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A randomized controlled trial comparing the diagnostic yield of using Rapid On-Site Cytology Evaluation (ROSE) and without using ROSE in Radial Probe Endobronchial Ultrasound (R-EBUS) guided sheath transbronchial lung biopsy with bronchial brushing in peripheral pulmonary lesions

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A Randomized Controlled Trial Comparing the Diagnostic Yield of using Rapid On-Site Cytology Evaluation (ROSE) and without using ROSE in Radial Probe Endobronchial Ultrasound (R-EBUS) Guided Sheath Transbronchial Lung Biopsy with Bronchial Brushing in Peripheral Pulmonary Lesions.

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การศึกษาเปรียบเทียบผลการวินิจฉัยรอยโรคในปอดส่วนปลายระหว่างการใช้การดูเซลล์ขณะทำหัตถการส่องกล้องทางเดินหายใจและการส่องกล้องทางเดินหายใจและแปรงผนังหลอดลมตามปกติแบบสุ่ม ในผู้ป่วยที่มีรอยโรคหรือก้อนในปอดส่วนปลาย

น.ส.กุลชไม สิลาฐาปนสกุล

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรมหาบัณฑิต
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Thesis Title	A Randomized Controlled Trial Comparing the Diagnostic Yield of using Rapid On-Site Cytology Evaluation (ROSE) and without using ROSE in Radial Probe Endobronchial Ultrasound (R-EBUS) Guided Sheath Transbronchial Lung Biopsy with Bronchial Brushing in Peripheral Pulmonary Lesions.
By	Miss Kulchamai Silathapanasakul
Field of Study	Medicine
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Accepted by the FACULTY OF MEDICINE, Chulalongkorn University in Partial Fulfillment of the Requirement for the Master of Science

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กุลชไม สิลาฐาปนสกุล : การศึกษาเปรียบเทียบผลการวินิจฉัยรอยโรคในปอดส่วนปลายระหว่างการใช้การดูเซลล์ขณะทำหัตถการส่องกล้องทางเดินหายใจและการส่องกล้องทางเดินหายใจและแปรงผนังหลอดลมตามปกติแบบสุ่ม ในผู้ป่วยที่มีรอยโรคหรือก้อนในปอดส่วนปลาย. (A Randomized Controlled Trial Comparing the Diagnostic Yield of using Rapid On-Site Cytology Evaluation (ROSE) and without using ROSE in Radial Probe Endobronchial Ultrasound (R-EBUS) Guided Sheath Transbronchial Lung Biopsy with Bronchial Brushing in Peripheral Pulmonary Lesions.) อ.ที่ปรึกษาหลัก : นพ.ธิติวัฒน์ ศรีประสาธน์, อ.ที่ปรึกษาร่วม : วิริสสร วงศ์ศรีชนาลัยพ.บ.

ความสำคัญและที่มา : การตรวจพบรอยโรคหรือก้อนในปอดส่วนปลายโดยการถ่ายภาพรังสีทรวงอกแม้ว่ารอยโรคเหล่านี้ส่วนใหญ่จะไม่ใช่มะเร็ง แต่ก็พบว่าเป็นมะเร็งได้บ่อย อัตราการรอดชีวิตของมะเร็งปอดนั้นแตกต่างกันไปตามขนาดของก้อนและระยะของโรค การส่องกล้องหลอดลมด้วยคลื่นอัลตราซาวนด์ (Radial Probe Endobronchial Ultrasonography, RP-EBUS) ช่วยเพิ่มความไวในการวินิจฉัยรอยโรคในปอดส่วนปลาย และการนำวิธีการดูเซลล์ระหว่างการทำหัตถการมาใช้ร่วมกับการส่องกล้อง (Rapid on-site Evaluation, ROSE) มีการศึกษาก่อนหน้าพบว่าสามารถเพิ่มความสามารถในการวินิจฉัยได้แต่ผลการศึกษายังไม่เป็นไปในทิศทางเดียวกันจึงเป็นที่มาของการศึกษาความสามารถในการวินิจฉัยรอยโรคในปอดส่วนปลาย
วัตถุประสงค์ของการวิจัย : เพื่อศึกษาเปรียบเทียบผลการวินิจฉัยรอยโรคหรือก้อนในปอดส่วนปลายจากการใช้การดูเซลล์ขณะทำหัตถการส่องกล้องทางเดินหายใจร่วมกับการส่องกล้องทางเดินหายใจเพื่อตัดเก็บชิ้นเนื้อและแปรงผนังหลอดลมในปอดส่วนปลายเทียบกับกลุ่มควบคุม

วิธีดำเนินการวิจัย : ผู้ป่วยทุกรายที่อายุมากกว่า 18 ปี ที่ตรวจพบรอยโรคของปอดขนาดน้อยกว่าหรือเท่ากับ 3 ซม. จากการตรวจเอกซเรย์คอมพิวเตอร์ทรวงอกจะถูกสุ่มออกเป็น 2 กลุ่มย่อยตามขนาดของก้อนในปอดจากนั้นอาสาสมัครในแต่ละกลุ่มจะถูกนำมาทำการสุ่มต่ออีกลำดับเพื่อแบ่งเป็นกลุ่มทดลองคือใช้ ROSE ร่วมกับการส่องกล้อง และกลุ่มควบคุมที่ไม่ใช้ROSE

ผลของงานวิจัย : ผู้เข้าร่วมวิจัยทั้งหมด 68 คนถูกแบ่งออกเป็นกลุ่มทดลองและกลุ่มควบคุมกลุ่มละ 34 คนแบบสุ่ม ข้อมูลพื้นฐาน และ ตำแหน่งของรอยโรคในปอดของผู้เข้าร่วมวิจัยทั้ง 2 กลุ่มไม่มีความแตกต่างกัน ผลของงานวิจัยพบว่าความสามารถในการวินิจฉัยรอยโรคในปอดส่วนปลายไม่มีความแตกต่างกันทางสถิติ นอกจากนี้พบว่าเวลาที่ใช้ในการทำหัตถการและปริมาณยานอนหลับและยาแก้ปวดที่ใช้ในกลุ่มทดลองน้อยกว่ากลุ่มควบคุมอย่างมีนัยสำคัญทางสถิติ (P=0.015 และ P<0.001 ตามลำดับ)

บทสรุปผลการวิจัย : การส่องกล้องทางเดินหายใจชนิด RP-EBUS ร่วมกับการใช้การดูเซลล์ระหว่างการทำหัตถการ (ROSE) มีความสามารถในการวินิจฉัยรอยโรคในปอดส่วนปลายไม่แตกต่างกับกลุ่มควบคุมแต่สามารถช่วยลดเวลาในการทำหัตถการและลดปริมาณยานอนหลับและยาแก้ปวดที่ใช้ระหว่างการทำหัตถการได้ จากผลของงานวิจัยจึงแนะนำให้ใช้ROSEในเคสที่เหมาะสม เช่นในผู้ป่วยที่ต้องการลดเวลาการทำหัตถการหรือต้องการใช้ปริมาณยานอนหลับและยาแก้ปวดในปริมาณน้อยลง อย่างไรก็ตามวิจัยนี้ทำในโรงพยาบาลที่มีแพทย์โรคปอดผู้เชี่ยวชาญและมีนักเซลล์วิทยาที่มีความชำนาญการซึ่งอาจเป็นข้อจำกัดในการนำผลของงานวิจัยไปใช้ ในอนาคตอาจพัฒนางานวิจัยโดยการเพิ่มจำนวนผู้เข้าร่วมวิจัยและทำในโรงพยาบาลหลายๆระดับต่อไป

สาขาวิชา	อายุรศาสตร์	ลายมือชื่อนิสิต .....
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		ลายมือชื่อ อ.ที่ปรึกษาร่วม .....

