The Role of Narrow Band Imaging (NBI) Bronchoscopy in Detecting Bronchial Squamous Dysplasia in Lung Cancer

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1. **Title**

   The Role of Narrow Band Imaging (NBI) Bronchoscopy in Detecting Bronchial Squamous Dysplasia in Lung Cancer

2. **Ethical clearance**

   The date of approval from Health Research Ethics Committee Faculty of Medicine Universitas Indonesia, Dr. Cipto Mangunkusumo General Hospital is 23rd March 2023 (KET-361/UN2.F1/ETIK/PPM.00.02/2023

3. **Study Protocol**

   - **Problem Statement**
     1. What are the NBI imaging criteria for detecting bronchial squamous dysplasia in lung tumor patients?
     2. How does the diagnostic profile of NBI bronchoscopy compare with standard bronchoscopy (white light bronchoscopy, WLB) in detecting bronchial squamous dysplasia in lung tumor patients?
     3. Can the addition of NBI to standard bronchoscopy procedures improve diagnostic accuracy in detecting bronchial squamous dysplasia in lung tumor patients?

   - **Research Objectives**

     This research aims to determine the diagnostic profile (area under the curve, AUC; sensitivity, specificity, positive predictive value, and negative predictive value) of NBI bronchoscopy in detecting bronchial squamous dysplasia in lung tumor patients.

4. **Method**
   - **Study Design**

     This is an observational diagnostic study. The research was conducted at the bronchoscopy suite of Persahabatan Hospital, where bronchoscopy procedures, bronchial biopsy collection, and specimen handling took place. The histopathological examinations were carried out in the Department of Anatomical Pathology, Faculty of Medicine, Universitas Indonesia, The patient recruitment time ranges from March to December 2023.
   - **Population**

     The target population consists of all lung tumor patients. The accessible population consisted of lung tumor patients who underwent bronchoscopy procedures at Persahabatan Hospital from March to December 2023.
   - **Study participants**

The study participants comprised individuals from the accessible population who met the research participants acceptance criteria and provided informed consent. The consecutive sampling method was employed.

- **Study participants calculation**

  The study participants size was calculated using the diagnostic research sample size formula. The minimum sample size required was 110 participants

- **Inclusion criteria**
  1. Patient aged > 18 years undergoing bronchoscopy for diagnostic evaluation of lung tumors
  2. Recent radiological examinations, including both chest X-ray and chest CT scans, within the last month, revealed a central lesion of lung cancer
- **Exclusion criteria**
  1. Refusal to provide informed consent
  2. Contraindications to bronchoscopy
- **Participants selection**

  Screening was conducted on all lung tumor patients scheduled for bronchoscopy procedures, and the participants selection was carried out in accordance with the inclusion and exclusion criteria

- **Sampling Technique**

  The preparation and execution of bronchoscopy and bronchial biopsy were performed in accordance with the standard operating procedures (SOP) at Persahabatan Hospital. The bronchoscopy and bronchial biopsy procedures were conducted by a single operator, the principal investigator. The bronchoscopy procedure uses general anesthesia. The flexible fiberoptic bronchoscopy was performed using an Olympus EVIS EXERA III with a Xenon light source, model CLV-190, and BF-1TQ170 series scope. The Boston Scientific Radial JawTM 4 disposable lung biopsy forceps were employed. Bronchoscopy was initially performed under the white light, followed by the activation of the NBI feature for airway inspection. Biopsies were obtained from areas identified through NBI bronchoscopy findings. Furthermore, the criteria for bronchoscopy images suspected for dysplasia included the presence of dotter vessels, capillary loops, tortuous vessels, and abrupt ending vessels. No biopsies were conducted on infiltrative neoplasms or tumors. The biopsied tissue was then preserved in a separate 10% formalin solution. Tissue processing involved paraffin embedding and Hematoxylin-Eosin staining. Tissue processing was performed using a Tissue Processor machine. Following tissue processing, paraffin blocks were created and sectioned. Hematoxylin-Eosin staining was then performed. Diagnosis of squamous bronchial dysplasia (pre-cancer lesion) was made by a specialist in Anatomical Pathology.

