Respiration

Respiration , DOI: 10.1159/000541675
Received: June 5, 2024
Accepted: September 25, 2024
Published online: October 4, 2024

Feasibility and impact on diagnosis of peripheral pulmonary lesions under real-time direct vision by Iriscope®

Recalde-Zamacona B, Alfayate J, Giménez-Velando A, Romero G, Fernández-Navamuel I, Flandes J

ISSN: 0025-7931 (Print), eISSN: 1423-0356 (Online)
https://www.karger.com/RES
Respiration

Feasibility and impact on diagnosis of peripheral pulmonary lesions under real-time direct vision by Iriscope®

Borja Recalde-Zamacona[1], borja.recalde@quironsalud.es
Javier Alfayate[1], javier.alfayate@quironsalud.es
Andrés Giménez-Velando[1], andres.gimenez@fjd.es
Gabriel Romero[1], gabromerocas@hotmail.com
Iker Fernández-Navamuel[1], iferbas@fjd.es
Javier Flandes[1*]. jflandes@quironsalud.es

[1]Interventional Pneumology Unit, Pulmonary Medicine Department, Fundación Jimenez Díaz Universitary Hospital, IIS, CIBERES, Madrid, Spain.

Short title: "Real-Time Visualization of Pulmonary Lesions with Iriscope"

[*]Correspondence author: jflandes@quironsalud.es

Keywords: Iriscope, Peripheral pulmonary lesion, Electromagnetic navigation bronchoscopy, radial endobronchial ultrasound, lung cancer.

Manuscript word count: 2790
Abstract word count: 289
Figures: 2
Tables: 3
References: 18

Abstract

Introduction
Interventional pneumology plays a crucial role in the diagnosis of peripheral pulmonary lesions (PPLs), offering a minimally invasive approach with a low risk of complications. Iriscope® is a novel device that provides a direct and real-time image of PPLs. The objective of this study is to demonstrate the feasibility and impact of Iriscope® in diagnosing PPLs by analyzing its ability to directly visualize lesions and support accurate sampling during radial endobronchial ultrasound (rEBUS) and electromagnetic navigation bronchoscopy (ENB) combined with rEBUS.

Methods
A single-center prospective study was conducted from December 2022 to October 2023 on patients with suspicious PPLs. The diagnostic approach involved either rEBUS alone or in combination with ENB. In all cases, an additional novel technique called Iriscope® (Lys Medical, Charleroi, Belgium) was also applied. Iriscope® findings of each lesion were evaluated individually by three expert interventional pulmonologists.

Results
Seventy PPLs suspected of malignancy were included in the study. The PPLs underwent examination by ENB combined with rEBUS (55) or by rEBUS alone (15). Diagnosis was obtained in 68.6% (48/70) of cases. Iriscope® provided a direct, real-time view of 57.1% (40/70) of PPLs with a positive predictive value of 92.5% (37/40). This technique was able to visualize 72% (39/54) of malignant lesions, while only 6.1% (1/16) of benign lesions showed pathologic changes. The most common findings observed with Iriscope® were: Mucosal thickening and infiltration (92,5%), increased capillary vascularization (82%), pale or grayish mucosa (72,5%), obstruction with accumulation of secretions (50%) and cobblestone mucosa (15%).

Conclusion
Iriscope® is a promising technique in the diagnostic process of PPLs, providing real-time pathologic imaging that facilitates accurate sampling. Further studies are needed to evaluate success rate of Iriscope-mediated repositioning and to establish predictive patterns for malignant or even benign diseases.

Introduction

Lung cancer is the second most common type of cancer and the leading cause of cancer-related deaths worldwide [1,2]. Early diagnosis is crucial for improving survival rates, as the disease often presents with symptoms at advanced stages.

Lung cancer screening programs aim to identify suspicious lung lesions and detect cancer at early stages. The National Lung Screening Trial (NLST) and the Dutch-Belgian Lung Cancer Screening Trial (NELSON) have demonstrated that implementing lung cancer screening programs using low-dose computed tomography (LDCT) significantly reduces lung cancer mortality in certain high-risk groups [3,4].

The incidence of peripheral pulmonary lesions (PPLs) has increased due to the implementation of lung cancer screening programs and routine imaging tests such as chest X-ray or thoracic computed tomography (CT). Interventional pulmonology plays a crucial role in the diagnosis of PPLs. Currently, multiple endoscopic techniques are available, including electromagnetic navigation bronchoscopy (ENB), radial probe endobronchial ultrasound (rEBUS), ultrathin bronchoscopy (UTB), and robotic-assisted bronchoscopy (RAB). All of these can be combined with fluoroscopy (Fl) or cone beam computed tomography (CBCT) in an attempt to achieve a higher diagnostic yield. Nevertheless, the diagnosis of PPLs remains a significant challenge.

Iriscope® is a novel device that comprises a reusable and radiopaque miniaturized videoendoscopic probe of 1.3mm. This device allows for direct visualization of the peripheral airways. When studying PPLs, Iriscope can be used to confirm under real-time vision the accurate positioning of the navigation or radial probes.

