is needed in the future [13].

## Conclusion

There is no correlation between lung tumor size and anatomic pathology findings in each biopsy technique. There is no correlation between lung tumor location and anatomic pathology findings in each biopsy technique. There is no correlation between tumor size, age, and the number of FNAB needle passes with the incidence of each complication. There appears to be a significant correlation between more than two CNB needle passes and the incidence of complications. CNB can detect anatomical malignancy and specimen adequacy better than FNAB.

## Provenance and peer review

Not commissioned, externally peer-reviewed.

## Conflict of interest

The authors declare that they have no conflict of interest.

**Acknowledgment**

We would like to thank our editor "Fis Citra Ariyanto".

**Funding**

None.

**Registration of research studies**

Name of the registry: Health Research Ethics Committee in the Dr. Soetomo General Academic Hospital, Surabaya, Indonesia.

Unique identifying number or registration ID: 1575/KEPK/X/2019.

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**Guarantor**

Anang Isnin Marhana.

**Author contributor**

All authors contributed toward data analysis, drafting and revising the paper, gave final approval of the version to be published and agree to be accountable for all aspects of the work.

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# Conformity of Fine Needle Aspiration Biopsy (FNAB) and Core Needle Biopsy (CNB) in Peripheral Lung Tumor Patients: A Cross-Sectional Study


## Abstract

**Background:** The problem of establishing lung tumor diagnostics is a challenge for clinicians, especially pulmonologists, in determining a definitive diagnosis of a lung tumor. **Objective:** Analyzing the conformity of anatomical pathology results between core needle biopsy (CNB) and fine-needle aspiration biopsy (FNAB) materials in peripheral lung tumors. **Methods:** A cross-sectional study was conducted from July 2019 to December 2020 with 66 participants. Participants were examined for CNB and FNAB, in which the results of these examinations were compared for conformity. Statistical analysis used the Kappa test with $p$ <0.05. **Result:** Most participants' tumor size was >70 mm, with FNAB results showing malignant category (39.5%), non-malignant (40.0%), and undiagnosed (38.9%; $p$ = 0.757). Meanwhile, CNB examination showed a tumor size of >70 mm that was categorized into malignant (40.4%) and non-malignant (33.3%; $p$ = 0.510). Most tumors were located in the right superior lobe that had FNAB results in the malignant (39.5%), non-malignant (30.0%) and undiagnosed (27.8%; $p$ = 0.306) categories. The CNB examination also showed that most tumors were located in the right superior lobe, which had resulted in the category of malignant (34.4%), non-malignant (26.7%), and undiagnosed (75.0%; $p$ = 0.240). Conformity of anatomical pathology results from FNAB and CNB subject such as malignancy category of 35 participants (74.5%), non-malignancy of 7 participants (53.8%) and undiagnosed of 4 participants (16.7%) with an accuracy of 69.69% ($K$ = 0.43; $p$ = 0.001). **Conclusion:** There is a conformity between the anatomical pathology results from FNAB and CNB materials for the diagnosis of lung tumors. CNB showed better results in the detection of anatomical malignancy and specimen adequacy.

**Keywords:** core needle biopsy, fine-needle aspiration biopsy, lung tumor

## Introduction

The problem of establishing lung tumor diagnostics is a challenge for clinicians, especially pulmonologists, in determining the diagnosis of lung tumors. Generally, patients are admitted to hospitals with advanced stage and physical limitations to carry out invasive diagnostic procedures. Even though the patient is willing to undergo a diagnostic procedure, there are limited diagnostic specimens for lung tumor material. Diagnostic modalities of peripheral lung lesions include traditional and advanced techniques. Traditional diagnostic techniques consist of percutaneous biopsy with transthoracic needle aspiration (TTNA) known as fine-needle aspiration biopsy (FNAB) and bronchoscopy, while advanced techniques include endobronchial ultrasound (EBUS) and electromagnetic navigation bronchoscopy (ENB) [1].

Fine needle aspiration biopsy is recognized as an initial diagnostic tool for all body lesions, whether suspected to be benign or malignant. In some cases, there are limitations and shortcomings where the cytological sample of FNAB material is not sufficient to determine lung tumor diagnosis. Therefore, the patient must undergo other diagnostic procedures by performing a repeat biopsy procedure using a larger needle (core needle biopsy/CNB) or an open biopsy [2]. This procedure does not rule out the possibility of causing the patient to become uncomfortable, prolonging the treatment period that leads to a higher cost of treatment [3, 4].

In several hospitals, concurrent FNAB and CNB procedures have been applied and show several advantages when these biopsies are combined at one time, which includes: (a) time efficiency since patients come in one visit and receive both procedures; (b) the specimens obtained by both procedures are more adequate, representative and

complementary to enable the anatomical pathologist to obtain an accurate diagnosis; (c) cost-effective since it is expected to eliminate second diagnostic procedure that is potentially more invasive [4, 5].

A thoracic ultrasonography (USG)-guided biopsy facilitates the process of determining the area of peripheral thoracic lesions, thereby increasing the success of sampling required for diagnosis [6]. Based on the description above, we are interested in analyzing the comparison between CNB and FNAB results with the help of thoracic ultrasound in peripheral lung tumors.

## Methods and Materials

### Participants

Participants in this study were lung tumor patients who met the inclusion and exclusion criteria. Participants included in this study were patients with peripheral lung tumors based on chest X-ray, ultrasound, and CT scan [7-9] and those who could perform a percutaneous biopsy using thoracic ultrasound guidance. Meanwhile, exclusion criteria were patients with a performance score of <50 or hemodynamically unstable, massive untreated pleural effusion, mediastinal tumor, central lung tumor, coexisting lung disease conditions, impaired hemostatic function, and anatomical pathology results from either biopsy or FNAB or CNB that didn't come out.

### Ethical Approval

This research has been submitted for ethical approval with registration research based on the Declaration of Helsinki at the Health Research Ethics Committee in the Hospital. All participants first filled out the informed consent form before the research was carried out.

## Study Design

A cross-sectional study was carried out at Hospital, from September 2019 to December 2020. The number of participants in this study was 66 participants with consecutive sampling. This study compared the results of sampling using FNAB and CNB techniques assisted by ultrasound. This research report used Strengthening the Reporting of Cohort Studies in Surgery (STROCSS) 2021 guidelines [10].

## Fine Needle Aspiration Biopsy Procedure

Fine needle aspiration biopsy is a diagnostic procedure in the form of a percutaneous biopsy of the thoracic region using a 25-gauge fine needle. The FNAB sampling technique is to lay the patient on the operating table, determine the biopsy site, disinfect the skin in the biopsy area with 10% povidone-iodine followed by 70% alcohol, install a sterile drape, perform 2% lidocaine infiltration (1-2 cc) at the biopsy site, intracutaneously, subcutaneously until it reaches the parietal pleura, perform a vertical spinal needle puncture until it reaches the lesion. The stylet is taken, the needle is connected to a 20 cc syringe, the suction is pulled firmly, the needle is moved up and down along 0.5-1 cm several times. The suction is slowly returned to its original position, the needle is removed. The aspirated biopsy material is removed onto a slide, a flat smear is made immediately, fixed, and then dried. If necessary, this procedure can be repeated a second or third time according to the initial assessment by an anatomical pathologist in assessing the adequacy of the specimen [8, 9, 11].