5. Statistical Analysis Plan (SAP)

The research data were recorded on research forms and subsequently entered into SPSS 26 software. the bivariate analysis was conducted between each vascular pattern based on NBI bronchoscopy and the histopathological result. The descriptive data will be presented by the text and tables consist of the basic characteristics of the study participants and research variables. The multivariate analysis was performed on all vascular patterns based on NBI bronchoscopy and histopathological results. Furthermore, a pre-cancer prediction score was generated. An analysis of the AUC (area under the curve) of the squamous dysplasia prediction model form NBI bronchoscopy findings was conducted with a significance level set at $p < 0.0.5$

6. Informed Consent Form (ICS)

RSUP PERSAHABATAN Jl. Persahabatan Raya No. 1 East Jakarta, Phone. 021-4891708 / Fax : 021-4711222	**MR Number** : …… **Name** : …… **Sex** : …… **Date of Birth** :……

MEDICAL PROCEDURE CONSENT FORM			
INFORMED CONCENT			
Principal Investogator		dr. Mia Elhidsi, SpP(K)	
Informant			
Recipient of Information			
NO	**Type of Information**	**Information**	**Checklist (V)**
1	**Aims**	To understand the relationship between narrow-band imaging (NBI) bronchoscopy and bronchial dysplasia abnormality	
2	**Research benefit**	To determine whether the patient has respiratory damage, to ascertain whether the patent is suffering from lung cancer; to establish whether the patient has lung cancer metastasis	
3	**Procedures**		
	a. Protocol	1. Participants over 18 years old with a diagnosis of lung tumor without metastasis to the adjacent lung tissue who undergo bronchoscopy procedure at Persahabatan Hospital between March to December 2023 will be invited to participate in the research	
		2. Research participants will sign an informed consent form	

		3. Some necessary data will be collected	
		4. Tissue samples will be taken from the tumor and the other lung using a bronchocope	
		5. The disposable equipment will be used for the tissue collection to avoid contamination	
		6. Bronchoscopy was initially performed under the white light, followed by the activation of the NBI feature for airway inspection.	
		7. Biopsies were obtained from areas identified through NBI bronchoscopy findings. No biopsies were conducted on infiltrative neoplasms or tumors.	
		8. The bronchoscopy procedure and tissue collection will be documented with video recording	
	b. Risk	1. Bronchoscopy procedures in patients may cause discomfort	
		2. There is a risk of respiratory tract infection due to the bronchoscopy procedure. However, this can be prevented by washing hands before and after the procedure, and using disposable biopsy tools	
		3. Some other risks, such as bleeding, may occur during the bronchoscopy procedure. Nevertheless, this can be prevented by conducting the procedure carefully based on standard operating procedures (SOP)	

	c. Complications/side effect	Complications that occur from bronchoscopy procedures include bleeding or anaesthesia-related issue during the procedure. However, these can be avoided by conducting the procedure carefully based on the SOP	
	d. Actions to be taken in case of complications/side effect	In the event of complications/side effects, the bronchoscopy procedure will be stopped, and appropriate measures will be taken to address the specific complication or side effect that arises.	
	e. Compensation in case of complications	There will be no additional compensation provided	
	1). Confidentiality	The identity of each research participants will be kept confidential.	
	2). Participants right to withdraw	Research participants have the right to withdraw from the study at any time.	
	3). Voluntary participation	Participation in the study is entirely voluntary, and potential research participants will be given the opportunity to read the informed consent document and have time to consider their participation before enrolling in the study.	
I declare that I have explained the above matters correctly and clearly, and have provided the opportunity for questions and/or discussion.			Signature
I acknowledge that I have received information from the researcher as described above, and I have placed my signature/initials in the right-hand column, indicating my understanding			Signature
) If the research participants is not competent or unwilling to receive information, then the recipient of the information will be the legal guardian or closest family member.			

Information for Potential Research Participants

My name is dr. Mia Elhidsi, SpP(K), the principal investigator at Persahabatan Hospital of a research study titled "The Role of Narrow-Band Imaging (NBI) Bronchoscopy in Detecting Bronchial Squamous Dysplasia in Lung Cancer. This document provides an explanation of the research study and can be read to understand what will be done and what is required if you choose to participate.

1. **Research Objectives**
   This research aims to determine the accuracy of NBI bronchoscopy in detecting pre-cancerous lesion in patients with lung tumor. What is NBI bronchoscopy? It is a bronchoscopy feature that provides images with higher contrast compared to standard bronchoscopy images. This feature enabling more accurate detection of airway abnormalities. Additionally, this study aims to investigate the correlation between NBI bronchoscopy findings and epithelian bronchial dysplasia in lung tumors.

2. **Participation in the Research**
   You are invited to participate in this research. Participation is voluntary. The research will run from approximately March to December 2023. Your involvement will include interviews, physical examinations, bronchoscopy procedures, and airway tissue biopsies. If you agree to participate and meet the research criteria, you will undergo a bronchoscopy procedure as usual, followed by bronchoscopy with narrow-spectrum light features and biopsy if abnormalities are detected. Tissue biopsies will be evaluated by the Department of Pathology at Persahabatan Hospital.

3. **Selection Criteria**
   Based on the initial criteria, you are considered a suitable candidate for this research if you are meet some criteria, including:
   - An adult, aged over 18 years at the time of consent.
   - Undergoing bronchoscopy due to a lung tumor for diagnostic purposes.