This study aims to demonstrate the feasibility and impact of Iriscope® in diagnosing PPLs by analyzing its ability to directly visualize lesions and support accurate sampling during rEBUS and ENB combined with rEBUS.

Methods

A single-center prospective study was conducted from December 2022 to October 2023 on patients with suspicious PPLs. The diagnostic approach involved either rEBUS alone or in combination with ENB. In all cases, an additional novel technique called Iriscope® (Lys Medical, Charleroi, Belgium) was also applied. The decision of perform ENB combined with rEBUS or rEBUS alone was made by an expert bronchoscopist committee.

The inclusion criteria comprised patients with PPLs exhibiting characteristics suggestive of malignancy on CT, with a diameter of greater than 8 mm, and confirmed by complementary positron emission tomography-computed tomography (PET-CT) imaging. Patients with any clinical condition that contraindicated the performance of the procedure, such as coagulation disorders and significant comorbidities, were excluded.

Characteristics of patients (age, sex, smoking condition, respiratory diseases), radiological features (lesion size, pulmonary lobe , CT bronchus sign, lesion density, SUVmax on PET-CT or distance to pleura), Ultrasonography (US) vision by rEBUS, Iriscope® findings (mucosal thickening and infiltration, increased capillary vascularization, pale or grayish mucosa, obstruction with accumulation of secretions or cobblestone mucosa) and pathological data were prospectively collected from electronic medical records and videos or images of each procedure. The study was approved by the institutional Ethics Committee. Informed consent was given to all patients.

ENB combined rEBUS

The ENB procedure utilizes the Illumisite system® (Medtronic, Minneapolis, Minnesota, USA). The bronchial pathway for accessing the lesion is created from CT chest data, using Superdimension® software (Medtronic, USA).

Then the patient is placed on the electromagnetic board and the procedure is initiated under deep sedation. Endobronchial mapping is accomplished by linking the virtual fiducial registration points to the actual position in the patient's thorax using a sensing probe.

After a routine inspection of the bronchial tree, the sensing probe is guided through the subsegments using the navigation images as a reference.

Upon completing navigation, the position of the navigation probe is first checked with Iriscope®. Subsequently, US vision of the target is verified using rEBUS.

Once the lesion location is confirmed, samples are obtained using forceps, fine needle, brush, or cryogenic biopsy.

rEBUS alone

Before the procedure, software (Superdimension®, Medtronic, USA or Synapse, Fujifilm, Japan) is used to plan in detail the bronchial pathway for accessing the lesion.

The examination is conducted under deep sedation. Following a routine inspection of the bronchial tree, the rEBUS probe (CODE; Olympus, Tokyo, Japan) is inserted through a guide sheath (outer diameter 2.6mm or 2.0mm; length, 850mm) and bronchoscope work channel into the bronchi leading to the area where the lesion is suspected.

Normal air-filled alveolar tissue typically produces a "snowstorm-like" whitish image. Pure ground glass opacities (GGO) lesions present a similar image. However, when the lesion is mixed (GGO with solid component), hyperechoic linear arcs and dots appear irregularly distributed over the snowstorm image. In contrast, solid lesions display a darker and more homogeneous appearance with a hyperechogenic peripheral halo, resembling a "black hole" image.

Samples are taken using disposable forceps, brush, or fine needle after removing the probe. If the lesion cannot be identified by rEBUS, blind biopsies are obtained from the suspected target area.

Iriscope® technique

Iriscope® is a novel device consisting of a reusable and radiopaque miniaturized 1.3mm videoendoscopic probe (Lys Medical, Charleroi, Belgium). It is equipped with a processor Iristar® from which images can be captured and recorded (Figure 1). The interpretation of findings acquired through this novel technique requires a learning curve. Thus, prior to patient inclusion, bronchoscopists underwent a rigorous two-month training period, conducting a minimum of 20 procedures with Iriscope®.

Once the PPL is reached by ENB or rEBUS, an adapter is attached to the proximal end of the navigation catheter or guide sheath through which the Iriscope® is inserted.

In some cases, it may be necessary to instill 2-5 ml of saline throught an extra sided luer-lock connection channel in the adapter to improve the endobronchial image. This can help address the collapsibility of the peripheral airway or clear secretions or blood from the lesion area.

Depending on the initial findings, corrections can be made by retracting, advancing or rotating navigational catheter to obtain a clear image of the lesion and to maintain the optimal position for sampling.

In this study, Iriscope® findings of each lesion were evaluated individually by three expert interventional pulmonologists. Iriscope was considered positive when at least 2 of 3 bronchoscopists confirmed the pathologic findings of PPLs.

Data Analysis

Statistical analysis was performed using Stata 12(StataCorp.2011. Stata Statistical Software:Release 12. College Station, TX: StataCorp LP). Continuous variables were expressed as means (standard deviation (SD)) or medians (interquartile range (IQR)) and were compared by t-test or para-metric tests as appropriate. Categorical variables were expressed as number (%) and compared by chi-square (v2) or Fisher exact test as appropriate. Significant factors associated to diagnostic yield of endoscopic testing identified on univariate analyses were further analysed by multivariate logistic regression. The significance level of the hypothesis tests was set at 0.05 (2-sided).