## Core Needle Biopsy Procedure

Core needle biopsy is a diagnostic procedure in the form of a percutaneous biopsy of the thoracic region using a 14-gauge core needle with the tip of the needle functioning as a cutter. The CNB sampling technique is carried out by inserting the core needle at the same location

at the previous FNAB needlepoint until it reaches the lesion according to the depth of the thoracic ultrasound. Biopsy material that has been cut through the core is removed onto a slide, immediately a flat smear is made, fixed, and then dried. If necessary, this procedure can be repeated a second or third time according to the initial assessment by the anatomical pathologist in assessing the adequacy of the specimen. Post-biopsy observations are conducted for inpatients while in the room. For outpatients, observation is carried out for 2 hours in the operating room, if there are no complications, the participant is allowed to go home with advice to return immediately if symptoms of shortness of breath or coughing up blood are found [12, 13].

**Statistical analysis**

The measured data were analyzed by univariate and bivariate analysis, in which univariate data was displayed in the form of a frequency distribution or mean ± standard deviation (SD). Measurement data were analyzed using IBM SPSS Statistics software version 21.0 (IBM Corp., Armonk, NY, USA). Statistical analysis in this study used the Kruskal Wallis, Fisher Exact, and Kappa test with $p < 0.05$ was considered significant.

## Results

**Characteristics of Participants**

Most participants were male (81.8%), aged >50 years (77.3%), with most respiratory symptoms being chronic cough (63.6%). Most tumors were located in the right lung (62.1%) and most were in the right superior lobe (34.8%). Most participants had a needle inserted in the anterior (66.7%). Most tumors sized >70 mm as much as 39.4%, and the majority of participants did not experience post-FNAB and CNB complications (95.5%; Table 1).

Most participants had two punctures in each technique (FNAB = 93.9% and CNB = 63.6%). In both groups, the results of anatomical malignancy were found, which FNAB of 57.6% and CNB of 71.2%. Materials in both groups were declared adequate, which FNAB of 72.7% and CNB of 89.4% (Table 2).

**Correlation between Tumor Size, Age, and Number of Punctures with Post-FNAB and CNB Complications**

Most participants had tumor size >70 mm in diameter, 23 participants (36.5%) had no complications, but 3.8% had hemoptysis and 7.7% had pneumothorax ($p$ = 0.857). Most uncomplicated participants were aged >50 years as much as 96%, but there were still participants who had hemoptysis (2%) and pneumothorax (2%) who were also >50 years old ($p$ = 0.198). Most FNAB participants did not experience complications on 2 punctures as much as 95.2% ($p$ = 1.000) and CNB participants did not experience complications on more than 2 punctures as much as 87.5%, but there were still occurrences of pneumothorax and hemoptysis on more than 2 punctures ($p$ = 0.040; Table 3).

**Correlation between Lung Tumor Size and Location with FNAB and CNB on Anatomic Pathology Findings**

Most participants' tumor size was >70 mm which had FNAB results in the malignant category (39.5%), non-malignant (40.0%), and undiagnosed (38.9%) with $p$ = 0.757. Meanwhile, the results of CNB categories were malignant (40.4%), non-malignant (33.3%) and undiagnosed (7.6%) with $p$ = 0.510. Most tumors were located in the right superior lobe, which FNAB results were malignant (39.5%), non-malignant (30.0%) and undiagnosed (27.8%; $p$ = 0.306). Meanwhile, CNB results were malignant (34.4%), non-malignant (26.7%), and undiagnosed (75.0%; $p$ = 0.240). The conformity level of anatomical pathology

results from FNAB and CNB subject were malignant category of 35 participants (92.1%), non-malignancy of 7 participants (70%) and undiagnosed of 4 participants (11.2%; $K = 0.43$; $p = 0.001$; Table 4). The accuracy value of the suitability of the results of anatomical pathology of the two techniques was 69.69%.

## Discussion

Several factors can increase the diagnostic value of transthoracic biopsy and prove the safety of thoracic ultrasound in guiding CNB in peripheral lung tumors, chest wall tumors, anterior mediastinal lesions. The size of the lesion does not appear to affect the diagnostic accuracy with thoracic ultrasound as a guide, but it is reported that the diagnostic rate is decreased in lesions located close to the ribs and influenced by the patient's respiratory movement and there are no serious complications from the procedure [14].

Core needle biopsy is significantly higher adequate material preparation than FNAB. Adequate material from the FNAB is found to correlate with tumor size. The addition of the number of needles passed in the FNAB technique is reported to increase the material to be more adequate. The operator's experience in the univariate analysis is reported to play a role in providing adequate material. FNAB specimens at a lesion size of 35 mm are reported to be adequate to obtain specimens to be used for further molecular testing. On the other hand, direct assessment by an on-site anatomic pathologist may be the best way to ensure sample adequacy [15].

The diagnostic accuracy of transthoracic biopsy material is significantly affected by the lesion size. Accuracy will decrease in lesions smaller than 20 mm and accuracy will increase in lesions measuring 50 mm. The larger the lesion, the greater the chance that the tissue or tumor cells will undergo necrosis, so that the more likely the specimen is inadequate to make a definitive diagnosis. Thoracic ultrasound cannot identify the incidence of necrosis of a

tumor lesion, so the strategy in sampling large lesions is to target the biopsy area at the periphery to avoid the central area of lung mass which has a high probability of necrosis area. The rates of necrosis in lesions measuring 20 mm, 21-49 mm, and 50 mm were 3.9%, 11.7%, and 28.8%, respectively [16].

The diagnostic accuracy of transthoracic biopsy decreases with lung tumor size. If the lesion is small, it may move during the respiratory phase so that the needle falls to accurately target the lesion throughout the patient's respiratory cycle. [8, 15, 17]. The location and size of the tumor lesion will affect FNAB accuracy. A good location for the FNAB technique is when the tumor lesion is located in the periphery with large size. Lung tumor located in the superior lobe is more easily accessible by the biopsy needle with a straight needle angle, as this position makes it easier for the needle to collect material without changing the pleural space [18]. The location of the mass attached to the pleura will also cause less movement during respiration to increase accuracy [18, 19].

This study found no correlation between age, lesion size, and the number of FNAB needle passes on the incidence of complications. A study conducted by Capalbo reported age as a factor that affects complications, with the incidence of pneumothorax due to CNB reported to be the majority in young patients, parenchymal bleeding in the elderly, and complications occurring more in the right lung. Fifty percent of pneumothorax cases occur in the superior lobe of the lung on the CNB technique, 40% of parenchymal hemorrhages in the inferior lobe on FNAB. In terms of size, the CNB technique is more complicated than the FNAB in lesions sized less than 3.5 cm. However, unlike our research, Capalbo's study was not performed at the same time as a biopsy so there was no detail provided regarding the incidence of complications of each technique. Parameters associated with complications were needle access, lesion size, age, needle diameter, and the number of needle passes. Concerning age, pulmonary parenchymal bleeding and hemoptysis complications occur more frequently

in the elderly who undergo CNB, possibly because they usually use anticoagulant therapy due to comorbid disease. There was no significant correlation between the number of needles passed with complications and diagnostic accuracy because the average success with only 1 pass, in contrast to other studies that reported pneumothorax will occur more often in those who undergo many needles passes because this can cause a lot of trauma to the pleura or so that coaxial needle is needed in the future [13].