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KEYWORD: Peripheral lung lesions Radial probe Endobronchial Ultrasound(RP-EBUS) Transbronchial lung biopsy Rapid Onsite Cytology Evaluation(ROSE)

Kulchamai Silathapanasakul : A Randomized Controlled Trial Comparing the Diagnostic Yield of using Rapid On-Site Cytology Evaluation (ROSE) and without using ROSE in Radial Probe Endobronchial Ultrasound (R-EBUS) Guided Sheath Transbronchial Lung Biopsy with Bronchial Brushing in Peripheral Pulmonary Lesions.. Advisor: Thitiwat Sriprasart, M.D. Co-advisor: Virissorn Wongsrichanalai, M.D.

BACKGROUND: Radial Probe Endobronchial Ultrasonography (RP-EBUS) guided transbronchial biopsy with bronchial brushing is an effective way of tissue assessment for evaluating peripheral lung lesion combined with Rapid on-site Evaluation (ROSE). Our study aimed to evaluate the efficacy of ROSE add on RP-EBUS guided sheath transbronchial lung biopsy to improve the overall diagnostic yield.

OBJECTIVES: The purpose of this study was to compare the diagnosis yield of peripheral lung lesions or nodules from the ROSE add on Radial Probe Endobronchial Ultrasonography (RP-EBUS) guided sheath transbronchial biopsy with bronchial brushing compared to the control group.

METHODS: In this prospective randomized controlled trial study. All patients age > 18 years old who diagnosed with peripheral lung lesions size < 3 cm. from chest computed tomography are randomized into 2 subgroups underwent RP-EBUS guided sheath transbronchial lung biopsy with bronchial brushing with and without using ROSE. The diagnostic yield was compared.

RESULTS : 68 patients were enrolled. 34 patients were randomized equally to ROSE group and control group. The diagnostic yield was similar in both groups without statistically significant. There was no significant differences in baseline characteristic. There was a trend toward reduce the procedure durations and amount of sedatives used in the ROSE group with statistically significance difference (P=0.015 and P<0.001 respectively). Complications rates in both groups are not different.

CONCLUSION: The diagnostic yield of peripheral lung lesions was similar in ROSE add on RP-EBUS and RP-EBUS alone. However routine use of ROSE in RP-EBUS guided sheath transbronchial biopsy with bronchial brushing associated with a reducing in procedure times and decreased amount of sedative use. We recommended ROSE add on RP-EBUS in selected cases. Our study could be applicable only in experienced center which available intervention pulmonologists and cytologists.

Field of Study:	Medicine	Student's Signature .....
Academic Year:	2022	Advisor's Signature .....
		Co-advisor's Signature .....

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Kulchamai Silathapanasakul

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

Page

CHAPTER ONE

INTRODUCTION

1.1 Historical background

Pulmonary nodules are detected by chest radiologic imaging. When a patient visit doctor with pulmonary symptoms such as cough, chest tightness or (1) asymptomatic accidentally detected by an annual medical examination. Approximately 0.1-0.2% were found from chest X-rays and 13% from chest computed tomography. Early diagnosis of pulmonary nodules is necessary for the treatment process.

According to statistics(1), cancer is the first leading cause of death in all deaths. Considering the causes of death caused by cancer, lung cancer is the first leading cause in both males and females.

(2)Almost all peripheral lung lesions are benign, they can be found to be malignant around 1-12%, especially in people who are at risk of smoking(3). Approximately 20-30% of lung cancer patients are present with peripheral lung nodule(4) especially adenocarcinoma and squamous cell lung cancer.

Survival rates of lung cancer vary depending on the size of the nodule, the stage of the disease and patient health conditions. The best treatment for lung cancer is early diagnosis(5), the survival rate in 5 years of early diagnosed lung nodules is 82% and reduced to only 6% in advanced stage. Therefore, it is very important to undergo treatment in the early stages, originally to get tissue diagnosis need surgical procedure and requires general anesthesia.

Radial probe Endobronchial Ultrasonography (R-EBUS) guided sheath transbronchial biopsy is an effective way to get tissue diagnosis from peripheral lung lesions. (6) Using R-EBUS, the sensitivity of diagnosing peripheral pulmonary lesions has increased to 88% from a traditional bronchoscopy with a sensitivity of only 59%.

Rapid on-site Evaluation (ROSE), which is an intraprocedural cytological assessment of a sample obtained from bronchial brushing. It is a useful technique for diagnose the peripheral lungs nodule or mediastinal lymph nodes (7), previous research showing that it can increase the success rate of diagnosing malignant tumors by up to 72%, and the accuracy of cytological diagnosis is very high.

The causes of undiagnosed tissue pathological specimens are inadequate and unqualified specimens, such as contain only mucus, respiratory mucosa, or blood. To increase the diagnostic yield of transbronchial biopsy, rapid site evaluation (ROSE) has been introduced. By add on ROSE requires a cytologist participated during bronchoscope and reported the results at the time.

(8) ROSE can increase the quality of the tissue biopsy specimens, reduce repetitive biopsies and delayed diagnosis. ROSE may result in fewer biopsies and fewer complications. The use of ROSE can reduce the number of biopsies, reduce the duration of the procedure for the patient, reduce potential complications that may be associated with increasing the number of visits and improve the use of laboratory resources.

1.2 Research questions

Primary Research Question: Does using rapid on-site cytology evaluation (ROSE) add on RP-EBUS guided transbronchial biopsy and bronchial brushing can increase the diagnostic yield of peripheral lung nodule compared to the control group?

Secondary Research Question

1. Does using rapid on-site cytology evaluation (ROSE) add on RP-EBUS guided transbronchial biopsy and bronchial brushing can shorten the procedure time compared to the control group?

2. Does using rapid on-site cytology evaluation (ROSE) add on RP-EBUS guided transbronchial biopsy and bronchial brushing can reduce sedative doses compared to the control group?

3. Does using rapid on-site cytology evaluation (ROSE) add on RP-EBUS guided transbronchial biopsy and bronchial brushing can reduce amount of blood loss compared to the control group?