Results

Seventy PPLs suspected of malignancy were included in the study. The PPLs underwent examination by ENB combined with rEBUS (55) or by rEBUS alone (15). Demographic, clinical and radiological characteristic are summarized in Table 1.

The radiological features reveal that the mean size of nodules was 22.6mm (SD 9.9mm). A majority (61.4%) of the lung nodules were located in the upper lobes, and the median distance to the pleura was 8.5mm (IQR 0-20mm). The bronchus sign was present in 97% of pulmonary lesions (55% direct and 45% adjacent). All patients underwent a PET-CT scan before the procedure. Of those, 84.3% showed an SUVmax greater than 2.5.

Diagnosis was obtained in 68.6% (48/70) of cases. ENB combined with rEBUS achieved a diagnosis in 65,5% (36/55), while rEBUS alone obtained a diagnosis in 80% (12/15) of PPLs. The most common malignant diagnosis was non-small cell lung cancer (NSCLC) (83.7%), followed by metastasis from other sites (colorectal and renal), small cell carcinoma, and typical carcinoid. Inflammatory changes were the most common non-malignant finding (Table 2).
For the remaining 22 PPLs with non-diagnostic endoscopic procedures, diagnosis was confirmed through surgery, percutaneous biopsy or by at least 6-month follow up with imaging tests. It is worth mentioning that 41% (9/22) were benign. However, they were not included as diagnostic because nonspecific result was obtained from the sample taken during the procedure. Several factors strongly related to the diagnostic yield of endoscopic procedures have been identified. These include lesion density, bronchus sign, PET-CT SUVmax, US vision by rEBUS, and Iriscope visualization. It is important to note that these factors apply to both ENB combined with rEBUS and rEBUS alone [Table 1].

Iriscope® provided a direct, real-time view of 57.1% (40/70) of PPLs with a positive predictive value of 92.5% (37/40) [Table 3]. When used in combination with ENB and rEBUS, Iriscope was positive in 52.7% of cases, while it was positive in 73.3% of cases when used with rEBUS alone. This technique was able to visualize 72% (39/54) of malignant lesions, while only 6.1% (1/16) of benign lesions showed pathologic changes [Table 2].
The most common findings observed with Iriscope® were: Mucosal thickening and infiltration (92,5%), increased capillary vascularization (82%), pale or grayish mucosa (72,5%), obstruction with accumulation of secretions (50%) and cobblestone mucosa (15%) [Figure 2]. Variables related to the visualization yield of Iriscope were lesion size, bronchus sign, and concentric vision with rEBUS.

Ultrasonography (US) vision by rEBUS enabled real-time imaging of 72.9% (51/70) of PPLs with a positive predictive value of 80.4% (41/51) [Table 3]. A concentric image (≥3/4 quarters affected) was obtained in 56.9% (29/51). It should be emphasized that 66.6% (4/6) of patients whose diagnosis was made with positive rEBUS, but without pathological findings on Iriscope®, were benign. The variables that were found to be related to US vision by rEBUS were lesion size and positive bronchus sign.

Pneumothorax rate was 4% (3/70). Only one patient required chest tube placement, while the remaining two cases were managed with observation and follow-up chest X-rays. No cases of hemorrhage requiring therapeutic interventions, such as instillation of ice-cold saline or placement of an endobronchial blocker, were reported. Using Iriscope® was not associated with any complications and proved to be safe.

Discussion

To our knowledge, this is the first study to demonstrate direct and real-time endoscopic visualization of suspicious PPLs using Iriscope®. It is a novel device that utilizes a 1.3mm optical fiber, which can be introduced through the bronchoscope or navigation probe to enable visualization of the peripheral airway.
In this single-center prospective cohort of 70 PPLs, a diagnosis was obtained in 68.6% of cases using ENB combined with rEBUS or rEBUS alone. This study followed the American Thoracic Society Delphi consensus definition of diagnostic yield [5].
These findings are in alignment with previous research outcomes [6,7]. Intriguingly, rEBUS alone exhibited a higher diagnostic yield than ENB combined with rEBUS (80% and 65.5%, respectively). This observation is potentially attributable to a selection bias in the choice of diagnostic modality, influenced by the characteristics and anatomical location of PPLs. As previously outlined, the selection of the endoscopic approach for PPLs was determined by a committee of bronchoscopists. It is essential to highlight that the indications for ENB and rEBUS are distinct and depend on the characteristics of the lesion. As is well-known, guidelines recommend ENB for peripheral lesions that are difficult to reach with conventional bronchoscopy alone [8].

Several studies have presented conflicting findings regarding the impact of rEBUS as an adjunct to ENB on diagnostic yield [9,10]. Concurrently, a recent meta-analysis has demonstrated that the use of advanced imaging techniques, such as CBCT or fluoroscopy during ENB, significantly improves diagnostic capability [11].