## Conclusion

There is no correlation between lung tumor size and anatomic pathology findings in each biopsy technique. There is no correlation between lung tumor location and anatomic pathology findings in each biopsy technique. There is no correlation between tumor size, age, and the number of FNAB needle passes with the incidence of each complication. There appears to be a significant correlation between more than two CNB needle passes and the incidence of complications. CNB can detect anatomical malignancy and specimen adequacy better than FNAB.

## Provenance and peer review

Not commissioned, externally peer-reviewed.

## Conflict of interest

The authors declare that they have no conflict of interest.

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**Registration of research studies**

Name of the registry: Health Research Ethics Committee in the Dr. Soetomo General Academic Hospital, Surabaya, Indonesia.

Unique identifying number or registration ID: 1575/KEPK/X/2019.

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**Guarantor**

Anang Isnin Marhana.

**Author contributor**

All authors contributed toward data analysis, drafting and revising the paper, gave final approval of the version to be published and agree to be accountable for all aspects of the work.

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## Table and Legend

Table 1. Characteristics of Participants

| Variables | n (%) |
|---|---|
| Sex | |
| Male | 54 (81.8) |
| Female | 12 (18.2) |
| Age | |
| 20-30 years old | 2 (3.0) |
| 31-40 years old | 2 (3.0) |
| 41-50 years old | 11 (16.7) |
| >51 years old | 51 (77.3) |
| Tumor Location | |
| Right lung | 41 (62.1) |
| Left lung | 25 (37.9) |
| Lung Lobe Location | |
| Right superior lobe | 23 (34.8) |
| Right middle lobe | 6 (9.1) |
| Right inferior lobe | 6 (9.1) |
| Left superior lobe | 20 (30.3) |
| Left inferior lobe | 2 (3.0) |
| > 1 right lobes | 5 (7.6) |
| > 1 left lobes | 4 (6.1) |
| Needle Access | |
| Anterior | 44 (66.7) |
| Posterior | 20 (30.3) |
| Lateral | 2 (3.0) |
| Tumor Size | |
| 21-30 mm | 2 (3.0) |
| 31-40 mm | 7 (10.6) |
| 41-50 mm | 1 (1.5) |
| 51-60 mm | 18 (27.3) |
| 61-70 mm | 12 (18.2) |
| >70 mm | 26 (39.4) |
| Complication | |
| Hemoptysis | 1 (1.5) |
| Pneumothorax | 2 (3.0) |
| None | 63 (95.5) |

Table 2. Characteristic Differences Between FNAB and CNB

| Variables | FNAB | CNB |
|---|---|---|
| Number of Punctures | | |
| 2 times | 62 (93.9) | 42 (63.6) |
| > 2 times | 4 (6.1) | 24 (36.4) |
| Findings | | |
| Malignant | 38 (57.6) | 47 (71.2) |
| Non-malignant | 10 (15.2) | 13 (19.7) |
| Undiagnosed | 18 (27.3) | 6 (9.1) |
| Anatomical Pathology Results | | |
| Malignant | | |

| | | |
|---|---|---|
| Squamous cell carcinoma | 5 (7.6) | 9 (13.6) |
| Adenocarcinoma | 19 (28.8) | 25 (37.9) |
| Small cell carcinoma | 0 (0.0) | 5 (7.6) |
| Atypical cells | 8 (12.1) | 1 (1.5) |
| Metastasis | 1 (1.5) | 5 (7.6) |
| Malignant round tumor cells | 5 (7.6) | 1 (1.5) |
| Non-malignant | | |
| Granulomatous inflammation | 1 (1.5) | 4 (6.1) |
| Non-specific chronic inflammation | 9 (13.6) | 9 (13.6) |
| Undiagnosed | 18 (27.3) | 7 (10.6) |
| Not representative/necrosis | | |
| Material Adequacy | | |
| Adequate material | 48 (72.7) | 59 (89.4) |
| Inadequate material | 18 (27.3) | 7 (10.6) |

Table 3. Complications of Patients with FNAB and CNB

| Variables | Complications | | | *p* |
|---|---|---|---|---|
| | Hemoptysis | Pneumothorax | None | |
| Tumor size | | | | |
| 21-30 mm | 0 (0.0) | 0 (0.0) | 2 (3.2) | 0.857 |
| 31-40 mm | 0 (0.0) | 0 (0.0) | 7 (11.1) | |
| 41-50 mm | 0 (0.0) | 0 (0.0) | 1 (1.6) | |
| 51-60 mm | 0 (0.0) | 0 (0.0) | 18 (28.6) | |
| 61-70 mm | 0 (0.0) | 0 (0.0) | 12 (19.0) | |
| >70 mm | 1 (100.0) | (100.0) | 23 (32.0) | |
| Age | | | | |
| 20-30 years old | 0 (0.0) | 0 (0.0) | 2 (3.2) | 0.198 |
| 31-40 years old | 0 (0.0) | 1 (50.0) | 1 (1.6) | |
| 41-50 years old | 0 (0.0) | 0 (0.0) | 11 (17.5) | |
| >51 years old | 1 (100.0) | 1 (50.0) | 49 (77.8) | |
| FNAB punctures | | | | |
| 2 times | 1 (1.6) | 2 (3.2) | 59 (95.2) | 1.000 |
| > 2 times | 0 (0.0) | 0 (0.0) | 4 (100.0) | |
| CNB punctures | | | | |
| 2 times | 0 (0.0) | 0 (0.0) | 42 (100.0) | 0.040* |
| > 2 times | 1 (4.2) | 2 (8.3) | 21 (87.5) | |

