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Broncoscopia com Navegação Eletromagnética e Tomografia de Feixes Cônicos

Bronchoscopy with Electromagnetic Navigation and Cone Beam Tomography

>>> RESUMO

A broncoscopia é o padrão ouro para obtenção de material em lesões pulmonares centrais e com acometimento endoluminal. Sua acurácia para alcançar lesões periféricas sempre foi prejudicada por limitações tecnológicas para navegação em brônquios sublobares de menor calibre. Com o aprimoramento de tecnologias digitais de navegação e obtenção de imagem radiológica vivenciamos uma mudança nesses paradigmas. Impulsionado por novos conceitos como único procedimento para diagnóstico e estadiamento além de novos desafios como biópsia e ablação de múltiplos nódulos, a broncoscopia vem agregando essas tecnologias a fim de equiparar a sua taxa de sucesso a dos procedimentos percutâneos. Dentre as tecnologias de navegação atualmente difundidas se destacam o EBUS radial e a navegação eletromagnética. No entanto, apesar da navegação aprimorada, facilitando a chegada até o nódulo essas tecnologias carecem de uma visualização em tempo real do instrumento de biópsia ou ablação durante o tempo principal do procedimento. Com o intuito de otimizar essa etapa, a tomografia de feixes cônicos associada à radioscopia 3D com fluoroscopia aumentada vem sendo utilizada. Nesse artigo iremos discorrer sobre os principais pontos envolvendo o EBUS radial, a navegação eletromagnética e o uso da tomografia de feixes cônicos para alcance de lesões pulmonares periféricas por via broncoscópica.

>>> PALAVRAS-CHAVE

Broncoscopia, biópsia guiada por imagem, broncoscopia intervencionista, broncoscopia com navegação eletromagnética, tomografia de feixes cônicos.

>>> ABSTRACT

Bronchoscopy is the gold standard for obtaining material in central lung lesions and those with endoluminal involvement. Its accuracy in reaching peripheral lung lesions has always been hampered by technological limitations for navigating smaller caliber sublobar bronchi. With the improvement of digital technologies for navigation and radiological images acquisition, we experience a change in these paradigms. Driven by new concepts such as a single procedure for diagnosis and staging, in addition to new challenges such as biopsy and ablation of multiple nodules, bronchoscopy has been adding these technologies to match its success rate with that of percutaneous procedures. Among the currently widespread navigation technologies, radial EBUS and electromagnetic navigation stand out. However, despite improved navigation, facilitating access to the nodule, these technologies lack real-time visualization of the biopsy or ablation instrument during the main time of the procedure. There for, to optimize this step, cone beam tomography associated with 3D radioscopy and augmented fluoroscopy has been used. In this article we will discuss the main points involving radial EBUS, electromagnetic navigation and the use of cone-beam tomography to reach peripheral lung lesions by bronchoscopic approach.

>>> KEYWORDS

Bronchoscopy; Image-guided biopsy; interventional bronchoscopy, navigational bronchoscopy. Cone beam tomography.

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>>> INTRODUÇÃO

The bronchoscopic diagnosis of peripheral lung lesions (PLL), especially pulmonary nodules, is always challenging, especially for small lesions, with dimensions smaller than 3 cm. This occurs due to the numerous variations in the bronchial path that reaches the lung lesion, the position of the nodule in relation to the bronchus, the difficulty in navigating the bronchoscope to smaller-caliber bronchi for material collection and the lack of accurate methods to guide collection procedures. These factors contribute to the low diagnostic sensitivity of conventional bronchoscopic methods, with great variability in results in different studies (14% to 65%), even when fluoroscopy or tomography are used to guide bronchoscopic collection in real time^{1,2}.

Although transthoracic needle puncture guided by chest tomography has a high sensitivity in peripheral lesions (90% or more), the risk of complications such as pneumothorax and bleeding are equally high when compared to bronchoscopy, which contributes to limiting its use in some cases of not so peripheral lesions³⁻⁴. Another great issue with transthoracic approach is the currently growing in multifocal lung lesions and the limited capacity to achieve the same accuracy after the first lung puncture by a transthoracic approach due to pneumothorax and lung movement in an air filled cavity⁵. Also, the worldwide trend to one-stop-shop evaluations, where diagnostic, staging and even treatment can be performed in a single anesthesia procedure favors one approach procedures. In this point, natural orificial procedures such as bronchoscopy takes over as an interesting approach⁶.

Thus, guided bronchoscopic methods has been developed with the aim of reaching PLL with greater precision, increasing diagnostic sensitivity and, at the same time, reducing the risk of complications. However, despite all the technological improvement, the exam planning is essential for the success of the procedure and includes careful evaluation of the chest tomography in order to understand which bronchial segment is likely to

correspond to the topography of the PLL, creating a pathway until the same. For this, it will be necessary to understand the previous segmental and subsegmental bronchial anatomy.