Presently, rEBUS, CBCT and Fluoroscopy are widely employed for real-time confirmation of successful ENB navigation [12,13]. Iriscope®, an innovative device, complements this armamentarium by furnishing direct, real-time visualization of lesions, particularly advantageous for lesions exhibiting a bronchus sign on CT imaging or bronchial mucosal involvement. This technique allows for dynamic adjustment of the navigation catheter, optimizing frontal lesion visualization for accurate sampling, without necessitating radiation exposure or substantially prolonging procedural duration. The repositioning capability is one of the most interesting features of this technique, especially in PPLs assessed via ENB. The angulation of the navigation catheter compared to the straight rEBUS guide sheath, allows for more precise adjustments when using the Iriscope®. The present study did not collect data related to success of Iriscope-mediated repositioning. Nevertheless, it can be confirmed that minor adjustments were made in the majority of procedures to optimize the sampling location or to obtain a direct view of the lesion.

Iriscope® proves most beneficial pre-sampling, as direct lesion visualization post-sampling may be impeded by potential bleeding. In such instances, rEBUS, CBCT, or fluoroscopy aids in confirming proper catheter positioning throughout the procedure. However, in this study, Iriscope® was occasionally employed post-sampling to asses for bleeding and target lesion alterations.
Iriscope® successfully captured pathologic images in 57.1% of PPLs, culminating in diagnostic confirmation in 92.5% of cases. Notably, it identified mucosal alterations in 72% of malignant lesions, contrasting with only 6.2% of benign lesions displaying pathological changes. This discrepancy suggests diminished visualization of benign lesions, which may exhibit subtler or absent mucosal changes, potentially presenting as normal mucosa.

In contrast, rEBUS vision was available in 72.9% of PPLs, with diagnostic confirmation achieved in 80.4% of cases. It demonstrated the ability to discern ecographic changes in 77% of malignant lesions and 56.2% of benign diseases. Moreover, it is important to emphasize that patients diagnosed solely based on positive US images were found to harbor benign lesions in 66.6% of cases. These results suggest that rEBUS, compared to Iriscope®, shows a higher capability of detecting alterations in the target area of benign lesions. This may be due to the fact that ultrasound imaging enables the detection of lesions that extend beyond the mucosal surface, thus facilitating the identification of parenchymal involvement. Benign lesions may manifest subtle alterations on the mucosal surface that could potentially be overlooked by the Iriscope. Indeed, it was only able to detect one case (6.1%) in which thickening and increased mucosal vascularization was observed, with no discernible changes in bronchial colouration or architecture. Nevertheless, both techniques are complementary and serve different roles during the diagnostic procedure.

The visualization of PPLs with this novel device could present certain challenges, such as collapsibility and bleeding of the mucosa at the peripheral level, especially when dealing with pathological tissue. However, the instillation of saline could help to reopen and clear the area of any blood content. In addition, the position of the catheter may sometimes be facing the bronchial wall, which requires reorienting the catheter towards the lumen of the airway to obtain a better image. This situation becomes more difficult when using rEBUS guide sheath because of its straightness and stiffness which could condition reduced maneuverability.

Consequently, this novel technique requires a learning curve comparable to that of other endoscopic procedures, such as ENB [14,15], which ensures optimal coordination between the Iriscope® probe and the catheter, as well as correct interpretation of the acquired images. In cases of normal mucosa, Iriscope® images resemble those of subsegmental bronchi obtained by UTB, featuring thin, pink, vascularized mucosa indicative of a healthy, non-friable capillary bed [16]. Pathological observations include mucosal thickening and infiltration, increased capillary vascularization, pale or grayish mucosa, obstruction with accumulation of secretions or cobblestone mucosa. These findings align with macroscopic observations post-surgical resection of pulmonary nodules [17,18]. However, to establish predictive patterns for malignant or even benign lesions, further studies are needed.

Regarding future applications, once ablative endoscopic treatments for peripheral pulmonary lesions (PPLs) are established, Iriscope® may have a role in pre- and post-treatment imaging of lesions and in targeting application sites for these techniques. However, further validation will be necessary to determine its effectiveness in this context.

Despite the strengths of our study, such as the high positive predictive value demonstrated by Iriscope®, several limitations exist. Although the sample size could be expanded, the inclusion of 70 PPLs was sufficient to observe a robust positive predictive value for Iriscope®.
Procedures were performed by various bronchoscopists, albeit all possessing extensive experience in ENB or rEBUS, and prior training in Iriscope® technique. Additionally, Iriscope® images were evaluated individually by three expert bronchoscopists to mitigate observer bias.
In light of other limitations, it is important to emphasize that the inclusion and exclusion criteria were relatively broad, particularly regarding nodule size, with no upper limit was specified. This allowed for the inclusion of nodules from 8 mm to 50mm. Additionally, this study was not designed as a randomized trial. Therefore, results should be interpreted with caution.

Conclusion
Iriscope® emerges as a promising complementary technique in PPLs diagnosis during ENB or rEBUS, offering direct and real-time visualization of peripheral airway. The main pathological mucosal alterations observed were thickening, infiltration, increased capillary vascularization and colour changes with pale or grayish mucosa.
The repositioning capability of navigation catheter or rEBUS guide sheath through forward, backward, or rotational adjustments under real-time vision, facilitates the determination of a precise sampling location.
However, further studies are required to determine predictive patterns for malignant or even benign lesions, the success rate of Iriscope-mediated repositioning and its true impact on PPLs diagnostic yield.

