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Minimally-invasive electrical impedance spectroscopy in lung tissue: present and future trends

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Abstract. Electrical impedance measurements performed in-vivo and in-situ in lung tissue so far have focused on detecting different pathologies, including neoplasm. Once its ability for this has been established, the authors intend to investigate whether it is possible to detect peripheral lung nodules. The preliminary measurements collected show differences in the measured spectra and model parameters between the different types of lesions collected (solid nodules, partially solid nodules and ground-glass nodules).

1. Introduction

Lung cancer is the first cause of global cancer incidence and mortality, being the second most common cause of diagnosis for men and women [1], [2].

Flexible bronchoscopy (FB) is effective for central neoplasms characterization but less for peripheral lesions [3], where biopsy site identification is challenging without direct visual reference. Electromagnetic Navigation Bronchoscopy (ENB) improves diagnostic accuracy for peripheral neoplasms, including solitary pulmonary nodules [4], by using pre-procedure CT scans to guide the biopsy catheter. However, ENB requires additional X-ray imaging to correct patient positioning shifts during the procedure, increasing radiation exposure for patients and medical staff.

To address this challenge, performing electrical impedance spectroscopy (EIS) measurements of lung tissue directly in a bronchoscopy procedure has demonstrated to be a useful tool to discriminate between different lung tissue pathologies. The first study performed by Sanchez *et al.* in 2033 [5] developed and validated a measurement method and instrument by describing its theoretical basis, characterizing, and calibrating it. It also assessed noise, nonlinear errors, and feasibility for monitoring in vivo lung tissue bioimpedance during bronchoscopy. In 2020, Riu *et al.* [6] differentiated lung tissues (bronchi, healthy, and pathological) using impedance modulus and phase angle with a 4-electrode method, which required all electrodes to maintain contact with lung tissue. Due to patient movement and the lung's trabecular structure, consistent contact was difficult. To address this, they proposed a 3-electrode method, requiring only the distal electrode in contact with the tissue, simplifying measurements. In 2022, Company-Se *et al*. [7] confirmed that 3-electrode measurements yielded results comparable to the 4-electrode method in terms of tissue differentiation. Since then, the 3-electrode approach has been used. Company-Se *et al*. [8] later introduced a calibration method that reduced data variability and improved tissue differentiation. Their latest study developed in 2023 [9] identified significant bioimpedance differences between neoplasm and pneumonia; neoplasm and healthy lung tissue; neoplasm and emphysema; fibrosis and healthy lung tissue; pneumonia and healthy lung tissue; fibrosis and emphysema; and between pneumonia and emphysema but not between neoplasm and fibrosis; fibrosis and pneumonia; and healthy lung tissue and emphysema.

All neoplasms studied were in the central bronchoalveolar tree. However, bioimpedance has not yet been proven to distinguish healthy from peripheral lung tumours.

For this reason, and to complement the ENB protocol, we intend to evaluate if bioimpedance is able to discriminate between neoplasm types (solid nodules, partially solid nodules (PSN) and ground-glass nodules (GGN)).

2. Materials and Methods

2.1 Participants
Minimally-invasive EIS measures were performed in 23 patients (age: 72±7 years; weight: 71.4±18.5 kg; BMI: 26.9±5.2 kgm^{-2}) with an electromagnetic navigation bronchoscopy prescribed between May 2023 and January 2024 at the Hospital de la Santa Creu i Sant Pau (HSCSP) in Barcelona. The research protocol was approved by the Ethics Committee for Clinical Investigations of the HSCSP (CEIm Fundació de Gestio Sanitaria HSCSP.)

2.2 EIS Measurements
Electrical impedance spectroscopy using the 3-electrode method was performed as described by Company-Se *et al*. [8]. Lung bioimpedance was measured by injecting a multisine current (26 frequencies, from 1 kHz to 1 MHz) between the distal electrode of a tetrapolar catheter (Medtronic 5F RF Marinr) and a skin electrode (3M, ref.: 9160F) at the rib level. The resulting voltage was recorded between the distal catheter electrode and a second skin electrode (Ambu BlueSensor VLC, ref.: VLC-00-s/10) nearby. Impedance data were collected over 12 seconds at 60 spectra per second. Measurements were calibrated using patient-specific bronchial data to correct for geometrical factors and reduce variability.

2.3 Measurement Protocol
Patients underwent ENB under sedation for peripheral lung lesion evaluation. A catheter was guided to the target using CT scans and real-time X-ray imaging. Bioimpedance was measured via the 3-electrode EIS system through the working channel of the bronchoscope.

2.4 Data Visualization and Analysis
Mean impedance spectrum was used to visualize the bioimpedance values for the solid nodules (N = 18), partially solid nodules (PSN, N = 3) and ground-glass nodules (GGN, N = 2)) along the frequency range selected (15 kHz to 307 kHz). Discriminant Function Analysis was used to find a linear combination of features that separates solid nodules, partially solid nodules and ground-glass nodules using bioimpedance parameters of impedance modulus (|Z|) and resistance (R) at 15kHz and phase angle (PA) and capacitive reactance (Xc) at 307kHz divided by the diameter of the lesion (D).

