nCLE-guided bronchoscopy for peripheral lung cancer diagnosis: a Randomized Controlled Trial

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To evaluate the added value of nCLE-imaging to conventional bronchoscopic peripheral lung lesion analysis on the diagnostic yield.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Respiratory and mediastinal neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON53986

Source
ToetsingOnline

Brief title
Confocal Laser Endomicroscopy Verification (CLEVER)

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
Peripheral lung cancer

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Mauna Kea Technologies,Mauna Kea Technologies financiert het onderzoek

Intervention

Keyword: Bronchoscopy, Confocal microscopy, Diagnosis, Lung Cancer

Outcome measures

Primary outcome

To determine if the addition of nCLE-imaging to conventional bronchoscopic peripheral lung lesion analysis results in an improved diagnostic yield.

Secondary outcome

1. Diagnostic sensitivity for malignancy (defined as the proportion of patients that have malignancy diagnosed by bronchoscopic tissue sampling, relative to the total number of patients with a final diagnosis of malignancy as determined by the reference standard).

2. Procedure duration (from bronchoscope insertion until removal)

3. Amount and proportion of needle repositionings (defined as the selection of a different distal airway for tissue sampling) and needle fine-tuning tuned (defined as moving the needle within the same distal airway) per arm

4. To assess the diagnostic yield for several lesion and procedural characteristics (lesion size, bronchus sign, eccentric vs concentric vs absent radial EBUS image, location)

5. Fluoroscopy time and radiation dose

6. To extend the nCLE image atlas for malignant and benign pathologies

7. To assess the yield of ROSE for a classifying diagnosis

8. To assess the ability of ROSE to provide tool-in-lesion-confirmation (the acquisition of tissue not related to airway/lung parenchyma sampling such as bronchus epithelium/blood contamination including tissue not suitable for a

specific diagnosis such as atypical cells)

9. Complication rate (defined as any complication occurring during or directly after the bronchoscopic procedure or any procedure-related complication in the follow-up period).

10. Proportion of patients per arm that need additional diagnostic procedures (CT-guided transthoracic biopsies, surgical diagnostics and/or additional bronchoscopy) after the bronchoscopy during the 6-month follow-up period.

11. Create an algorithm for automated nCLE criteria recognition (for example machine learning)

Study description

Background summary

Lung cancer screening and the increasing use of chest-computed tomography (CT) has led to an increase in the number of (incidental) found suspected malignant lung lesions. Since tissue acquisition for pathological analysis is prerequisite for diagnosis and optimal treatment, a drastic increase in the number of patients that need to undergo bronchoscopy is expected.

Over 70% of the suspected lesions develop in the periphery of the lung and are therefore not visible during conventional bronchoscopy. Although several bronchoscopic navigational techniques demonstrated an improved navigation towards the target lesion, the diagnostic yield remains suboptimal due to a substantial near-miss rate. As a result, the need for complementary bronchoscopic guidance that provides real-time feedback on the correct positioning of the biopsy instruments is urgent.

Needle-based Confocal laser endomicroscopy (nCLE) is a novel high-resolution imaging technique that uses an excitation laser light to create 'real-time' microscopic images of tissues. nCLE can be integrated into the biopsy needle, allowing real-time cancer detection at the tip of the biopsy needle during bronchoscopy. The confocal microscope captures autofluorescence of tissues or, combined with intravenously (IV) infused fluorophores (such as fluorescein) allows imaging of individual tumor cells. Recent studies on nCLE-imaging in lung tumors and metastatic lymph nodes have identified and validated nCLE

criteria for malignancy (enlarged pleomorphic cells, dark clumps and directional streaming) and airway/lung parenchyma (alveoli, elastin fibres of the conducting airway, bronchial epithelium and still image) and granuloma. Preliminary results of an ongoingstudy in our center demonstrate that these nCLE-criteria can be used in real-time to fine-tune the needle positioning during ongoing bronchoscopy and thereby potentially improve the diagnostic yield.

In the present study, we aim to evaluate the added value of nCLE-imaging (smart needle) to the conventional used bronchoscopic approach for peripheral lung lesion analysis.

Study objective

To evaluate the added value of nCLE-imaging to conventional bronchoscopic peripheral lung lesion analysis on the diagnostic yield.

Study design

Investigator-initiated, international, multi-center randomized controlled trial including university and general hospitals.

Intervention

Bronchoscopy will be performed as usual, including radial endobronchial ultrasound (r-EBUS) and optionally fluoroscopy, followed by transbronchial needle aspiration (TBNA and (cryo-)biopsies (control arm). In the study arm, nCLE-imaging will be added prior to tissue acquisition to fine-tune the sampling area. Cytology staining for rapid onsite evaluation (ROSE) and cellblock will be performed according to local practice (ROSE mandatory for first pass).

Study burden and risks

A participating patient who enters the study and will be randomized to the interventional arm might benefit from improved diagnostic accuracy, however this has yet to be proven and is subject of the study. However, future patients might benefit from improved lung cancer diagnostics based on study findings. The risks of study participation is neglectable as previous study publications showed that nCLE-imaging and IV fluorescein administration are safe. In the prior bronchoscopic nCLE studies in Amsterdam UMC, including over 50 patients, no study related adverse events occurred. Right before nCLE-imaging, fluorescein will be administered intravenously through an existing venous entrance. Fluorescein is a commonly used dye in hospitals (e.g. in ophthalmology) and adverse reactions are rare (1.1%) and mild in character. In 2010, Wallace et al. published a retrospective study of all confocal laser

endomicroscopy procedures performed between January 2003 and November 2008, with in total 2,272 procedures and no serious adverse events related to fluorescein injection were identified (1). nCLE measurements will be performed during bronchoscopic work-up and is followed by conventional cytological aspirations (routine work up), without the need for additional aspirations or biopsies for research purposes. Estimated prolonged endoscopy time due to study participation is approximately 10 minutes. Patient will not be aware of this as patients are already sedated for the bronchoscopic procedure. In conclusion we believe that the burden and risks associated with study participation (up to 10 minutes additional sedation time and application of fluorescein) are neglectable.

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

• >=18 years of age
• Suspected malignant peripheral lung lesion with an indication for a bronchoscopic diagnostic work-up
• Solid part of the lesion must be >10 mm
• Largest dimension of lesion size on CT equal to or less than 30 mm
• Bronchus sign on pre-procedural CT or estimated confidence for successful navigation to the nodule resulting in a r-EBUS signal
• Ability to understand and willingness to sign a written informed consent

Exclusion criteria

• Inability or non-willingness to provide informed consent
• Patients with an endobronchial visible lung tumor on bronchoscopic inspection
• Patients in which the target lesion is within reach of the linear EBUS scope
• Failure to comply with the study protocol
• Patients with known allergy for fluorescein or risk factors for an allergic reaction
• Pregnant or breastfeeding women
• Patients with hemodynamic instability
• Patients with refractory hypoxemia
• Patients with a therapeutic anticoagulant that cannot be held for an appropriate interval before the procedure
• Patients who are unable to tolerate general anesthesia according to the anesthesiologist
• Patient undergoing chemotherapy as several chemotherapies have fluorescent properties at the same wavelength (e.g. doxorubicin)
• Inability to follow-up

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	17-10-2023
Enrollment:	45
Type:	Actual

Medical products/devices used

Generic name:	Cellvizio
Registration:	Yes - CE intended use

Ethics review

Approved WMO Date:	10-05-2023
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-04-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
ClinicalTrials.gov	NCT06079970
CCMO	NL83267.018.22