Acknowledgments
We thank our patients for their participation in the study.
The procedures were performed with the help of the nursing and auxiliary team (Susana, Montserrat, Pedro, Irene, Carlos), pulmonology residents (Javier, Pablo) and interventional pulmonology fellows.

Ethics
This study protocol was reviewed and approved by Fundacion Jimenez Diaz University Hospital Ethics Committee, approval number PIC013-23.
Written Informed consent was obtained from all patients.

Conflict of Interest
The authors have no conflicts of interest to declare.

Funding sources
This study was not supported by any sponsor or funder.

Author Contributions
Recalde-Zamacona B: Conceptualization; Data curation; Formal analysis; Methodology; Writing original draft,

Alfayate J: Data curation; Formal analysis; Writing reviewing and editing

Gimenez-Velando A: Data curation; Methodology; Writing reviewing and editing

Romero GA: Data curation

Fernandez-Navamuel I: Conceptualization; Formal analysis; Writing reviewing and editing

Flandes J: Conceptualization; Methodology; Writing reviewing and editing

Data availability Statement

The data that support the findings of this study are not publicly available due to the fact that they contain information that could compromise the privacy of research participants. However, they are available from the corresponding author (JF) upon reasonable request.

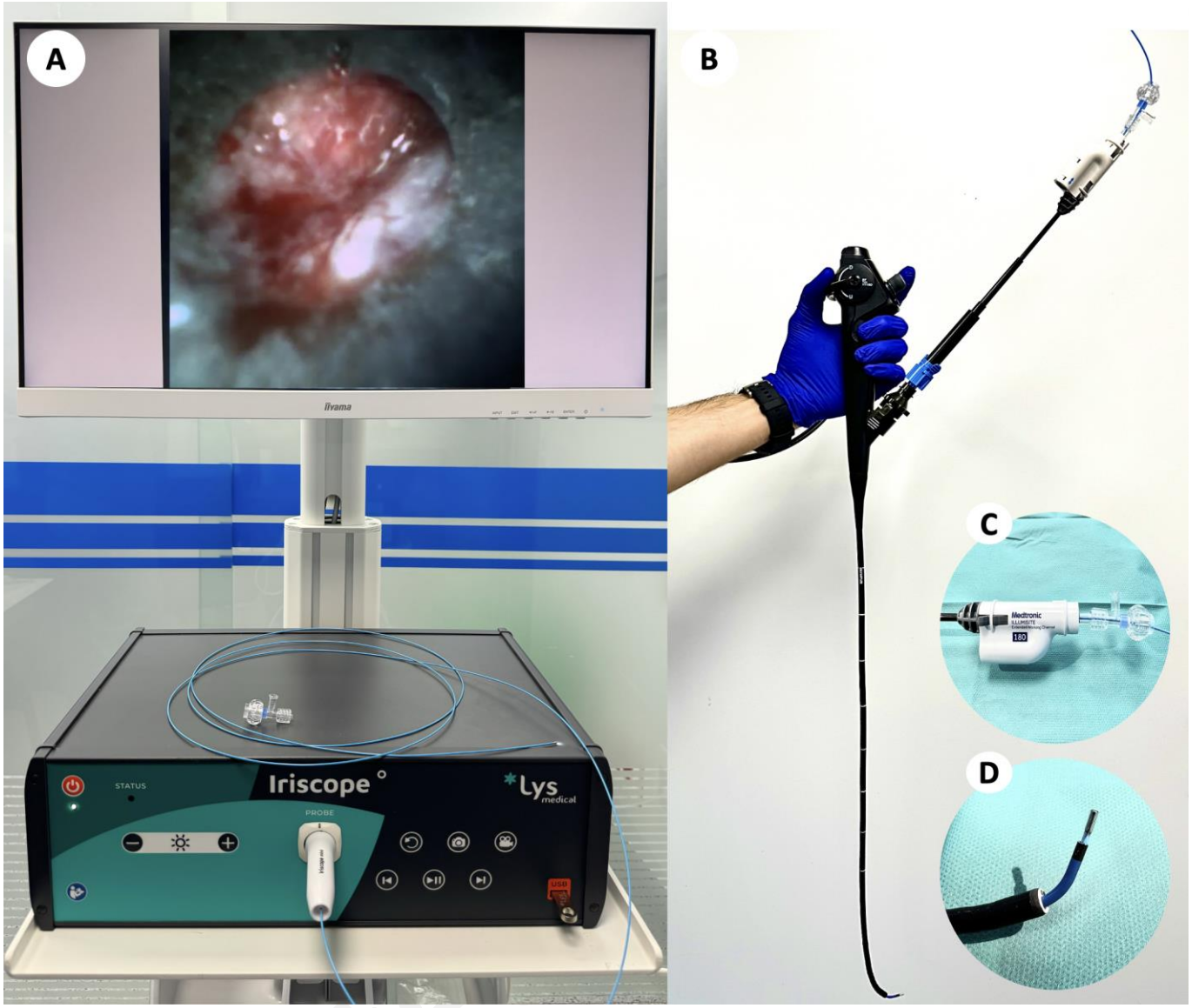
Bibliography

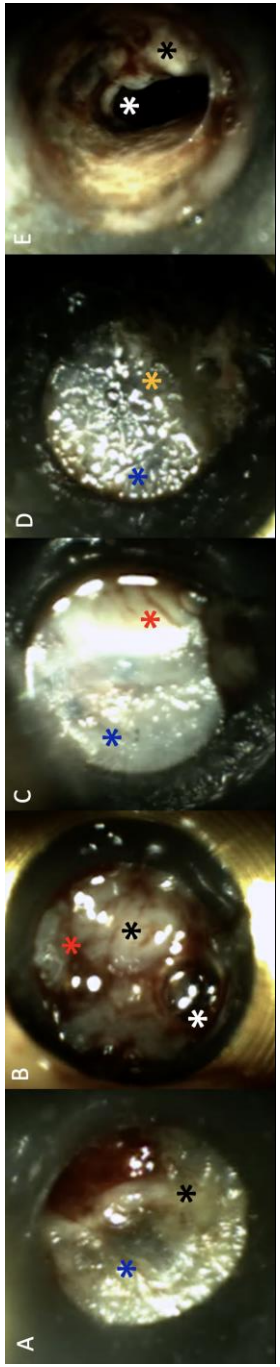
1. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. CA Cancer J Clin. 2023 Jan;73(1):17-48. doi: 10.3322/caac.21763. PMID: 36633525.
2. Zhang Y, Vaccarella S, Morgan E, Li M, Etxeberria J, Chokunonga E, Manraj SS, Kamate B, Omonisi A, Bray F. Global variations in lung cancer incidence by histological subtype in 2020: a population-based study. Lancet Oncol. 2023 Nov;24(11):1206-1218. doi: 10.1016/S1470-2045(23)00444-8. Epub 2023 Oct 11. PMID: 37837979.