Note: *significant $p < 0.05$

Table 4. Correlation of Lung Tumor Location with FNAB and CNB Techniques

| Variables | FNAB | | | *p* | CNB | | | *p* |
|---|---|---|---|---|---|---|---|---|
| | Malignant | Non-malignant | Undiagnosed | | Malignant | Non-malignant | Undiagnosed | |
| Tumor size | | | | | | | | |
| 21-30 mm | 0 (0.0) | 1 (10.0) | 1 (5.6) | 0.757 | 0 (0.0) | 2 (13.3) | 0 (0.0) | 0.510 |
| 31-40 mm | 3 (7.9) | 2 (20.0) | 2 (11.1) | | 4 (8.5) | 3 (20.0) | 0 (0.0) | |
| 41-50 mm | 1 (2.6) | 0 (0.0) | 0 (0.0) | | 1 (2.1) | 0 (0.0) | 0 (0.0) | |
| 51-60 mm | 11 (28.9) | 2 (20.0) | 5 (27.8) | | 14 (29.8) | 2 (13.3) | 2 (50.0) | |
| 61-70 mm | 8 (21.0) | 1 (10.0) | 3 (16.7) | | 8 (19.1) | 3 (20.0) | 0 (0.0) | |
| >70 mm | 15 (39.5) | 4 (40.0) | 7 (38.9) | | 19 (40.4) | 5 (33.3) | 2 (50.0) | |
| Lung Lobe Location | | | | | | | | |
| Right superior lobe | 15 (39.5) | 3 (30.0) | 5 (27.8) | 0.306 | 16 (34.4) | 4 (26.7) | 3 (75.0) | 0.240 |
| Right middle lobe | 4 (10.5) | 1 (10.0) | 1 (5.6) | | 6 (12.8) | 0 (0.0) | 0 (0.0) | |
| Right inferior lobe | 2 (5.3) | 1 (10.0) | 3 (16.7) | | 3 (6.4) | 3 (20.0) | 0 (0.0) | |
| Left superior lobe | 13 (34.2) | 3 (30.0) | 4 (22.0) | | 15 (31.9) | 5 (33.3) | 0 (0.0) | |
| Left inferior lobe | 1 (2.6) | 0 (0.0) | 1 (5.6) | | 1 (2.1) | 1 (6.7) | 0 (0.0) | |
| > 1 right lobes | 0 (0.0) | 2 (20.0) | 3 (16.7) | | 2 (4.3) | 2 (13.3) | 1 (25.0) | |
| > 1 left lobes | 3 (7.9) | 0 (0.0) | 1 (5.6) | | 4 (8.5) | 0 (0.0) | 0 (0.0) | |

* The results of Kappa test = 0.43; p <0.001

| The STROCSS 2021 Guideline | | |
|---|---|---|
| **Item no.** | **Item description** | **Page** |
| **TITLE** | | |
| 1 | **Title**<br>• The word cohort or cross-sectional or case-control is included*<br>• Temporal design of study is stated (e.g. retrospective or prospective)<br>• The focus of the research study is mentioned (e.g. population, setting, disease, exposure/intervention, outcome etc.)<br><br>*STROCSS 2021 guidelines apply to cohort studies as well as other observational studies (e.g. cross-sectional, case-control etc.) | 1 |
| **ABSTRACT** | | |
| 2a | **Introduction** – briefly describe:<br>• Background<br>• Scientific rationale for this study<br>• Aims and objectives | 1 |
| 2b | **Methods** - briefly describe:<br>• Type of study design (e.g. cohort, case-control, cross-sectional etc.)<br>• Other key elements of study design (e.g. retro-/prospective, single/multi-centred etc.)<br>• Patient populations and/or groups, including control group, if applicable<br>• Exposure/interventions (e.g. type, operators, recipients, timeframes etc.)<br>• Outcome measures – state primary and secondary outcome(s) | 1 |
| 2c | **Results** - briefly describe:<br>• Summary data with qualitative descriptions and statistical relevance, where appropriate | 1 |
| 2d | **Conclusion** - briefly describe:<br>• Key conclusions<br>• Implications for clinical practice<br>• Need for and direction of future research | 2 |
| **INTRODUCTION** | | |
| 3 | **Introduction** – comprehensively describe:<br>• Relevant background and scientific rationale for study with reference to key literature<br>• Research question and hypotheses, where appropriate<br>• Aims and objectives | 2-4 |
| **METHODS** | | |
| 4a | **Registration**<br>• In accordance with the Declaration of Helsinki*, state the research registration number and where it was registered, with a hyperlink to the registry entry (this can be obtained from ResearchRegistry.com, ClinicalTrials.gov, ISRCTN etc.)<br>• All retrospective studies should be registered before submission; it should be stated that the research was retrospectively registered<br><br>** "Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject"* | 5 |
| 4b | **Ethical approval**<br>• Reason(s) why ethical approval was needed<br>• Name of body giving ethical approval and approval number<br>• Where ethical approval wasn't necessary, reason(s) are provided | 5 |

| | | |
|---|---|---|
| 4c | **Protocol**<br>• Give details of protocol (*a priori* or otherwise) including how to access it (e.g. web address, protocol registration number etc.)<br>• If published in a journal, cite and provide full reference | 4 |
| 4d | **Patient and public involvement in research**<br>• Declare any patient and public involvement in research<br>• State the stages of the research process where patients and the public were involved (e.g. patient recruitment, defining research outcomes, dissemination of results etc.) and describe the extent to which they were involved. | 4 |
| 5a | **Study design**<br>• State type of study design used (e.g. cohort, cross-sectional, case-control etc.)<br>• Describe other key elements of study design (e.g. retro-/prospective, single/multi-centred etc.) | 4 |
| 5b | **Setting and timeframe of research** – comprehensively describe:<br>• Geographical location<br>• Nature of institution (e.g. primary/secondary/tertiary care setting, district general hospital/teaching hospital, public/private, low-resource setting etc.)<br>• Dates (e.g. recruitment, exposure, follow-up, data collection etc.) | 4 |
| 5c | **Study groups**<br>• Total number of participants<br>• Number of groups<br>• Detail exposure/intervention allocated to each group<br>• Number of participants in each group | 4 |
| 5d | **Subgroup analysis** – comprehensively describe:<br>• Planned subgroup analyses<br>• Methods used to examine subgroups and their interactions | 4 |
| 6a | **Participants** – comprehensively describe:<br>• Inclusion and exclusion criteria with clear definitions<br>• Sources of recruitment (e.g. physician referral, study website, social media, posters etc.)<br>• Length, frequency and methods of follow-up (e.g. mail, telephone etc.) | 4 |
| 6b | **Recruitment** – comprehensively describe:<br>• Methods of recruitment to each patient group (e.g. all at once, in batches, continuously till desired sample size is reached etc.)<br>• Any monetary incentivisation of patients for recruitment and retention should be declared; clarify the nature of any incentives provided<br>• Nature of informed consent (e.g. written, verbal etc.)<br>• Period of recruitment | 4 |
| 6c | **Sample size** – comprehensively describe:<br>• Analysis to determine optimal sample size for study accounting for population/effect size<br>• Power calculations, where appropriate<br>• Margin of error calculation | 4 |
| **METHODS - INTERVENTION AND CONSIDERATIONS** | | |
| 7a | **Pre-intervention considerations** – comprehensively describe:<br>• Preoperative patient optimisation (e.g. weight loss, smoking cessation, glycaemic control etc.)<br>• Pre-intervention treatment (e.g. medication review, bowel preparation, correcting hypothermia/-volemia/-tension, mitigating bleeding risk, ICU care etc.) | 5 |

