Mini invasive pleural probe based confocal laser endomicroscopy for malignant pleural effusion diagnosis

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Study protocol

Introduction

Confocal laser microscopy was first introduced at the Princeton University by Professor Marvin Minsky. This optical imaging technique uses a pinhole at the confocal plane of a lens, selecting a very narrow parallel shaped beam coming from the confocal plane (located in the object of interest) and eliminating out of focus light. A laser is used as illuminating source of light, hence the technique name, because of its optical properties allowing better resolution. The LASER beam can then excite molecules in the confocal plane of the sample examined, resulting in autofluorescence of some molecules. The autofluorescent light emission can then be captured and analyzed (1,2). In probe-based confocal laser endomicroscopy (pCLE), a confocal laser microscope is associated with a probe of multiple optical fibers allowing introduction (cross sectional diameter 1.2 mm) through the working channel of endoscopes. Confocal microscope can be located at the tip of the probe or in an external unit. This technique can show in vivo imaging at a cellular level with a video frame of 12 images per second, a lateral resolution of 3 µm, an optical area of 1.13 mm² and a depth of focus of 0-50 µm.With this technology, clinicians can obtain in vivo and live imaging at the cellular level called "optical biopsies". Furthermore, pCLE allows to see some details not visible during classic histology (due to fixation process) as blood flow (3), microorganisms (4) ...
Probe based confocal laser endomicroscopy was fisrt used in gastroenterology (endobrachy oesophage, bilio-pancreatic lesions, colorectal polyps, inflammatory bowel disease…) (5). In pulmonary medicine pCLE came later to the light and is still an experimental technique but several studies are on going. Domains of interest are numerous:

- Pulmonary nodules evaluation;
- Interstitial lung dieases;
- Lung and bronchus infections;
- Lung rejection after transplantation (6);
- Lung emphysema (7);
- Mediastinal adenopathy (8);
- Pleural malignancies ;

Pleural effusion is a common finding in medical practice and often requires thoracocentesis and pleural biopsies to determine the underlying disease. However, thoracocentesis with pleural fluid cytology has limited sensitivity (up to 60% for repeated thoracocentesis) for a malignant pleural effusion diagnosis, one of the most common cause of pleural effusion (9–11). Therefore, thoracoscopy is often required, allowing direct pleural examination and biopsies with a sensitivity and a specificity of 94% and 100 % for malignant diseases(12,13). Nonetheless, this procedure is more invasive than a simple thoracocentesis. Recently, four studies demonstrated that pleural pCLE could be of value for the diagnosis of malignant pleural effusion. In 2018 Zirlik et al. showed that pCLE with fluoresceine performed in the pleural fluid after thoracocentesis was able to identify a malignant pleural effusion with 87 % sensitivity and 99% specificity compared

pleural fluid cytology (14). In 2019 Wijmans et al. showed that pCLE was able to guide pleural biopsies when the probe was passed through the biopsy needle during a thoracoscopy, an open thoracotomy or an ultra-sound or CT guided pleural biopsy when a malignant pleural mesothelioma was suspected(15). In 2021 our team published a prospective trial showing that pCLE during medial thoracoscopy was able to discriminate malignant from benign pleura(16,17). The same year, Sawada et al. showed that pCLE performed during surgery for lung cancer was able to identify a visceral pleural involvement with 100% sensitivity and 83% specificity(18). Considering these results and the low sensitivity of thoracocentesis for malignant pleural effusion identification, we conducted this proof of concept study to determine if mini-invasive close-blinded pleural pCLE performed through a Boutin's needle was feasible, safe and had a better sensitivity than thoracocentesis.

Study design

Exploratory study on a diagnostic procedure based on a cross-sectional study. We will prospectively include all patients referred to medical pleuroscopy for pleural effusion treatment or work-up.

The intervention was divided into four parts realized by the two same experienced investigators: First, the thoracocentesis for pleural fluid sampling and pathological examination; Second, the mini-invasive pleural pCLE (Alveoflex ®, lateral resolution 3 µm, optical area 1.13 mm^2, depth of focus 0 - 50 µm) (Cellvizio®, Maunakea technologies®, Paris, France); Third, the invasive pleural pCLE through the thoracoscope; Fourth, the traditional medical thoracoscopy with pleural examinations, biopsies and talc poudrage if required. Two different thoracoscopes were used during this study: A Wolf thoracoscope with an outer diameter of 7 mm (Richard Wolf GmbH, Knittlingen Germany ®) and a Storz single puncture thoracoscope with an outer diameter of 10 mm (Karl Storz GmbH, Tuttlingen, Germany ®). For pleural staining, 5ml of fluorescein 10% were intravenously administrated 5 min before pCLE acquisition. The investigators were aware of the clinical history of the patients during the intervention as it happens in real clinical practice.

For the mini-invasive pleural pCLE, the probe was blindly introduced in the pleural space through the Boutin's needle (traditionally used in medical thoracoscopy to induce a pneumothorax before insertion of the trocar) until satisfying images were recorded. At the same time, the two endoscopists rated 7 criteria (see the table 1 for the criteria and their interpretation). The part three (invasive pleural pCLE) started by the insertion of the trocar allowing to perform the medical thoracoscopy. For this part, the probe was gently applied on the parietal pleura through the working channel of the thoracoscope under vision control. If macroscopic abnormalities were noticed, pCLE was performed on the affected zones. In the absence of macroscopic abnormality, three random sites were selected. The same criteria were rated by the same two investigators. Finally, biopsies were systematically performed on the same sites for pathological diagnosis.

The assessed visual criteria were chosen in accordance with our previous publications and experience(16,17).

Methods

Inclusion/exclusion criteria

Every patient referred to medical thoracoscopy for pleural effusion willing to participate and signing informed consent.
Exclusion: unwilling to participate or unable to give informed consent; <18 years; pregnant woman; known allergy to fluorescein

Controls:

Pleural fluid cytological analysis

Aims:

To determine the feasibility and safety of mini invasive pleural pCLE assessment
To determine the sensitivity of mini invasive pleural pCLE compared to pleural fluid cytological analysis

Standard demographic, clinical, biological and endoscopic assessment

Gender, age
Medical background
Smoking habit
Current therapy
Blood: CRP, Albumin, total proteins, Hemoglobin, Platelet count, White blood cells, LDH
Pleural fluid: Cytological and bacteriological studies, LDH, Albumin, proteins

Sample size

No formal sample size calculation can be performed for such exploratory study. Every major patient referred for medical pleuroscopy will be proposed the study and screened if they give their informed consent.

Statistical analysis

The Fisher's exact test was used to analyze the link between pCLE qualitative variables and the final histological diagnosis. No adjustments are made for multiple variable testing.

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