1.3 Objectives

The primary objective to compare the diagnosis yield of peripheral lung lesions or nodules from the use of rapid on-site cytological evaluation (ROSE) during RP-EBUS guided transbronchial biopsy and brushing in versus the control group.

The Secondary objectives

1.To compare the duration of RP-EBUS guided transbronchial biopsy and brushing in peripheral lung lesions between ROSE group versus control groups.

2. To compare the sedative doses used during RP-EBUS guided transbronchial biopsy and brushing in peripheral lung lesions between ROSE group versus control groups.

3.To compare the amounts of blood loss during RP-EBUS guided transbronchial biopsy and brushing in peripheral lung lesions between ROSE group versus control groups.

1.4 Hypothesis

Using rapid on-site cytological evaluation (ROSE) in combination with REBUS transbronchial biopsy and brushing can increase the diagnostic yield of peripheral lung lesions.

1.5 Conceptual framework

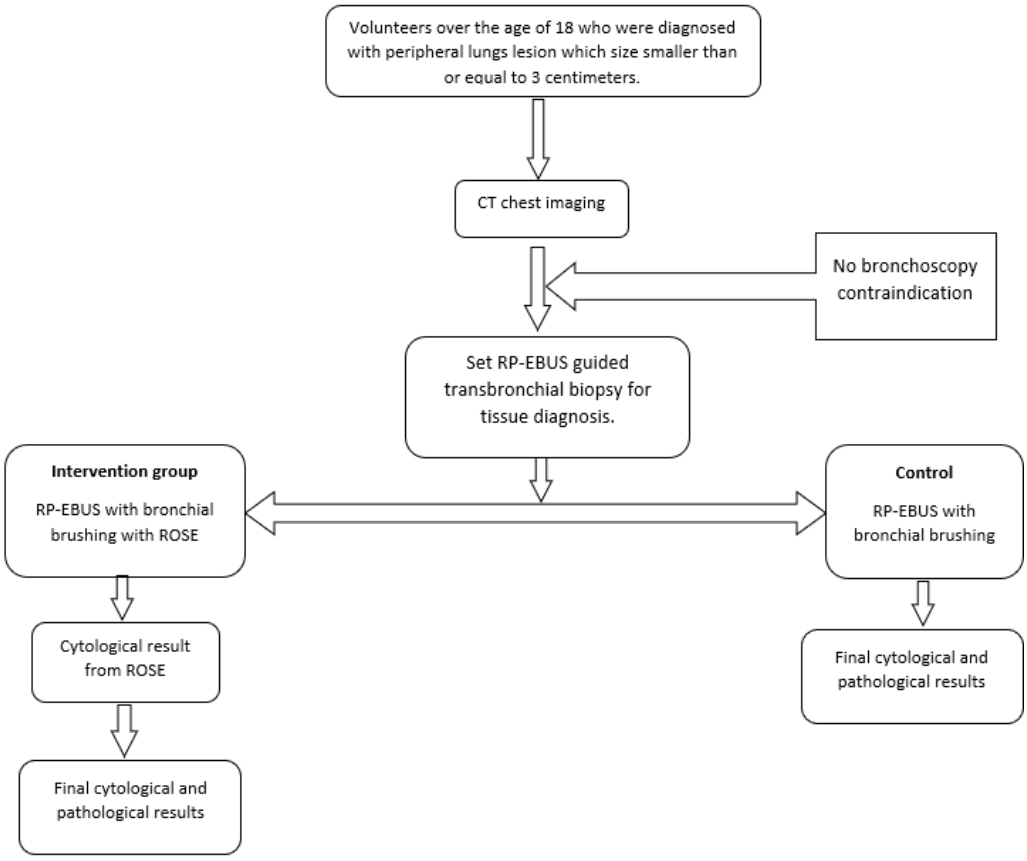

Figure 1 Conceptual Framework

1.6 Definitions

Performance of RP-EBUS is a bronchoscopy procedure performed by using Radial Probe endobronchial ultrasound (R-EBUS), an endobronchial ultrasound which ultrasonic probe located at the end of the endoscopy under sedation. All bronchoscopies were performed by fellow under supervision of experienced intervention pulmonologists. Following topical anesthesia with lidocaine.
Using The 20 MHz radial EBUS probe (UM-S20-20R 1.7mm, UM-S20-17S 1.4mm; Olympus, Tokyo, Japan), Guide sheath K-201: 2.0 mm K-203: 2.6 mm and cytology brush (BC-204D-2010, BC-202D-2010)

Performance of ROSE; Bronchial brush specimens were smeared onto two, positively charged, frosted glass slides. Slide was fixed immediately in 95% alcohol for Papanicolaou stain. The microscopic examination was performed within the bronchoscopy by a cytology scientist and the ROSE diagnosis was communicated immediately to the proceduralists. Diagnostic ROSE specimens are defined by clearly demonstrating the typical cytological features of malignancy or benign. Non-diagnostic specimens are defined by specimens demonstrated only normal epithelial cells or specimens demonstrated a scantly cell.

Bronchial brushing: technics using a small brush to rub a bronchial wall to collect a cytological specimen.

1.7 Ethical Consideration

The study was approved by the Institutional Review Board (IRB) of the faculty of Medicine, Chulalongkorn University, Bangkok, Thailand (COA No. 0328/2022, IRB No.0058/65) and written informed consent was obtained before bronchoscopy from all patients. The investigators comply with the following conditions:
1. Respect for person: the patients were informed all information without bias and discussed the benefit and risk before consent in this trial. Investigators respect the confidentiality of their subjects. The information obtained from the study, including the patient's history, will be kept confidential, considering the patient's

rights, and the presentation of the results will be an overview of all studies, which will not be presented individually. The volunteers will receive information and details about the research objectives and benefits of participating in the research. Volunteers make their own decisions to participate in research projects that match the principles of respect for individuals.

2. Beneficence/Non-Maleficence: Volunteers participating in the intervention group may benefit from research, they may be able to obtain a preliminary diagnosis by ROSE technics during the procedure, and the resulting biopsy may be effectively diagnosed. This allows doctors to plan treatments and diagnose diseases more quickly, which results in patients receiving appropriate treatment sooner than possible. Common risks associated with routine bronchoscopy procedures which are usually resolved without treatment such as sore throat, cough after procedure, aspiration, or nausea and vomiting.

3. Justice: Patients were included and excluded according to the criteria and no bias to inform to include in this trial.

1.8 Limitation

The RP-EBUS is a complicated technique that requires advanced bronchoscopic skills and RP-EBUS is not available in all hospitals. ROSE required an available experienced cytologist.

1.9 Expected or Anticipated Benefit Gain

1. If the use of ROSE during the procedure It can improve the ability to diagnose lesions or nodules in the peripheral lungs. It will be able to adjust the method for bronchoscopy procedure in the future. For example, ROSE may be prescribed in every bronchoscopy performed to collect tissue biopsy from peripheral lung lesions.