| | | |
|---|---|---|
| 7b | **Intervention** – comprehensively describe:<br>• Type of intervention and reasoning (e.g. pharmacological, surgical, physiotherapy, psychological etc.)<br>• Aim of intervention (preventative/therapeutic)<br>• Concurrent treatments (e.g. antibiotics, analgesia, anti-emetics, VTE prophylaxis etc.)<br>• Manufacturer and model details, where applicable | 5 |
| 7c | **Intra-intervention considerations** – comprehensively describe:<br>• Details pertaining to administration of intervention (e.g. anaesthetic, positioning, location, preparation, equipment needed, devices, sutures, operative techniques, operative time etc.)<br>• Details of pharmacological therapies used, including formulation, dosages, routes, and durations<br>• Figures and other media are used to illustrate | 5 |
| 7d | **Operator details** – comprehensively describe:<br>• Requirement for additional training<br>• Learning curve for technique<br>• Relevant training, specialisation and operator's experience (e.g. average number of the relevant procedures performed annually) | 5 |
| 7e | **Quality control** – comprehensively describe:<br>• Measures taken to reduce inter-operator variability<br>• Measures taken to ensure consistency in other aspects of intervention delivery<br>• Measures taken to ensure quality in intervention delivery | 5 |
| 7f | **Post-intervention considerations** – comprehensively describe:<br>• Post-operative instructions (e.g. avoid heavy lifting) and care<br>• Follow-up measures<br>• Future surveillance requirements (e.g. blood tests, imaging etc.) | 5 |
| 8 | **Outcomes** – comprehensively describe:<br>• Primary outcomes, including validation, where applicable<br>• Secondary outcomes, where appropriate<br>• Definition of outcomes<br>• If any validated outcome measurement tools are used, give full reference<br>• Follow-up period for outcome assessment, divided by group | 5 |
| 9 | **Statistics** – comprehensively describe:<br>• Statistical tests and statistical package(s)/software used<br>• Confounders and their control, if known<br>• Analysis approach (e.g. intention to treat/per protocol)<br>• Any sub-group analyses<br>• Level of statistical significance | 6 |
| **RESULTS** | | |
| 10a | **Participants** – comprehensively describe:<br>• Flow of participants (recruitment, non-participation, cross-over and withdrawal, with reasons). Use figure to illustrate.<br>• Population demographics (e.g. age, gender, relevant socioeconomic features, prognostic features etc.)<br>• Any significant numerical differences should be highlighted | 6 |
| 10b | **Participant comparison**<br>• Include table comparing baseline characteristics of cohort groups<br>• Give differences, with statistical relevance<br>• Describe any group matching, with methods | 6 |
| 10c | **Intervention** – comprehensively describe: | 7 |

| | | |
|---|---|---|
| | • Degree of novelty of intervention<br>• Learning required for interventions<br>• Any changes to interventions, with rationale and diagram, if appropriate | |
| 11a | **Outcomes** – comprehensively describe:<br>• Clinician-assessed and patient-reported outcomes for each group<br>• Relevant photographs and imaging are desirable<br>• Any confounding factors and state which ones are adjusted | 7 |
| 11b | **Tolerance** – comprehensively describe:<br>• Assessment of tolerability of exposure/intervention<br>• Cross-over with explanation<br>• Loss to follow-up (fraction and percentage), with reasons | 7 |
| 11c | **Complications** – comprehensively describe:<br>• Adverse events and classify according to Clavien-Dindo classification*<br>• Timing of adverse events<br>• Mitigation for adverse events (e.g. blood transfusion, wound care, revision surgery etc.)<br><br>*Dindo D, Demartines N, Clavien P-A. Classification of Surgical Complications. A New Proposal with Evaluation in a Cohort of 6336 Patients and Results of a Survey. Ann Surg. 2004; 240(2): 205-213 | 7 |
| 12 | **Key results** – comprehensively describe:<br>• Key results with relevant raw data<br>• Statistical analyses with significance<br>• Include table showing research findings and statistical analyses with significance | 7-8 |
| **DISCUSSION** | | |
| 13 | **Discussion** – comprehensively describe:<br>• Conclusions and rationale<br>• Reference to relevant literature<br>• Implications for clinical practice<br>• Comparison to current gold standard of care<br>• Relevant hypothesis generation | 8-10 |
| 14 | **Strengths and limitations** – comprehensively describe:<br>• Strengths of the study<br>• Weaknesses and limitations of the study and potential impact on results and their interpretation<br>• Assessment and management of bias<br>• Deviations from protocol, with reasons | 10 |
| 15 | **Relevance and implications** – comprehensively describe:<br>• Relevance of findings and potential implications for clinical practice<br>• Need for and direction of future research, with optimal study designs mentioned | - |
| **CONCLUSION** | | |
| 16 | **Conclusions**<br>• Summarise key conclusions<br>• Outline key directions for future research | 10 |
| **DECLARATIONS** | | |
| 17a | **Conflicts of interest**<br>• Conflicts of interest, if any, are described | - |
| 17b | **Funding**<br>• Sources of funding (e.g. grant details), if any, are clearly stated<br>• Role of funder | - |

| | | |
|---|---|---|
| 17c | **Contributorship**<br>• Acknowledge patient and public involvement in research; report the extent of involvement of each contributor | - |

*Table 2: The full revised STROCSS 2021 checklist*

Cross-sectional Study

# Conformity of Fine Needle Aspiration Biopsy (FNAB) and Core Needle Biopsy (CNB) in peripheral lung tumor patients: A cross-sectional study

Q1 Q2



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## Abstract

***Background*:** The problem of establishing lung tumor diagnostics is a challenge for clinicians, especially pulmonologists, in determining a definitive diagnosis of a lung tumor.

***Objective*:** Analyzing the conformity of anatomical pathology results between fine-needle aspiration biopsy (FNAB) and core needle biopsy (CNB) ~~and fine-needle aspiration biopsy (FNAB)~~ materials in peripheral lung tumors.

***Methods*:** A cross-sectional study was conducted from July 2019 to December 2020 with 66 participants. Participants were examined for CNB and FNAB, in which the results of these examinations were compared for conformity. Statistical analysis used the Kappa test with $p < 0.05$.

***Result*:** Most participants' tumor size was >70 mm, with FNAB results showing malignant category (39.5%), non-malignant (40.0%), and undiagnosed (38.9%; $p = 0.757$). Meanwhile, CNB examination showed a tumor size of >70 mm that was categorized into malignant (40.4%) and non-malignant (33.3%; $p = 0.510$). Most tumors were located in the right superior lobe that had FNAB results in the malignant (39.5%), non-malignant (30.0%) and undiagnosed (27.8%; $p = 0.306$) categories. The CNB examination also showed that most tumors were located in the right superior lobe, which had resulted in the category of malignant (34.4%), non-malignant (26.7%), and undiagnosed (75.0%; $p = 0.240$). Conformity of anatomical pathology results from FNAB and CNB subject such as malignancy category of 35 participants (74.5%), non-malignancy of 7 participants (53.8%) and undiagnosed of 4 participants (16.7%) with an accuracy of 69.69% ($K = 0.43$; $p = 0.001$).

***Conclusion*:** There is a conformity between the anatomical pathology results from FNAB and CNB materials for the diagnosis of lung tumors. CNB showed better results in the detection of anatomical malignancy and specimen adequacy.