3. National Lung Screening Trial Research Team; Aberle DR, Adams AM, Berg CD, Black WC, Clapp JD, Fagerstrom RM, Gareen IF, Gatsonis C, Marcus PM, Sicks JD. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med. 2011 Aug 4;365(5):395-409. doi: 10.1056/NEJMoa1102873. Epub 2011 Jun 29. PMID: 21714641; PMCID: PMC4356534.
4. de Koning HJ, van der Aalst CM, de Jong PA, Scholten ET, Nackaerts K, Heuvelmans MA, Lammers JJ, Weenink C, Yousaf-Khan U, Horeweg N, van 't Westeinde S, Prokop M, Mali WP, Mohamed Hoesein FAA, van Ooijen PMA, Aerts JGJV, den Bakker MA, Thunnissen E, Verschakelen J, Vliegenthart R, Walter JE, Ten Haaf K, Groen HJM, Oudkerk M. Reduced Lung-Cancer Mortality with Volume CT Screening in a Randomized Trial. N Engl J Med. 2020 Feb 6;382(6):503-513. doi: 10.1056/NEJMoa1911793. Epub 2020 Jan 29. PMID: 31995683.
5. Gonzalez AV, Silvestri GA, Korevaar DA, Gesthalter YB, Almeida ND, Chen A, Gilbert CR, Illei PB, Navani N, Pasquinelli MM, Pastis NJ, Sears CR, Shojaee S, Solomon SB, Steinfort DP, Maldonado F, Rivera MP, Yarmus LB. Assessment of Advanced Diagnostic Bronchoscopy Outcomes for Peripheral Lung Lesions: A Delphi Consensus Definition of Diagnostic Yield and Recommendations for Patient-centered Study Designs. An Official American Thoracic Society/American College of Chest Physicians Research Statement. Am J Respir Crit Care Med. 2024 Mar 15;209(6):634-646. doi: 10.1164/rccm.202401-0192ST. PMID: 38394646; PMCID: PMC10945060.
6. Oh JH, Choi CM, Kim S, Kim WS, Hwang HS, Jang SJ, Oh SY, Kim MY, Lee JC, Ji W. Diagnostic yield and safety of biopsy guided by electromagnetic navigation bronchoscopy for high-risk pulmonary nodules. Thorac Cancer. 2021 May;12(10):1503-1510. doi: 10.1111/1759-7714.13930. Epub 2021 Mar 21. PMID: 33749120; PMCID: PMC8107026.