2. To assess the relationship of using ROSE during the procedure, whether there are positive or negative effects in various aspects such as the effect on the duration of the procedure, the amount of sedative used, the amount of blood loss

during the procedure and the quality of the tissue biopsy specimens. The data can be further analyzed together on the benefits of using ROSE during the procedure.

3. If the use of ROSE does not increase diagnostic yield of peripheral lung lesion. For example, ROSE does not reduce procedure time or has more disadvantages than the benefits, it may be used to refer to the use of ROSE is not superior to bronchoscopy without ROSE, which reduces the procedure process, reduces the number of personnel used for bronchoscopy and reduces resource consumption.

CHAPTER TWO
LITERATURE REVIEW

According to Robertson D. Davenport(8), a Randomized Controlled Trail study was conducted in the United States, from 1986 to 1988, studying the diagnostic yield of rapid on-site evaluation of transbronchial aspirates. Compared the ROSE group that used ROSE add on transbronchial biopsy with the control group. A total of 161 participants were enrolled, with a total of 207 biopsy cells. The results of the study showed that the use of ROSE increased the quality of tissue biopsy specimens and reduced the number of non-quality samples from 56% in the control group to 18% in the group using ROSE.

According to a study by Lonny Yarmus et al.,(9), a Prospective Randomized Controlled Trail study the diagnostic yield of using ROSE add on EBUS-TBN. The study was conducted in the United States. A total of 68 participants were divided into 34 experimental subjects who used ROSE during the procedure and 34 control subjects who did not use ROSE. The results of the study showed that the use of ROSE increased the tissue specimen adequacy by 94% compared to the control group that achieved 88%, but the diagnostic yield did not differ in both groups, 55% in the group using ROSE and 53% in the control group. The sedative doses were not different in both groups, it was found that the ROSE group can reduce the number of biopsies, especially in the malignancy group.

According to a study conducted by Chunhua Xu et al.,(10), a Prospective Randomized Controlled Trail study was conducted in China from February 2016 to August 2017, study of the diagnose yield of peripheral lung lesions and the duration on R-EBUS transbronchial biopsy comparing ROSE with controls group. A total of 158 participants were divided into 84 participants in the ROSE group and 74 participants in control group. The results of the study showed that the use of ROSE improved the diagnostic yield of transbronchial biopsies by 85.7% in the ROSE group and 70.3% in the control group. The duration of procedure in ROSE group is an average of 24.6

minutes, compared to an average of 31.5 minutes for the control group. This study concluded that the use of ROSE could increase the ability to diagnose yield of transbronchial biopsies and statistically significantly reduce the duration of bronchoscope.

Consistent with the study of Danial P.Steinfort (11). A Prospective Cohort Study was conducted in Australia from August 2011 to April 2013, studying the increase in the diagnostic yield of lung cancer from transbronchial biopsy. Using R-EBUS guided transbronchial biopsy and bronchial brushing, the group that used ROSE during R-EBUS guided transbronchial biopsy compared with the control group. A total of 118 participants were involved in the study who used ROSE during the procedure and found a total of 65(50.8%) specimens and the total biopsy resulted in malignancy 83(65%) specimens and the biopsy results did not match the ROSE cytology results in 22 specimens. From this study, it was concluded that the use of ROSE can be sensitive. Sensitivity in diagnosing malignancy was 76%, specificity 96%, positive predictive value 97% and negative predictive value 68%. It was also found that the ROSE group have an average bronchoscopy time of 19.2 minutes, compared to the control group which average 31 minutes, and found that the size of lung nodule was not associated with the results obtained from ROSE. 86 patients obtained R-EBUS transbronchial biopsy with bronchial brushing, 37 patients were diagnosed with malignancy and 49 patients were benign. 79% of ROSE cytology results were consistent with the final pathological result.

According to a study conducted by Masahide Oki et al.,(12), a Prospective Randomized Controlled Trail study was conducted in Japan studied the ability to diagnose peripheral lung nodules and mediastinal lymph nodes in participants suspected of lung cancer. Using the Endobronchial Ultrasound Guided Transbronchial Needle Aspiration (EBUS-TBNA) compared the group that used ROSE with the control group. A total of 108 participants were included in the study, 55 in the ROSE group and 53 in the control group. Diagnostic yield was 88% sensitive and 89% accurate in the ROSE group. and 86% sensitivity and 89% accuracy in the control group. It was found that there was no difference in bronchoscopy time in both groups. However, it was found that the group that used ROSE was able to reduce other procedures for

additional biopsies, and statistically significantly reduced the number of the biopsy needle was used compared to the control group: 2.2 times in the group using ROSE and 3.1 in the control group.

CHAPTER THREE

MATERIAL AND METHODOLOGY

3.1 Study Design and Population

Study design

Patients were enrolled between September 2021 to February 2023, we enrolled patients over the age of 18 who had been scheduled for bronchoscope to get the tissue diagnosis from the peripheral lung lesions in a single center randomized control study.

Population and setting

The study was conducted in Pulmonary division, Department of medicine, King Chulalongkorn Memorial Hospital, The Thai Red Cross Society, Thailand. Written informed consent was obtained from all patients before inclusion in the study. Chulalongkorn Medical Institutional Review Board approved the study. (IRB No. 0058/65)

All patients over the age of 18 who have been diagnosed with nodules or lesions in the peripheral lungs from chest computed tomography, which nodules or lesions are smaller than or equal to 3 centimeters.

Inclusion criteria

1. All patients over 18 years old

2.All patients diagnosed with peripheral lung lesions or nodule size smaller than or equal to 3 centimeters from chest computed tomography.

Exclusion criteria

1.Patients who have bronchoscopy contraindications (13) include:

-No consent for the procedure

-Patients do not cooperate during the procedure.

-Risk of hemorrhagic conditions such as Severe Thrombocytopenia (Platelet <20000), Coagulopathy (INR < 2) that have not been resolved.

-Severe or refractory hypoxia (SpO2 < 90%)

-Unstable Hemodynamic Status: BP<90/60, MAP< 65, HR < 50 or > 130, RR>30

-Myocardial Infarction within 4-6 weeks

-Patients who increased intracranial pressure

-Severe pulmonary arterial hypertension

-Other relative contraindication conditions depend on judgement of doctor, such as uremia and Superior Vena Cava Obstruction.

3.2 Randomization

Computerized randomization was used with a block of 4 participants unknown to investigators. A 1:1 ratio was randomly assigned for patients to go on bronchoscopy with RP-EBUS using ROSE (intervention group) or go on bronchoscopy with RP-EBUS without ROSE (control group).

3.3 Informed Consent Process

The researcher who conducts the research asks for consent when volunteers visit respiratory center at Bhumisirimangalajarn Building 10th floor, Chulalongkorn Hospital, where the doctor who conducts the research will explain the information and provide a document clarifying the research information include objective of study and algorithms. The researcher will answer questions until the patients understand and give them time to make independent decisions before signing their consent to participate in the research.