**Keywords**:

Core needle biopsy, Fine-needle aspiration biopsy, Lung tumor

**Abbreviations**

No keyword abbreviations are available

# 1 Introduction

The problem of establishing lung tumor diagnostics is a challenge for clinicians, especially pulmonologists, in determining the diagnosis of lung tumors. Generally, patients are admitted to hospitals with advanced stage and physical limitations to carry out invasive diagnostic procedures. Even though the patient is willing to undergo a diagnostic procedure, there are limited diagnostic specimens for lung tumor material. Diagnostic modalities of peripheral lung lesions include traditional and advanced techniques. Traditional diagnostic techniques consist of percutaneous biopsy with transthoracic needle aspiration (TTNA) known as fine-needle aspiration biopsy (FNAB) and bronchoscopy, while advanced techniques include endobronchial ultrasound (EBUS) and electromagnetic navigation bronchoscopy (ENB) [1].

Fine needle aspiration biopsy is recognized as an initial diagnostic tool for all body lesions, whether suspected to be benign or malignant. In some cases, there are limitations and shortcomings where the cytological sample of FNAB material is not sufficient to determine lung tumor diagnosis. Therefore, the patient must undergo other diagnostic procedures by performing a repeat biopsy procedure using a larger needle (core needle biopsy/CNB) or an open biopsy [2]. This procedure does not rule out the possibility of causing the patient to become uncomfortable, prolonging the treatment period that leads to a higher cost of treatment [3,4].

In several hospitals, concurrent FNAB and CNB procedures have been applied and show several advantages when these biopsies are combined at one time, which includes: (a) time efficiency since patients come in one visit and receive both procedures; (b) the specimens obtained by both procedures are more adequate, representative and complementary to enable the anatomical pathologist to obtain an accurate diagnosis; (c) cost-effective since it is expected to eliminate second diagnostic procedure that is potentially more invasive [4,5].

A thoracic ultrasonography (USG)-guided biopsy facilitates the process of determining the area of peripheral thoracic lesions, thereby increasing the success of sampling required for diagnosis [6]. Based on the description above, we are interested in analyzing the comparison between CNB and FNAB results with the help of thoracic ultrasound in peripheral lung tumors.

# 2 Methods and materials

## 2.1 Participants

Participants in this study were lung tumor patients who met the inclusion and exclusion criteria. Participants included in this study were patients with peripheral lung tumors based on chest X-ray, ultrasound, and CT scan [7–9] and those who could perform a percutaneous biopsy using thoracic ultrasound guidance. Meanwhile, exclusion criteria were patients with a performance score of <50 or hemodynamically unstable, massive untreated pleural effusion, mediastinal tumor, central lung tumor, coexisting lung disease conditions, impaired hemostatic function, and anatomical pathology results from either biopsy or FNAB or CNB that didn't come out.

## 2.2 Ethical approval

This ~~research~~study has been submitted for ethical approval with registration research based on the Declaration of Helsinki at the Health Research Ethics Committee in the Hospital. All participants first filled out the informed consent form before the ~~research~~study was carried out.

## 2.3~~2~~ Study design

A cross-sectional study was carried out at Hospital, from September 2019 to December 2020. The number of participants in this study was 66 participants with consecutive sampling. This study compared the results of sampling using FNAB and CNB techniques assisted by ultrasound. This study~~research~~ report used Strengthening the Reporting of Cohort Studies in Surgery (STROCSS) 2021 guidelines [10].

## 2.4~~3~~ Fine needle aspiration biopsy procedure

Fine needle aspiration biopsy is a diagnostic procedure in the form of a percutaneous biopsy of the thoracic region using a 25-gauge fine needle. The FNAB sampling technique is to lay the patient on the operating table, determine the biopsy site, disinfect the skin in the biopsy area with 10% povidone-iodine followed by 70% alcohol, install a sterile drape, perform 2% lidocaine infiltration (1–2 cc) at the biopsy site, intracutaneously, subcutaneously until it reaches the

parietal pleura, perform a vertical spinal needle puncture until it reaches the lesion. The stylet is taken, the needle is connected to a 20 cc syringe, the suction is pulled firmly, the needle is moved up and down along 0.5–1 cm several times. The suction is slowly returned to its original position, the needle is removed. The aspirated biopsy material is removed onto a slide, a flat smear is made immediately, fixed, and then dried. If necessary, this procedure can be repeated a second or third time according to the initial assessment by an anatomical pathologist in assessing the adequacy of the specimen [8,9,11].

### 2.54 Core needle biopsy procedure

Core needle biopsy is a diagnostic procedure in the form of a percutaneous biopsy of the thoracic region using a 14-gauge core needle with the tip of the needle functioning as a cutter. The CNB sampling technique is carried out by inserting the core needle at the same location at the previous FNAB needlepoint until it reaches the lesion according to the depth of the thoracic ultrasound. Biopsy material that has been cut through the core is removed onto a slide, immediately a flat smear is made, fixed, and then dried. If necessary, this procedure can be repeated a second or third time according to the initial assessment by the anatomical pathologist in assessing the adequacy of the specimen. Post-biopsy observations are conducted for inpatients while in the room. For outpatients, observation is carried out for 2 h ~~hours~~ in the operating room, if there are no complications, the participant is allowed to go home with advice to return immediately if symptoms of shortness of breath or coughing up blood are found [12,13].

### 2.65 Statistical analysis

The measured data were analyzed by univariate and bivariate analysis, in which univariate data was displayed in the form of a frequency distribution or mean ± standard deviation (SD). Measurement data were analyzed using IBM SPSS Statistics software version 21.0 (IBM Corp., Armonk, NY, USA). Statistical analysis in this study used the Kruskal Wallis, Fisher Exact, and Kappa test with $p < 0.05$ was considered significant.

## 3 Results

### 3.1 Characteristics of participants

Most participants were male (81.8%), aged >50 years (77.3%), with most respiratory symptoms being chronic cough (63.6%). Most tumors were located in the right lung (62.1%) and most were in the right superior lobe (34.8%). Most participants had a needle inserted in the anterior (66.7%). Most tumors sized >70 mm as much as 39.4%, and the majority of participants did not experience post-FNAB and CNB complications (95.5%; Table 1).

alt-text: Table 1

**Table 1**

The table layout displayed in this section is not how it will appear in the final version. The representation below is solely purposed for providing corrections to the table. To preview the actual presentation of the table, please view the Proof.

Characteristics of participants.

| Variables | n (%) |
|---|---|
| Sex | |
| Male | 54 (81.8) |
| Female | 12 (18.2) |
| Age | |
| 20–30 years old | 2 (3.0) |
| 31–40 years old | 2 (3.0) |
| 41–50 years old | 11 (16.7) |
| >51 years old | 51 (77.3) |
| Tumor Location | |
| Right lung | 41 (62.1) |
| Left lung | 25 (37.9) |
| Lung Lobe Location | |
| Right superior lobe | 23 (34.8) |
| Right middle lobe | 6 (9.1) |

| | |
|---|---|
| Right inferior lobe | 6 (9.1) |
| Left superior lobe | 20 (30.3) |
| Left inferior lobe | 2 (3.0) |
| >1 right lobes | 5 (7.6) |
| >1 left lobes | 4 (6.1) |
| Needle Access | |
| Anterior | 44 (66.7) |
| Posterior | 20 (30.3) |
| Lateral | 2 (3.0) |
| Tumor Size | |
| 21–30 mm | 2 (3.0) |
| 31–40 mm | 7 (10.6) |
| 41–50 mm | 1 (1.5) |
| 51–60 mm | 18 (27.3) |
| 61–70 mm | 12 (18.2) |
| >70 mm | 26 (39.4) |
| Complication | |
| Hemoptysis | 1 (1.5) |
| Pneumothorax | 2 (3.0) |
| None | 63 (95.5) |

Most participants had two punctures in each technique (FNAB = 93.9% and CNB = 63.6%). In both groups, the results of anatomical malignancy were found, which FNAB of 57.6% and CNB of 71.2%. Materials in both groups were declared adequate, which FNAB of 72.7% and CNB of 89.4% (Table 2).

alt-text: Table 2

**Table 2**

The table layout displayed in this section is not how it will appear in the final version. The representation below is solely purposed for providing corrections to the table. To preview the actual presentation of the table, please view the Proof.