   You cannot participate in the research if:
   - You do not consent to the research's informed consent form.
   - You have contraindications related to bronchoscopy procedures, such as blood pressure and heart rhythm-related conditions, recent heart attacks, uncontrolled heart rhythm disorders, a history of chest pain, and blood oxygen gas level disturbances. Additionally, you cannot undergo bronchoscopy if you have contraindications related to the pre-procedure anaesthesia, such as a history of severe bleeding disorders.
   - You are severely ill patients (bedridden category) or require assistance with daily activities.

Based on the initial criteria, we will conduct a comprehensive review to determine your eligibility for our research.

4. Research Procedures

a. Information about Intervention Procedures

Before participating in the research, you will undergo several examinations to ensure your suitability for the research.

- Prior to research participation, you will undergo initial examinations to assess your eligibility.
- You will be interviewed by a doctor to inquire about your name, age, medical history, pain complaints, family history of cancer, and smoking history.
- The doctor will conduct a physical examination and enter data from additional supportive examinations, such as laboratory and radiological tests.
- If you meet the criteria for research participation and agree to sign the consent form, the doctor will prepare you for bronchoscopy and airway tissue biopsy procedures according to the standard operating procedures at Persahabatan Hospital
- The bronchoscopy and biopsy procedures will be performed by the researcher. Before the procedure, you will be anesthetized according to Persahabatan Hospital's standard operating procedures.
- The researcher will use a disposable biopsy forceps for tissue sampling.
- Biopsies were obtained from areas identified through NBI bronchoscopy findings.
- The doctor will assess and collect tissue (biopsy) from three airway areas: Area 1: Trachea and carina, Area 2: Main right and left bronchi and their branches.
- Biopsies were obtained from areas identified through NBI bronchoscopy findings. No biopsies were conducted on infiltrative neoplasms or tumors.
- Tissue samples from each area will be placed in separate 10% formalin solution.
- Subsequently, the tissues will be processed using paraffin blocks and Haematoxylin-Eosin staining by technicians from the Department of Pathology at Persahabatan Hospital
- The examination results will be recorded on research forms.

b. Currently Available Alternative Procedures

If you choose not to participate in this research, the alternative procedure available at this time is white light bronchoscopy, which provides images without contrast.

5. Risk, Side Effect, and Management

NBI bronchoscopy itself does not have side effects or complications. Additionally, the side effects can occur due to the bronchoscopy intervention procedure. Possible complications and side effects are include pain, discomfort during the procedure, increased risk of respiratory

infections, bleeding in the airway, and complications due to pre-procedure anaesthesia. However, these risks and side effects can be minimized by conducting the procedure carefully and in accordance with standard operating procedures (SOP). The bronchoscopy procedures conducted at Persahabatan Hospital have been safe.

In the case of complications/side effects, the bronchoscopy procedure will be stopped, and management will be carried out according to the specific complication/side effect by the bronchoscopy and anaesthesia team.

If needed, you are free to contact us and discuss any concerns. You will be informed before proceeding with the next steps of the research.

6. Benefits

The use of NBI bronchoscopy imaging to assess airway abnormalities in lung tumor patients offers the benefit of improving the accuracy of early lung cancer detection. It also contributes to the foundation of knowledge for the development of further lung cancer management**.**

7. Compensation

By participating in this research, you will receive additional examinations that are not routinely performed on other patients, such as NBI bronchoscopy.

8. Financing

You will not incur additional charges for NBI bronchoscopy. The costs of bronchoscopy and other diagnostic procedures will be covered based on your healthcare insurance.

9. Confidentiality

If you choose to participate in this research, all your data will be kept confidential. Research presentations at scientific meetings/conferences and publications in scientific journals will not include your name.

10. Research Participants Obligations

As a research participants, you are obligated to follow the research rules and guidelines as outlined above. If anything is unclear, you can ask the researcher for further clarification.

11. Right to Refuse and Withdraw

You are not obligated to participate in this research, and if you choose not to, your decision will not affect the treatment you receive at our hospital. You are also free to withdraw from the research at any time. It is your personal choice, and your rights will be respected.

We will provide you with an opportunity at the end of this explanation to consider your decision.

12. Additional Information

You are encouraged to ask any questions about the research that are not yet clear. If you experience any side effects or require further explanations, you can contact:

Dr. Mia Elhidsi, Sp.P(K)
Rawamangun, East Jakarta 13220
Phone: 081386633191
Email: miapulmo.ui@gmail.com

This proposal has been reviewed and approved by the Research Ethics Committee of the Faculty of Medicine, Universitas Indonesia, and Persahabatan Hospital; a committee responsible for ensuring participant protection from harm.