3.4 Procedures

The eligible volunteer would be described by the research physician. The doctor would hand out the information sheets. Research protocol, detailed procedures, and the risk of complications may arise from participating in the research. If the patient agreed to participate in the research project, the consent form was distributed for the patient to re-read and sign. The researcher would ask for consent after being approved by the Research Ethics Review Board.

Volunteers would enter the study, where the following essential characteristics were recorded: gender, age, current medications, height, diagnosis, indications for bronchoscopy, size, and location of the lesion and bronchus sign.

All subjects were divided into 3 subgroups based on the size of the pulmonary nodules, divided into groups with nodules sizes equal to 1 and less than 2 centimeters (1-2cm), similar to 2 and less than 3 centimeters (2-3 cm) and lesion equal to 3 centimeters. The number of subjects in each group was randomized and divided into intervention and control groups to reduce bias in diagnostic outcomes based on the size of nodules.

The subjects were randomly divided into intervention and control groups using blocked randomization. A computer-generated random number list was used to create a sealed opaque envelope.

In the intervention group, the participants proceed to bronchoscopy procedures using RP-EBUS. Once the target site was located, bronchial brushing was done. Cytologists evaluated cytology using ROSE with the Papanicolaou Stain method, i.e., Specimens obtained from bronchial brushing were applied to the slide and stained with Papanicolaou Stain. To view the cells under a microscope during the procedure. If abnormal cells were found during the first bronchial brushing, the next step was immediately transbronchial biopsy. Bronchial Brushing to collect cells from the target lesions to be viewed by the ROSE method 2 more times (no more than 3 times in total). Once it had been done 3 times, whether abnormal cells were found or not, the next step was transbronchial biopsy. The Specimen obtained from bronchial brushing and transbronchial biopsy would be sent for further examination of cytology and pathology.

Diagnostic ROSE specimens defined that specimen was clearly demonstrating the typical cytological features of alveolar tissue shown malignancy or benign. On the other hand, Non-diagnostic specimens defined that specimen demonstrated only normal epithelial cells or specimens demonstrated a scantly cell.

In the control group, the participants proceed to bronchoscopy procedures using RP-EBUS. Once the target site was located, bronchial brushing was done 3 times without ROSE, then the next step would be transbronchial biopsy immediately,

where 5 biopsies would be performed, then the specimen obtained from bronchial brushing and biopsy would be sent for cytology and pathology.

3.5 Specimen Handling

1)Tissue biopsy collection equipment

- Glass or plastic bottles with tight lids, containing 40% Formalin, about half of the bottles. The bottles label the volunteer's name, last name, age, patient number. There must be no tear marks and clearly visible letters.

2)Tissue biopsy collection procedure

- Once the biopsy has been performed, the medical assistant opens the Forceps and uses a pointed object to collect the biopsy that has been placed in the biopsy jar. Pack 40% Formalin immediately. If the tissue specimens cannot be removed completely, the end of the Forceps may be used to swing in 0.9% NaCl. Once the tissue specimens are fully collected, close the bottle cap tightly and attach the label, making sure the letter is clear and the name matches the patient's name then deliver to laboratory.

3)Collecting specimens from Bronchial brushing and performed ROSE

- Bronchial brushing specimen collection equipment is made by sending a cytology test by smearing the specimen onto a slide.
- Glass slide, clearly write the patient's name and number to identify the patient and show which side is in front of the slide.
- The bottle holds 95% Ethanol with a flood slide.
- labels on bottles enter volunteer's name, last name, age, patient number. There must be no tear marks and clearly visible letters.

4) Specimen collection procedures

- Brush the specimen label on the slide without getting too thick. Immediately immerse the slide in 95% Ethanol, flooding the entire slide. Label the bottle. Make sure the letter is clear and matches the patient's name and send it to the laboratory.

-Brush the specimen label on the slide without getting too thick and then dye it with Papanicolaou staining method to evaluate cytology by using ROSE technics.

3.6 Data Collection

During both the intervention and control groups, diagnostics and indications for the procedure, the duration of the bronchoscopy, the position RP-EBUS, the number of tissue biopsies, the number of bronchial brushings, the cytologic result from the ROSE method, the sedative doses, amounts of blood loss during the procedure and other complications that occur during the procedure were recorded.

When cytologic and pathological results were returned, the obtained data were corrected to interpret and analyze the diagnostic yield of final tissue pathological diagnosis from ROSE in combination with RP-EBUS procedures compared to the control group for further study of statistical associations. It also brings additional results, including the quality of the tissue biopsy and the cytological result. Other data, including the number of biopsies, the number of bronchial brushings, the cytologic result from the ROSE method, the sedative doses, blood loss during the procedure, and other complications that occurred during the procedure, were analyzed for statistical correlation.

3.7 Outcome Measures

The primary outcome is the diagnostic yield of peripheral lung lesions or nodules from the rapid on-site cytological evaluation (ROSE) during RP-EBUS transbronchial biopsy and brushing compared to the control group.

The Secondary outcomes are the duration of the procedure, the sedative doses, and amounts of blood loss during RP-EBUS transbronchial biopsy and brushing in peripheral lung lesions between the ROSE group versus control groups.

3.8 Data analysis and Statistical Analysis

Baseline Characteristic of populations and others qualitative data, including diagnostic results of biopsies. The quality of the tissue specimens, the position of RP-EBUS will be displayed as number and percentage Comparing data between groups using Fisher's Exact Test of Probability, $P<0.05$ is considered statistically significant.

Quantitative data including age, weight, height, number of brushing and biopsy, sedative doses, the amount of blood loss, with the normal distribution

shown in the table in the form of mean and standard deviation and compared data using Student's T-test. Non-Normal Distribution, displayed in a table in the form of median and interquartile Range, and compared the data using Mann-Whiney U Test.

The enrollment of 64 patients was determined to provide a power of 80% and to show the absolute difference in the diagnostic yield between the intervention group using ROSE add-on R-EBUS compared with the control group according to a prospective cohort study from (14) Diette G.G. et al. at alpha 2- sided (α) level equal to 0.05, The probability of a Type II error (β) as 0.2. The total number of each group was 34.

The statistician performed the analysis data on all randomized patients who met the inclusion criteria. Categorical variables were presented as numbers and percentages, and Fisher's exact test was used to compare them. Depending on the distribution of data, continuous variables were presented as mean or median and compared using an independent t-test or a Wilcoxon signed-rank test. Intention-to-treat analysis, as well as per protocol analysis, were analyzed. A p-value of less than 0.05 was considered to indicate statistical significance. STATA version 15 was used for all analyses.

3.9 Sample Size Calculation

Based on (14) Diette G.G. et al study the Utility of On-Site Cytopathology Assessment for bronchoscopic Evaluation of Lung Masses and Adenopathy to determine the extent to which on-site cytopathology assessment improves diagnostic yield when sampling lung nodules or masses and/or hilar or mediastinal lymphadenopathy by fiberoptic bronchoscopy (FOB) compared between groups that used the ROSE technique and those that did not use the ROSE technique.