7. Makris D, Scherpereel A, Leroy S, Bouchindhomme B, Faivre JB, Remy J, Ramon P, Marquette CH. Electromagnetic navigation diagnostic bronchoscopy for small peripheral lung lesions. Eur Respir J. 2007 Jun;29(6):1187-92. doi: 10.1183/09031936.00165306. Epub 2007 Mar 14. PMID: 17360724.
8. Rivera MP, Mehta AC, Wahidi MM. Establishing the diagnosis of lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013 May;143(5 Suppl):e142S-e165S. doi: 10.1378/chest.12-2353. PMID: 23649436.
9. Folch EE, Pritchett MA, Nead MA, Bowling MR, Murgu SD, Krimsky WS, Murillo BA, LeMense GP, Minnich DJ, Bansal S, Ellis BQ, Mahajan AK, Gildea TR, Bechara RI, Sztejman E, Flandes J, Rickman OB, Benzaquen S, Hogarth DK, Linden PA, Wahidi MM, Mattingley JS, Hood KL, Lin H, Wolvers JJ, Khandhar SJ; NAVIGATE Study Investigators. Electromagnetic Navigation Bronchoscopy for Peripheral Pulmonary Lesions: One-Year Results of the Prospective, Multicenter NAVIGATE Study. J Thorac Oncol. 2019 Mar;14(3):445-458. doi: 10.1016/j.jtho.2018.11.013. Epub 2018 Nov 23. PMID: 30476574.
10. Eberhardt R, Anantham D, Ernst A, Feller-Kopman D, Herth F. Multimodality bronchoscopic diagnosis of peripheral lung lesions: a randomized controlled trial. Am J Respir Crit Care Med. 2007 Jul 1;176(1):36-41. doi: 10.1164/rccm.200612-1866OC. Epub 2007 Mar 22. PMID: 17379850.
11. Kops SEP, Heus P, Korevaar DA, Damen JAA, Idema DL, Verhoeven RLJ, Annema JT, Hooft L, van der Heijden EHFM. Diagnostic yield and safety of navigation bronchoscopy: A systematic review and meta-analysis. Lung Cancer. 2023 Jun;180:107196. doi: 10.1016/j.lungcan.2023.107196. Epub 2023 Apr 19. PMID: 37130440.
12. Katsis J, Roller L, Lester M, Johnson J, Lentz R, Rickman O, Maldonado F. High Accuracy of Digital Tomosynthesis-Guided Bronchoscopic Biopsy Confirmed by Intraprocedural Computed Tomography. Respiration. 2021 Feb 5:1-8. doi: 10.1159/000512802. Epub ahead of print. PMID: 33550284.
13. Verhoeven RLJ, van der Sterren W, Kong W, Langereis S, van der Tol P, van der Heijden EHFM. Cone-beam CT and Augmented Fluoroscopy-guided Navigation Bronchoscopy: Radiation Exposure and Diagnostic Accuracy Learning Curves. J Bronchology Interv Pulmonol. 2021 Oct 1;28(4):262-271. doi: 10.1097/LBR.0000000000000783. PMID: 34162799; PMCID: PMC8460082.
14. Toennesen LL, Vindum HH, Risom E, Pulga A, Nessar RM, Arshad A, Christophersen A, Konge L, Clementsen PF. Learning Curves for Electromagnetic Navigation Bronchoscopy Using CUSUM Analysis. J Bronchology Interv Pulmonol. 2022 Jul 1;29(3):164-170. doi: 10.1097/LBR.0000000000000815. Epub 2021 Sep 27. PMID: 34561367.
15. Lee HJ, Argento AC, Batra H, Benzaquen S, Bramley K, Chambers D, Desai N, Dincer HE, Ferguson JS, Kalanjeri S, Lamb C, Meena N, Reddy C, Revelo A, Sachdeva A, Seides B, Shah H, Shojaee S, Sonetti D, Thiboutot J, Toth J, Van Nostrand K, Akulian JA. A Multicenter Study Assessing Interventional Pulmonary Fellow Competency in Electromagnetic Navigation Bronchoscopy. ATS Sch. 2022 Jun 30;3(2):220-228. doi: 10.34197/ats-scholar.2021-0121OC. PMID: 35924198; PMCID: PMC9341475.
16. Oki M, Saka H, Asano F, Kitagawa C, Kogure Y, Tsuzuku A, Ando M. Use of an Ultrathin vs Thin Bronchoscope for Peripheral Pulmonary Lesions: A Randomized Trial. Chest. 2019 Nov;156(5):954-964. doi: 10.1016/j.chest.2019.06.038. Epub 2019 Jul 26. PMID: 31356810.
17. Raso MG, Bota-Rabassedas N, Wistuba II. Pathology and Classification of SCLC. Cancers (Basel). 2021 Feb 16;13(4):820. doi: 10.3390/cancers13040820. PMID: 33669241; PMCID: PMC7919820.
18. Hino H, Nishimura T, Usuki C, Sazuka M, Ito T, Seki A, Nitadori JI, Yamada H, Arai T, Yamamoto H, Nakajima J. Salvage surgery for primary lung cancer after chemotherapy in octogenarians. Thorac Cancer. 2017 May;8(3):271-274. doi: 10.1111/1759-7714.12423. Epub 2017 Feb 27. PMID: 28239985; PMCID: PMC5415469.

Figure1. Iriscope® device (Lys Medical, Charleroi, Belgium). (A) Processor (Iristar®), miniaturized videoendoscopy probe of 1.3 mm, luer-lock connector and monitor. (B) Iriscope probe introduced through navigation catheter of Illumisite system® (Medtronic, Minneapolis, Minnesota, USA) via flexible bronchoscope (BF-180 Olympus, Tokyo, Japan). (C) The luer-lock connector, which is attached to the proximal end of the navigation catheter, has been augmented in detail. (D) magnified detail of the Iriscope® probe exit from the distal end of the navigation catheter, both of which were introduced through the working channel of the flexible bronchoscope.