Characteristic differences between FNAB and CNB.

| Variables | FNAB | CNB |
|---|---|---|
| Number of Punctures | | |
| 2 times | 62 (93.9) | 42 (63.6) |
| >2 times | 4 (6.1) | 24 (36.4) |
| Findings | | |
| Malignant | 38 (57.6) | 47 (71.2) |
| Non-malignant | 10 (15.2) | 13 (19.7) |
| Undiagnosed | 18 (27.3) | 6 (9.1) |
| Anatomical Pathology Results | | |
| Malignant | | |
| Squamous cell carcinoma | 5 (7.6) | 9 (13.6) |
| Adenocarcinoma | 19 (28.8) | 25 (37.9) |
| Small cell carcinoma | 0 (0.0) | 5 (7.6) |
| Atypical cells | 8 (12.1) | 1 (1.5) |
| Metastasis | 1 (1.5) | 5 (7.6) |

| | | |
|---|---|---|
| Malignant round tumor cells | 5 (7.6) | 1 (1.5) |
| Non-malignant | | |
| Granulomatous inflammation | 1 (1.5) | 4 (6.1) |
| Non-specific chronic inflammation | 9 (13.6) | 9 (13.6) |
| Undiagnosed | | |
| Not representative/necrosis | 18 (27.3) | 7 (10.6) |
| Material Adequacy | | |
| Adequate material | 48 (72.7) | 59 (89.4) |
| Inadequate material | 18 (27.3) | 7 (10.6) |

### 3.2 Correlation between tumor size, age, and number of punctures with Post-FNAB and CNB complications

Most participants had tumor size >70 mm in diameter, 23 participants (36.5%) had no complications, but 3.8% had hemoptysis and 7.7% had pneumothorax ($p = 0.857$). Most uncomplicated participants were aged >50 years as much as 96%, but there were still participants who had hemoptysis (2%) and pneumothorax (2%) who were also >50 years old ($p = 0.198$). Most FNAB participants did not experience complications on 2 punctures as much as 95.2% ($p = 1.000$) and CNB participants did not experience complications on more than 2 punctures as much as 87.5%, but there were still occurrences of pneumothorax and hemoptysis on more than 2 punctures ($p = 0.040$; Table 3).

alt-text: Table 3

**Table 3**

The table layout displayed in this section is not how it will appear in the final version. The representation below is solely purposed for providing corrections to the table. To preview the actual presentation of the table, please view the Proof.

Complications of patients with FNAB and CNB.

| Variables | Complications | | | *p* |
|---|---|---|---|---|
| | Hemoptysis | Pneumothorax | None | |
| Tumor size | | | | |
| 21–30 mm | 0 (0.0) | 0 (0.0) | 2 (3.2) | 0.857 |
| 31–40 mm | 0 (0.0) | 0 (0.0) | 7 (11.1) | |
| 41–50 mm | 0 (0.0) | 0 (0.0) | 1 (1.6) | |
| 51–60 mm | 0 (0.0) | 0 (0.0) | 18 (28.6) | |
| 61–70 mm | 0 (0.0) | 0 (0.0) | 12 (19.0) | |
| >70 mm | 1 (100.0) | (100.0) | 23 (32.0) | |
| Age | | | | |
| 20–30 years old | 0 (0.0) | 0 (0.0) | 2 (3.2) | 0.198 |
| 31–40 years old | 0 (0.0) | 1 (50.0) | 1 (1.6) | |
| 41–50 years old | 0 (0.0) | 0 (0.0) | 11 (17.5) | |
| >51 years old | 1 (100.0) | 1 (50.0) | 49 (77.8) | |
| FNAB punctures | | | | |
| 2 times | 1 (1.6) | 2 (3.2) | 59 (95.2) | 1.000 |
| >2 times | 0 (0.0) | 0 (0.0) | 4 (100.0) | |
| CNB punctures | | | | |
| 2 times | 0 (0.0) | 0 (0.0) | 42 (100.0) | 0.040* |
| >2 times | 1 (4.2) | 2 (8.3) | 21 (87.5) | |

Note: *significant $p < 0.05$.

### 3.3 Correlation between lung tumor size and location with FNAB and CNB on anatomic pathology findings

Most participants' tumor size was >70 mm which had FNAB results in the malignant category (39.5%), non-malignant (40.0%), and undiagnosed (38.9%) with $p = 0.757$. Meanwhile, the results of CNB categories were malignant (40.4%), non-malignant (33.3%) and undiagnosed (7.6%) with $p = 0.510$. Most tumors were located in the right superior lobe, which FNAB results were malignant (39.5%), non-malignant (30.0%) and undiagnosed (27.8%; $p = 0.306$). Meanwhile, CNB results were malignant (34.4%), non-malignant (26.7%), and undiagnosed (75.0%; $p = 0.240$). The conformity level of anatomical pathology results from FNAB and CNB subject were malignant category of 35 participants (92.1%), non-malignancy of 7 participants (70%) and undiagnosed of 4 participants (11.2%; $K = 0.43$; $p = 0.001$; Table 4). The accuracy value of the suitability of the results of anatomical pathology of the two techniques was 69.69%.

alt-text: Table 4

**Table 4**

The table layout displayed in this section is not how it will appear in the final version. The representation below is solely purposed for providing corrections to the table. To preview the actual presentation of the table, please view the Proof.