The primary outcome measure was a new diagnosis obtained by FOB. On-site assessment was used in 81 of 204 cases (40%), and overall diagnostic yield was 62%. Yield was greater when on-site cytopathology assessment was used, in unadjusted analysis (81% vs 50%, $p < 0.001$) and in a multivariate model (odds ratio, 4.5; 95% confidence interval, 2.1 to 10.0). Other significant predictors of a new diagnosis

included older patient age, higher dose of narcotic used during FOB, and shorter procedure time.

Using the calculation formula for a randomized controlled study dichotomous endpoint, Two Independent Sample Study. The proportion is 1:1 with the probability of a Type I error (α) equal to 0.05, The probability of a Type II error (β) as 0.2, and Power as 0.8 Estimated sample size for two proportions with independent sample.

Fundamentals of Biostatistics (5th ed.) Duxbery: Thomson learning, 384-385.
Fleiss, J. L., Levin, B., &Paik, M.C. (2003) Statistical Methods for Rates and Proportions, (3rd ed.). John Wiley&Sons, 76.

$$n = \frac{\{Z_{1-\frac{\alpha}{2}}\sqrt{\bar{p}(1-\bar{p})\left(1-\frac{1}{r}\right)} + Z_{1-\beta}\sqrt{p_1(1-p_1)+\frac{p_2(1-p_2)}{r}}\}^2}{(p_1-p_2)^2}$$

$\bar{p} = \frac{p_1+p_2}{2}, r = \frac{n_2}{n_1}$

It requires Beta (β) = 0.1 , Alpha (α) = 0.05.

$\bar{p} = \frac{0.815+0.496}{2} = 0.6555, r = 1$

$$n = \frac{\{1.96\sqrt{0.6555(1-0.6555)(1-1)} + 1.28\sqrt{0.815(1-0.815)+\frac{0.496(1-0.496)}{1}}\}^2}{(0.815-0.496)^2}$$

= 34 /Group

P1 is the diagnostic rate of distal pulmonary nodules from pulmonary laparoscopy in combination with the use of the ROSE technique. It's 0.815.
P2 is Diagnostic rate of nodules in the peripheral lungs from pulmonary laparoscopy without the use of the ROSE technique. It's 0.496.

Δ = |p2-p1| = Differences in diagnosis rates between the two groups
n1 = calculated sample size, i.e., a group of 34 people each.
α = probability of type I error = 0.05 β = probability of type II error =0.2
z = critical Z value for a given α or β
K = ratio of sample size for group #2 to group #1

CHAPTER FOUR

RESULT

Overall, 80 patients who were assessed for eligibility were enrolled (Figure 1). After randomization, 10 patients were excluded due to severe thrombocytopenia and coagulopathy, or diagnosis was made by other procedures or severe hypoxemia. The final intention-to-treat population consisted of 68 patients; 34 patients per group were equally randomized.

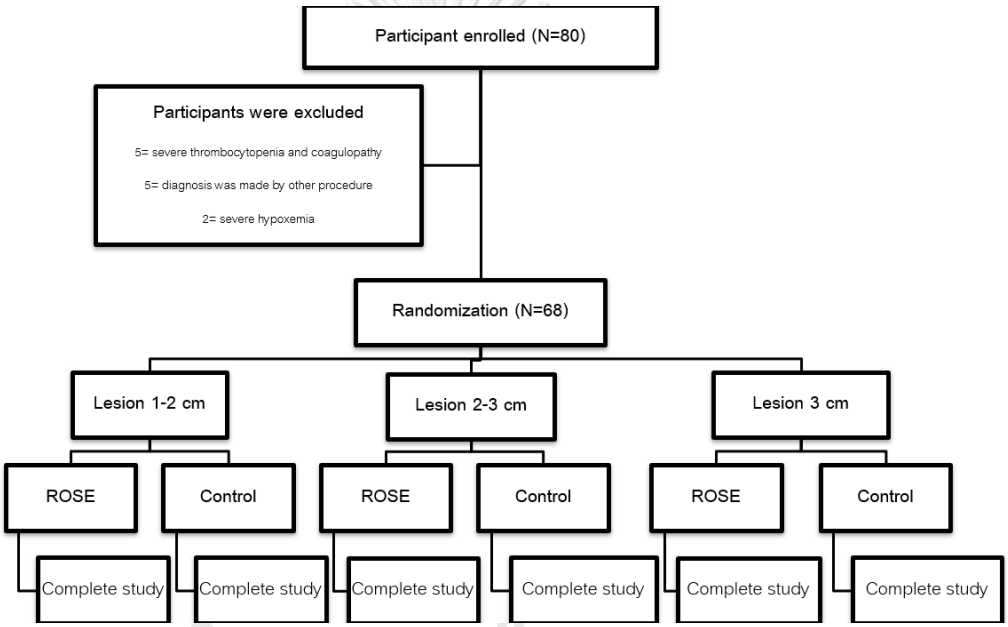

Figure 2 Study flow and Randomization

Demographic data of patients in the two groups was shown in **Table 1**; there were similarities in age, sex, indication for bronchoscopy, size and location of lesions, and position REBUS. The majority indication for bronchoscopy is suspected malignancy.

Only the number of brushings in the ROSE group was significantly less than the control; the median was 2 in ROSE and 3 in the control group. Meanwhile, the number of biopsies and tissue specimens obtained had no statistical difference.

Both groups' final tissue pathological results are benign diseases such as acute infection, chronic infection, and granulomatous. There were no significant differences between the two groups in terms of experience in bronchoscopy, all procedures were done under the supervision of an intervention pulmonologist.

The primary outcome is shown in **Table 2**. The diagnostic yield was similar in both groups; ROSE was 91.18%, and non-ROSE was 88.24%, not statistically significant (P=0.999). The diagnosis of malignancy was made in 32.6 % of ROSE and 41.19% of non-ROSE groups, respectively, without statistically different (P=0.523).