Figure 2. Pathology findings from Iriscope® imaging: (A) Mucosal thickening and infiltration (black asterisk) and pale or grayish mucosa (blue asterisk). (B) Mucosal thickening and infiltration (black asterisk), obstruction with accumulation of secretions (white asterisk) and increased capillary vascularization (red asterisk). (C) Pale or grayish mucosa (blue asterisk) and increased capillary vascularization (red asterisk). (D) Pale or grayish mucosa (blue asterisk) and cobblestone mucosa (yellow asterisk). (E) Mucosal thickening and infiltration (black asterisk) and obstruction with accumulation of secretions (white asterisk).





Variable	(N: 70 patients) N (%)	OR (95% CI)	P value
Demographic and clinical characteristics			
Age (years)	Mean: 68.5 SD: 9.2	1.04 (0.99, 1.11)	0.153
Sex			0.626
Male	38 (54.3)	Ref	
Female	32 (45.7)	0.78 (0.28, 2.15)	
Smoking			0.433
Current	25 (35.7)	0.41 (0.08, 1.71)	
Former	29 (41.4)	0.44 (0.09, 1.77)	
Never	16 (22.9)	Ref	
Respiratory disease			
COPD	36 (51.4)	1.42 (0.52, 3.97)	0.498
Emphysema	22 (31.4)	1.33 (0.45, 4.30)	0.610
PPLs features			
Size (mm)	Mean: 22.6 SD: 9.9 Max. 50 / Min. 8	1.05 (0.99, 1.12)	0.110
Pulmonary lobe			**0.013**
RUL	22 (31.4)	Ref	
RML	7 (10)	NA	
RLL	7 (10)	0.09 (0.01, 0.57)	
LUL	21 (30)	0.36 (0.08, 1.40)	
LLL	13 (18.6)	0.36 (0.07, 1.68)	
Distance to pleura	Mean: 10.9 SD: 9.8	1.00 (0.95, 1.05)	0.908
Lesion density			**0.003**
Solid	56 (80)	Ref	
Subsolid	4 (5.7)	0.91 (0.11, 19.2)	
Mixed	10 (14.3)	0.08 (0.01, 0.35)	
CT bronchus sign			**0.002**
Direct	38 (54.3)	NA	
Adjacent	30 (42.9)	NA	
Outside	2 (2.9)	Ref	
PET-CT SUVmax	Mean: 7.89 SD: 6.32	1.36 (1.16, 1.67)	< **0.001**
Intra-procedural considerations			
US visión by rEBUS			**0.001**
Yes	51(72.9)	7.03 (2.27, 23.6)	
No	19 (27.1)	Ref	
Iriscope®			**<0.001**
Positive	40 (57.1)	21.3 (5.96, 104)	
Negative	30 (42.9)	Ref	

Table1. Baseline characteristics. Multivariate analysis for predictors of diagnostic yield. Bold P-values indicates statistically significant results.

Diagnosis	Visualized by rEBUS (%)	Visualized by Iriscope® (%)	Diagnosed by ENB + rEBUS/rEBUS alone (%)	Final diagnosis (%)
Malignant lesions	42/54 (77.7)	39/54 (72)	41/54 (76)	54/70 (77)
NSLC	34/43 (79)	34/43 (79)	36/43 (83.7)	43/70 (61.4)
Adenocarcinoma	27/34 (79,4)	27/34 (79.4)	27/34 (79.4)	34/70 (48.5)
Squamous cell carcinoma	7/9 (77.7)	7/9 (77.7)	9/9 (100)	9/70 (12.8)
SCLC	3/3 (100)	2/3 (66.6)	1/3 (33.3)	3/70 (4.2)
Carcinoid tumor	1/1 (100)	1/1 (100)	1/1 (100)	1/70 (1.5)
Pulmonary Metastasis	4/7 (57)	2/7 (28.5)	3/7 (42.8)	7/70 (10)
Benign lesions	9/16 (56.2)	1/16 (6.2)	7/16 (43.7)	16/70 (23)
Inflammatory changes	6/12 (50)	0/12 (0)	3/12 (25)	12/70 (17)
Cryptogenic organizing pneumonia	1/2 (50)	0/2 (0)	2/2 (100)	2/70 (3)
Desquamative interstitial pneumonia	1/1 (100)	1/1 (100)	1/1 (100)	1/70 (1,5)
Silicosis	1/1 (100)	0/1 (0)	1/1 (100)	1/70 (1,5)
Total	51/70 (72.8)	40/70 (57.1)	48/70 (68.5)	70/70 (100)

Table 2. Histological diagnosis and capability of visualization with rEBUS and Iriscope®.

	rEBUS + (Diagnosed)	rEBUS – (Diagnosed)	Total	PPV (%)
Iriscope® +	37 (35)	3 (2)	40	37/40 (92.5)
Iriscope® -	14 (6)	16 (5)	30	
	PPV (%)			
	41/51 (80)			

Table 3. Visualization and diagnosis in peripheral pulmonary lesions "PPLs" with Iriscope® and rEBUS. Positive predictive value of each technique. PPV, positive predictive value.