Correlation of lung tumor location with FNAB and CNB techniques.

| Variables | FNAB | | | *p* | CNB | | | *p* |
|---|---|---|---|---|---|---|---|---|
| | Malignant | Non-malignant | Undiagnosed | | Malignant | Non-malignant | Undiagnosed | |
| Tumor size | | | | | | | | |
| 21–30 mm | 0 (0.0) | 1 (10.0) | 1 (5.6) | 0.757 | 0 (0.0) | 2 (13.3) | 0 (0.0) | 0.510 |
| 31–40 mm | 3 (7.9) | 2 (20.0) | 2 (11.1) | | 4 (8.5) | 3 (20.0) | 0 (0.0) | |
| 41–50 mm | 1 (2.6) | 0 (0.0) | 0 (0.0) | | 1 (2.1) | 0 (0.0) | 0 (0.0) | |
| 51–60 mm | 11 (28.9) | 2 (20.0) | 5 (27.8) | | 14 (29.8) | 2 (13.3) | 2 (50.0) | |
| 61–70 mm | 8 (21.0) | 1 (10.0) | 3 (16.7) | | 8 (19.1) | 3 (20.0) | 0 (0.0) | |
| >70 mm | 15 (39.5) | 4 (40.0) | 7 (38.9) | | 19 (40.4) | 5 (33.3) | 2 (50.0) | |
| Lung Lobe Location | | | | | | | | |
| Right superior lobe | 15 (39.5) | 3 (30.0) | 5 (27.8) | 0.306 | 16 (34.4) | 4 (26.7) | 3 (75.0) | 0.240 |
| Right middle lobe | 4 (10.5) | 1 (10.0) | 1 (5.6) | | 6 (12.8) | 0 (0.0) | 0 (0.0) | |
| Right inferior lobe | 2 (5.3) | 1 (10.0) | 3 (16.7) | | 3 (6.4) | 3 (20.0) | 0 (0.0) | |
| Left superior lobe | 13 (34.2) | 3 (30.0) | 4 (22.0) | | 15 (31.9) | 5 (33.3) | 0 (0.0) | |
| Left inferior lobe | 1 (2.6) | 0 (0.0) | 1 (5.6) | | 1 (2.1) | 1 (6.7) | 0 (0.0) | |
| >1 right lobes | 0 (0.0) | 2 (20.0) | 3 (16.7) | | 2 (4.3) | 2 (13.3) | 1 (25.0) | |
| >1 left lobes | 3 (7.9) | 0 (0.0) | 1 (5.6) | | 4 (8.5) | 0 (0.0) | 0 (0.0) | |

* The results of Kappa test = 0.43; $p < 0.001$.

## 4 Discussion

Several factors can increase the diagnostic value of transthoracic biopsy and prove the safety of thoracic ultrasound in guiding CNB in peripheral lung tumors, chest wall tumors, anterior mediastinal lesions. The size of the lesion does not appear to affect the diagnostic accuracy with thoracic ultrasound as a guide, but it is reported that the diagnostic rate is decreased in lesions located close to the ribs and influenced by the patient's respiratory movement and there are no serious complications from the procedure [14].

Core needle biopsy is significantly higher adequate material preparation than FNAB. Adequate material from the FNAB is found to correlate with tumor size. The addition of the number of needles passed in the FNAB technique is reported to increase the material to be more adequate. The operator's experience in the univariate analysis is reported to play a role in providing adequate material. FNAB specimens at a lesion size of 35 mm are reported to be adequate to

obtain specimens to be used for further molecular testing. On the other hand, direct assessment by an on-site anatomic pathologist may be the best way to ensure sample adequacy [15].

The diagnostic accuracy of transthoracic biopsy material is significantly affected by the lesion size. Accuracy will decrease in lesions smaller than 20 mm and accuracy will increase in lesions measuring 50 mm. The larger the lesion, the greater the chance that the tissue or tumor cells will undergo necrosis, so that the more likely the specimen is inadequate to make a definitive diagnosis. Thoracic ultrasound cannot identify the incidence of necrosis of a tumor lesion, so the strategy in sampling large lesions is to target the biopsy area at the periphery to avoid the central area of lung mass which has a high probability of necrosis area. The rates of necrosis in lesions measuring 20 mm, 21–49 mm, and 50 mm were 3.9%, 11.7%, and 28.8%, respectively [16].

The diagnostic accuracy of transthoracic biopsy decreases with lung tumor size. If the lesion is small, it may move during the respiratory phase so that the needle falls to accurately target the lesion throughout the patient's respiratory cycle [8,15,17]. The location and size of the tumor lesion will affect FNAB accuracy. A good location for the FNAB technique is when the tumor lesion is located in the periphery with large size. Lung tumor located in the superior lobe is more easily accessible by the biopsy needle with a straight needle angle, as this position makes it easier for the needle to collect material without changing the pleural space [18]. The location of the mass attached to the pleura will also cause less movement during respiration to increase accuracy [18,19].

This study found no correlation between age, lesion size, and the number of FNAB needle passes on the incidence of complications. A study conducted by Capalbo reported age as a factor that affects complications, with the incidence of pneumothorax due to CNB reported to be the majority in young patients, parenchymal bleeding in the elderly, and complications occurring more in the right lung. Fifty percent of pneumothorax cases occur in the superior lobe of the lung on the CNB technique, 40% of parenchymal hemorrhages in the inferior lobe on FNAB. In terms of size, the CNB technique is more complicated than the FNAB in lesions sized less than 3.5 cm. However, unlike our study~~research~~, Capalbo's study was not performed at the same time as a biopsy so there was no detail provided regarding the incidence of complications of each technique. Parameters associated with complications were needle access, lesion size, age, needle diameter, and the number of needle passes. Concerning age, pulmonary parenchymal bleeding and hemoptysis complications occur more frequently in the elderly who undergo CNB, possibly because they usually use anticoagulant therapy due to comorbid disease. There was no significant correlation between the number of needles passed with complications and diagnostic accuracy because the average success with only 1 pass, in contrast to other studies that reported pneumothorax will occur more often in those who undergo many needles passes because this can cause a lot of trauma to the pleura or so that coaxial needle is needed in the future [13].

## 5 Conclusion

There is no correlation between lung tumor size and anatomic pathology findings in each biopsy technique. There is no correlation between lung tumor location and anatomic pathology findings in each biopsy technique. There is no correlation between tumor size, age, and the number of FNAB needle passes with the incidence of each complication. There appears to be a significant correlation between more than two CNB needle passes and the incidence of complications. CNB can detect anatomical malignancy and specimen adequacy better than FNAB.

## ~~Ethical approval~~

~~We have conducted an ethical approval base on Declaration of Helsinki at Ethical Committee in Dr. Soetomo General Academic Hospital, Surabaya, Indonesia.~~


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None.


## Author contribution

All authors contributed toward data analysis, drafting and revising the paper, gave final approval of the version to be published and agree to be accountable for all aspects of the work.

## Trial registry number

1. Name of the registry: Health Research Ethics Coommitee in the Dr. Soetomo General Academic Hospital, Surabaya, Indonesia
2. Unique Identifying number or registration ID: 1575/KEPK/X/2019.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): -.

## Guarantor

Isnin Anang Marhana.

## Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

## Provenance and peer review

Not commissioned, externally peer-reviewed.

## Declaration of competing interest

Isnin Anang Marhana, Kadek Widianiti, and Etty Hary Kusumastuti~~The authors~~ declare that they have no conflict of interest.

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## Appendix A Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2022.103423.

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The corrections made in this section will be reviewed and approved by a journal production editor. The newly added/removed references and its citations will be reordered and rearranged by the production team.

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## Highlights

- There is a conformity between the results of FNAB and CNB assisted by ultrasound.
- FNAB and CNB results in lung cancer are similar >70%.
- The use of FNAB followed by CNB minimizes misdiagnosis.

# Appendix A Supplementary data

The following is/are the supplementary data to this article:

Multimedia Component 1

**Multimedia component 1**

alt-text: Multimedia component 1

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