There was a concordant between the ROSE cytological result and the final tissue pathological diagnosis, which was a malignancy. The discordance between the ROSE cytological result and the final pathological result was founded in only benign tissue diagnosis. Within these, 8/34 (23.53%) ROSE results were normal respiratory epithelium, but the final tissue pathological result demonstrated a valid diagnosis, which was benign disease., shown in **Table 3.**

Table 1 Baseline characteristics and Procedure outcomes

	Control Group (N=34)	Rose Group (N=34)	P-value
Sex, N (%)			0.808
Male	17 (50.00)	18 (52.94)	
Female	17 (50.00)	16 (47.06)	
Age, Mean ± SD	65.68 ± 13.29	65.82 ± 11.7	0.962
Indication for bronchoscope, N (%)			0.709
Malignancy	31 (91.18)	29 (85.29)	
Benign	3 (8.82)	5 (14.71)	
Size of lesion, N (%)			0.402
1-2 cm	10 (29.41)	14 (41.18)	
> 2-2.9 cm	22 (64.71)	16 (47.06)	
3 cm	2 (5.88)	4 (11.76)	
Location, N (%)			0.396
upper lobe	14 (41.18)	16 (47.06)	
middle lobe	3 (8.82)	6 (17.65)	
lower lobe	17 (50.00)	12 (35.29)	
Bronchus sign, N (%)			0.787
yes	24 (70.59)	25 (73.53)	
no	10 (29.41)	9 (26.47)	
Position REBUS, N (%)			1.000
intralesional	26 (76.47)	26 (76.47)	
adjacent lesion	8 (23.53)	8 (23.53)	
Number of brushings, Median (IQR)	3 (3 - 3)	2 (1 - 2)	**<0.001***
Number of biopsies, Median (IQR)	7 (6 - 9)	7 (6 - 8)	0.812
Number of tissues, Median (IQR)	7 (5 - 7)	6.5 (6 - 7)	0.614
Bronchoscopists			0.452
Fellow 1st year	13 (38.24)	9 (26.47)	
Fellow 2nd year	10 (29.41)	12 (35.29)	
Fellow intervention	1 (2.94)	4 (11.76)	
IP staff	10 (29.41)	9 (26.47)	

Note: IQR; inter-quartile range, SD; standard deviation, N; number of patients

Table 2 Primary Outcome

	Control Group (N=34) N (%)	Rose Group (N=34) N (%)	P-value
Diagnostic yield (%)			0.999
Diagnose	30 (88.24)	31 (91.18)	
Non-diagnose	4 (11.75)	3 (8.82)	

Table 3 Final tissue pathological diagnosis and ROSE cytological report

	Control group (N=34) N (%)	ROSE group (N=34) N (%)	P-value
Pathological Tissue Diagnosis			**0.523**
Malignant	14 (41.19)	11 (32.36)	
benign	16 (47.05)	20 (58.82)	
Inadequate specimen	4 (11.76)	3 (8.82)	
ROSE cytology			NA
Malignant		11 (32.35)	
Benign		15 (44.12)	
Inadequate specimen		8 (23.53)	

The secondary outcome is shown in **Table 4**. There was statistically significantly reduced the procedure duration, 29.5 minutes (27-41) in the control group and 25 minutes (25-29) in the ROSE group [Median (IQR), P<0.001]. We also found that ROSE statistically significantly reduced the dosage of analgesic and sedative drug. The ROSE group used an average of 37.5 mcg (25-50) of fentanyl, whereas the control group used 75 mcg (50-100) of fentanyl [Median (IQR), P<0.001]. We were corresponding to the dose of midazolam. The mean of midazolam was 1.74±0.79 mg for the ROSE group, while the control group was 2.97±1.51 [Mean ± SD, P<0.001]. On the contrary, our study showed no statistical difference in the amounts of blood loss between the two groups.

Table 4 Secondary Outcome

	Control Group (N=34)	Rose Group (N=34)	P-value
	N (%)	N (%)	
Blood loss			0.779
Minimal blood loss	25 (73.53)	26 (76.47)	
Bleeding was controlled by endobronchial instillation of epinephrine#	9 (26.47)	8 (23.53)	
Procedure times (min)			**0.015***
0-30	20 (58.82)	29 (85.29)	
>30	14 (41.18)	5 (14.71)	
Mean ± SD	35.56 ± 11.93	25.79 ± 4.40	
Median (IQR)	**29.5 (27 - 41)**	**25 (22 - 29)**	**<0.001***
Dose fentanyl (mcg)			
0-50	10 (29.41)	30 (88.24)	
>50	24 (70.59)	4 (11.76)	
Mean ± SD	75.00 ± 31.98	41.91 ± 20.15	
Median (IQR)	**75 (50 - 100)**	**37.5 (25 - 50)**	**<0.001***
Dose midazolam (mg)			
Mean ± SD	**2.97 ± 1.51**	**1.74 ± 0.79**	**<0.001***
Median (IQR)	2 (2 - 4)	2 (1 - 2)	

#Minor bleeding was controlled by endobronchial instillation of epinephrine

Other significant predictors of diagnostic outcome shown in **Tables 5 and 6** included the position of RP-EBUS, presence of bronchus sign from chest computer topography, and size of lesions.

The position of RP-EBUS had an important effect on the diagnostic outcome; The intralesional RP-EBUS gave more diagnostic results than the adjacent RP-EBUS position, which was 96.15% vs. 68.75%, respectively (P<0.001).

Similarly, the Bronchus sign from chest computer topography had 97.96% on the diagnostic outcome versus 68.42 % in the negative bronchus sign group, P<0.001. Corresponding with the size of the lesions that strongly affected diagnostic outcomes. The lesion which a diameter of 2-3 cm had given 100% diagnostic results, while the lesions which a diameter less than 2 cm had only 70.83% diagnostic results, with statistically significant (P<0.001).

Table 5 Bivariate analysis for associated factors related to diagnostic outcomes

	Diagnose	Non-diagnose	P-value
	N=61	N=7	
Group, N (%)			0.999
Control Group (N=34)	30 (88.24)	4 (11.76)	
Rose Group (N=34)	31 (91.18)	3 (8.82)	
Age, Mean ± SD	61.14 ± 18.57	66.28 ± 11.63	0.304
Sex, N (%)			0.252
Male	33 (94.29)	2 (5.71)	
Female	28 (84.85)	5 (15.15)	
Position rebus, N (%)			**0.006***
Intralesional	**50 (96.15)**	2 (3.85)	
Adjacent to lesion	**11 (68.75)**	5 (31.25)	
Bronchus sign from CT chest, N (%)			**0.001***
yes	**48 (97.96)**	1 (2.04)	
no	**13 (68.42)**	6 (31.58)	
Indication for bronchoscope, N (%)			0.587
Malignancy	53 (88.33)	7 (11.67)	
Benign	8 (100.00)	-	
Size of lesion, cm, N (%)			**0.001***
1-2 cm	**17 (70.83)**	7 (29.17)	
> 2-3 cm	**44 (100.00)**	-	
Bronchoscopists			**0.026***
Fellow 1st year	**16 (72.73)**	6 (27.27)	
Fellow 2nd year	**21 (95.45)**	1 (4.55)	
Fellow intervention	**5 (100.00)**	-	
IP staff	**19 (100.00)**	-	
Blood loss, N (%)			0.999
Minimal blood loss	46 (90.20)	5 (9.80)	
Bleeding was controlled by endobronchial instillation of epinephrine	15 (88.24)	2 (11.76)	
Procedure Times (minute)			0.089
0-30	46 (93.88)	3 (6.12)	
>30	15 (78.95)	4 (21.05)	
Dose Fentanyl (mcg)			0.691
0-50	35 (87.50)	5 (12.50)	
>50	26 (92.86)	2 (7.14)	
Dose Midazolam (mg)			0.175
0-3	49 (92.45)	4 (7.55)	
>3	12 (80.00)	3 (20.00)	