3. Results

Figure 1 shows the mean impedance spectrum obtained from 15 kHz to 307 kHz for the solid nodules (red), PSN (black) and GGN (blue) for the impedance |Z|, PA, R and Xc.

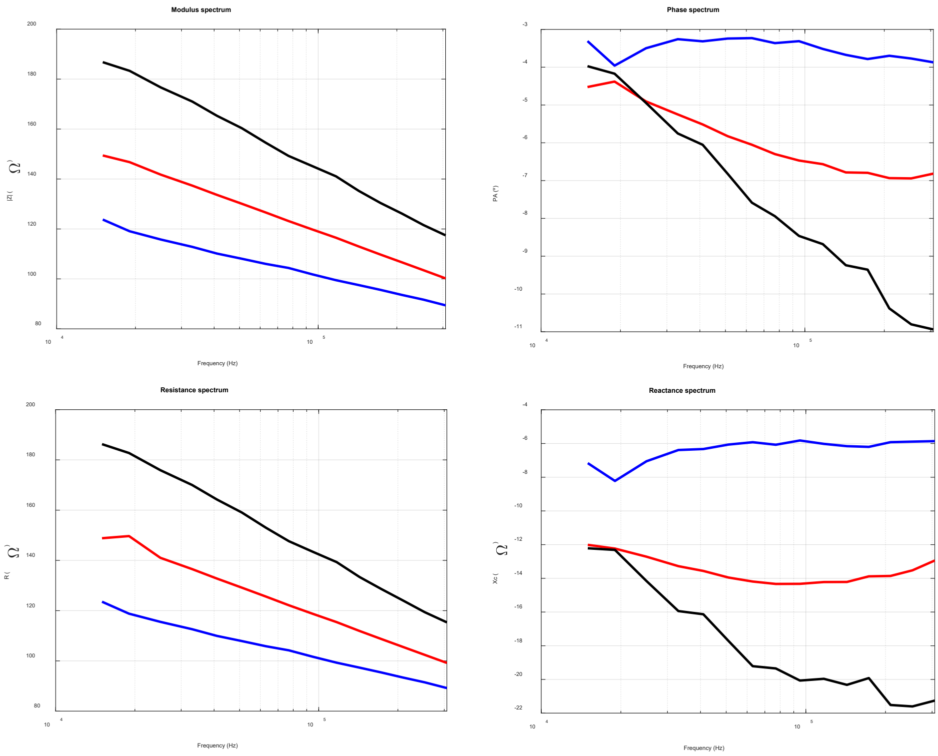
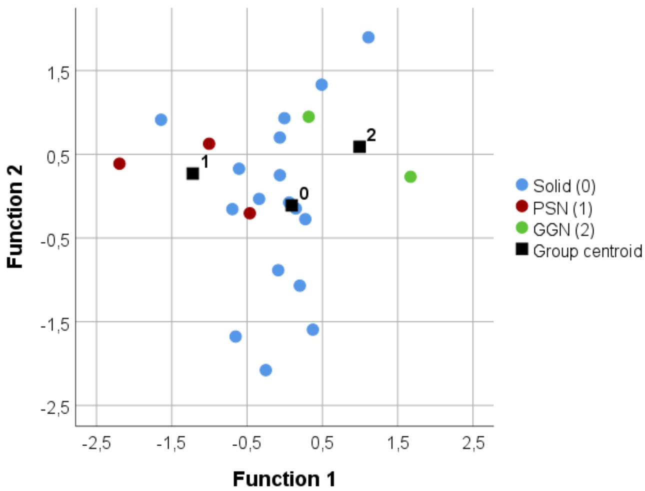


Figure 1. Mean values from the bioimpedance signal along the different frequencies analysed for modulus, phase angle, resistance and capacitive reactance. Red: solid nodules; Black: PSN and Blue: GGN.

Figure 2 shows the canonical discriminant functions, by Discriminant Function Analysis of the bioimpedance parameters (|Z|, R, PA and Xc) divided by the diameter of the lesion (D).



Function 1 = 0.983 * |Z|/D + 1.154 * R/D + 0.825 * PA/D + 1.226 * Xc/D

Function 2 = 2.686 * |Z|/D - 1.077 * R/D - 0.847 * PA/D + 2.909 * Xc/D

Figure 2. Canonical discriminant functions for the bioimpedance parameters (|Z|, R, PA and Xc) divided by the diameter of the lesion for solid nodules, PSN and GGN.

4. Discussion

The present article shows the present and future trends of the bioimpedance measurements in lung tissue obtained minimally-invasively. The diagnostic of peripheral lung tumours remains suboptimal nowadays and for this reason it is important to develop new methods of diagnostic, as it could be the bioimpedance measurement of the tissue obtained through a working channel of the bronchoscope.

Preliminary measurements obtained through an ENB showed visual differences between the three types of lung neoplasms analysed (solid nodules, PSN and GGN) at lower frequencies in |Z| and R and at higher frequencies in PA and Xc (Figure 1). Furthermore, after performing a linear discriminant analysis, results are promising as it shows linear separation between lesions (Figure 2). It seems that the most significant discriminatory bioimpedance parameter would be the Xc, that describes the behaviour of the cell membranes.

5. Conclusion

Although the results are very preliminary, they are optimistic as the trend shows a separation between lesions, that could help in the sampling location of the lesions more easily.

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