Table 6 Multivariate analysis for associated factors related to diagnostic outcomes

	Diagnose	non-diagnose	Crude OR (95%CI)	P-value	Adjusted OR (95%CI)	P-value
	N =61	N =7				
Position rebus, N (%)						
Intralesional	**50 (96.15)**	2 (3.85)	**11.36 (1.95 - 66.38)**	**0.007**	2.08 (0.16 - 27.15)	0.575
Adjacent to lesion	**11 (68.75)**	5 (31.25)				
Bronchus sign from CT chest, N (%)						
yes	**48 (97.96)**	1 (2.04)	**22.15 (2.45 -200.72)**	**0.006**	11.60 (0.60 - 223.41)	0.104
no	**13 (68.42)**	6 (31.58)				
Procedure Times (minute)						
0-30	46 (93.88)	3 (6.12)	4.09 (0.82 - 20.38)	0.086	1.79 (0.19 - 16.84)	0.612
>30	15 (78.95)	4 (21.05)				
Dose Midazolam (mg)						
0-3	49 (92.45)	4 (7.55)	3.06 (0.60 - 15.55)	0.177	2.55 (0.23 - 28.31)	0.445
>3	12 (80.00)	3 (20.00)				

CHAPTER FIVE
DISCUSSION AND CONCLUSION

5.1 Discussion

The potential impact of ROSE during bronchoscopy had been previously reported to result in an increased diagnostic yield for TBNA in several previous retrospective and prospective cohort studies.

Our study is the first accurate randomized study on the effect of ROSE during RP-EBUS TBLB in the diagnosis of peripheral lung lesions. ROSE feeds back valuable information to the examiner on the adequacy of cytologic samples at the time of brushing procedures, which indicates whether the process should be repeated or not. In a previous study, conventional EBUS-TBNA and R-EBUS –TBLB many investigators have reported the usefulness of ROSE, but the role is controversial. Davenport (8) retrospective review of 207 bronchoscopy cases that involved TBNA, some of which (73 of 207 cases) involved ROSE.

In Bivariate analysis, reported improvements in yield in TBNA with on-site assessment (81% improvement). In this study, the location of TBNA is a central lesion 50%, and only the other half is peripheral lung lesions. This non-randomized study is limited by potential selection bias, as the decision to use ROSE was based on the physician's preference. Furthermore, Lonny (9), a Prospective Randomized Controlled Trail, studied the diagnostic yield of using the ROSE add-on EBUS-TBNA. The study's results showed that ROSE was not associated with an improved diagnostic yield or specimen adequacy, reduced (or increased) procedure time, or the amount of sedation/topical anesthesia required. According to a study conducted by Masahide Oki et al. (12), a Prospective Randomized Controlled Trail study was conducted in Japan studied the ability to diagnose mediastinal lymph nodes by EBUS-TBNA compared the group that used ROSE with the control group. Diagnostic yields were similar in both groups, 88% sensitive and 89% accurate in the ROSE group. And 86% sensitivity and 89% accuracy in the control group. It was found that there was no difference in bronchoscopy time in both groups. However, it was found that the

group that used ROSE could reduce other procedures for additional biopsies and statistically significantly reduced the number of biopsy needles used compared to the control group. Reasons for the different improvement rates in the previous study could include a different patient and process-of-care factors, although different study designs and reported clinical detail preclude direct comparison. All previous studies had limitations in observational study and the decision to use ROSE was not controlled.

Our study showed that all baseline characteristics and bronchoscopy indications were similar. There is no significant difference between RP-EBUS TBLB with brushing with and without ROSE in terms of diagnostic yield. This could be explained by the high diagnostic yields of REBUS-TBLB regardless of using ROSE and our intervention pulmonologist's high expertise and experience. Compared to a previous study, when subsequent diagnostic procedures and follow-ups were assessed, there was no difference in malignancy rates between the ROSE and non-ROSE groups, suggesting that randomization may have prevented a preferential use of ROSE in patients with malignant versus benign.

The current results support the possibility that previous reports suggesting an increased diagnostic yield with ROSE may have resulted from selection bias. Routine use of ROSE in all RP-EBUS procedures in which TBNA is anticipated may not be optimal due to the lack of additional diagnostic benefits with ROSE. The bronchoscopists in this study have a great deal of experience with TBNA. Less-experienced operators may improve their yield by performing other needle passes if on-site cytology indicates that initial specimens need to be improved. ROSE may be beneficial in cases where malignancy is likely by avoiding additional procedures, such as transbronchial biopsies, and their associated risks.

In our study, ROSE could be reduced procedure times and dose of sedative drugs. From bivariate analysis, the factors that affect the diagnostic outcome are the position of REBUS, the presence of bronchus signs on the CT chest, the size of the lesion, and the bronchoscopist’s experience.

From the multivariate analysis in unadjusted analysis, the factors that affect the diagnostic outcome are the intralesional presence of RP-EBUS and. Still, there were bronchus signs, but there were not statistically significant in adjusted OR.

There are several limitations in our study. This study was carried out at a single institution, and all bronchoscopies have been performed under the supervision of an intervention pulmonologist. RP-EBUS is not available in every hospital. Also, ROSE requires available experienced cytologists. Therefore, the results may need to be more generalizable to other centers and bronchoscopists.

In the future, a multicenter and larger study should be performed investigating the utility of ROSE add-on RP-EBUS TBLB and the incremental yield of RP-EBUS-TBLB over standard RP-EBUS-TBLB in other hospital settings, such as general hospitals, and performed by non-intervention pulmonologists, which may yield different diagnostic outcomes.

5.2 Conclusion

To our knowledge, our study is the first randomized control study on the diagnostic yield of peripheral lung lesions using ROSE add-on RP-EBUS TBLB with bronchial brushing. The diagnostic yield of peripheral lung lesions was similar in ROSE add-on RP-EBUS guided sheath bronchial brushing and transbronchial biopsy and RP-EBUS guided sheath transbronchial biopsy with bronchial brushing alone. However, routine ROSE in RP-EBUS can be reduced in procedure times and decreased sedative use. ROSE may be beneficial by reducing the number of bronchial brushings.

We recommended ROSE add on REBUS-guided sheath transbronchial biopsy with bronchial brushing in selected cases. Our study was done in the experienced center which available intervention pulmonologists and cytologists. In the future, larger and multicenter studies are needed to compare the diagnostic yield of RP-EBUS with or without ROSE.

5.3 Limitation

1) Limit of generalization; our study was performed only in tertiary hospital setting.

2) RP-EBUS are not available in all hospitals and ROSE required available experienced cytologist.

3) There are same ratio of position RP-EBUS in both group, further subgroup analysis may be shown the different outcome on diagnostic yield.

5.4 Recommendation

Implementation of ROSE with RP-EBUS Guided Sheath Transbronchial lung biopsy and brushing may be considered case by case.

Further research is needed to determine whether the statistically significant reduced procedure time and sedative doses influence clinical outcomes.

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