Below we will describe bronchoscopy navigation methods, including radial echo bronchoscopy, electromagnetic navigation bronchoscopy (ENB), and cone beam CT technique (CBCT).

DISCUSSION <<<

1. Radial EBUS (Rp-EBUS):

Also known as Radial Endobronchial Ultrasound Probe (Rp-EBUS - Olympus Medical Systems, Tokyo, Japan) and it has been used in conjunction with ENB and CBCT to improve the localization of PLL. This technology uses a flexible radial ultrasound probe (20 MHz), which will be connected to a device that rotates its end (driving unit) and to a dedicated endoscopic ultrasound processor. This probe, when introduced through the bronchoscope working channel, is directed to the peripheral pulmonary region to identify the topography of the lesion more precisely through a 360° rotation, and the formation of an interface generated by the difference in echogenicity between the pulmonary lesion and the normal parenchyma (Figure 1). Thus, Rp-EBUS is important to understand the path of the bronchus that reaches the lung lesion (probe inside the lesion) or closer to it (probe adjacent to the lesion), to perform the collection by cytological brushing, needle aspiration or transbronchial biopsy.

This technology has been used worldwide for some years, and in Brazil since 2012. Studies with Rp-EBUS show that the use of the method increased the diagnostic yield of bronchoscopy to values around 60 to 70%⁷⁻⁸. In a retrospective cohort published by Jacomelli et al in 2016 with 39 nodules and 19 masses the overall sensitivity of RP-EBUS was 66.7%. In lesions that were visible with Rp-EBUS the sensitivity for nodules and masses was 74% and 92%, respectively⁷. Ali et al. performed a systematic review with metanalysis enrolling 57 papers with a total of 7872 lesions⁸. The observed overall diagnostic yield was 70.6%

(95% CI: 68.0–73.1%) with a range between studies from 49.4% to 92.3%. I^2 index of 81.6% (95% CI: 76.5–85.5%) observing a substantial heterogeneity across studies.

Rp-EBUS proves to be an important alternative to guide the location of PLL. However, its use does not include two important factors: navigation through the path until reaching the nodule and real-time confirmation of the biopsy instrument position during material acquisition. Those factors can be overcome by the association of electromagnetic navigation (ENB) and cone beam CT (CBCT).

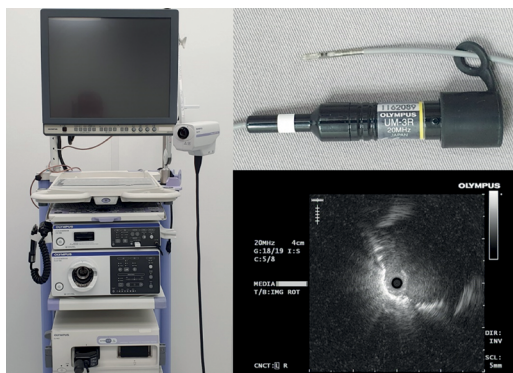


Figura 1. Equipment of RP-EBUS (image processor for bronchoscopy and endobronchial ultrasound), Radial probe and the image of the probe inside the lesion.

2. Electromagnetic Navigation Bronchoscopy (ENB):

The ENB becomes spread in early 20's with the dissemination of superDimension system (in-Reach system, superDimension Ltd, Minneapolis, Minnesota) and is the most used system. The set consists of a virtual pathway planning software based on CT-scan uploaded to the navigation system (planning phase – virtual pathway is delineated in retrograde fashion from the lesion to trachea), and a location board (around patient's chest) associated to a locatable probe that communicates (by electromagnetic field) with each other providing the navigation capability (registration phase – synchronization between airway map and patient's airway). The locatable probe is introduced through the working channel of a therapeutic bronchoscope. Is capable to

provide orientation and positional information about itself and related to the target lesion previously defined (navigation phase- the probe is advanced under virtual guidance and the position can be confirmed with Rp-EBUS or fluoroscopy). The ENB set also provides an extended working channel that works like a guided sheath allowing the maintenance of the pathway between the locatable probe take off and the biopsy instrument insertion. ENB system is not available in Brazil.

The NAVIGATE Study was a prospective multicenter cohort study that enrolled 1388 patients submitted to ENB for different purposes (dye marking, fiducial placement, lung lesion biopsy and lymph node biopsy)⁹. The primary endpoint was safety, by measuring the incidence of grade 2 or higher pneumothorax rate (3.2%) and hemorrhage (1.7%). However, they also analyzed the diagnostic yield of 1329 cases of lung lesion biopsy. In those cases, the ENB had successfully obtained samples in 94.8% of cases and after a 24-month follow-up the diagnostic yield was 67.8% with a maximum sensitivity for malignance 70.4%. Folch et al, published a systematic review with metanalysis including 40 studies and 3342 patients. They observed a pooled sensitivity of 77% (95% CI, 72 – 82%), $I^2= 80.6%$, and a risk of pneumothorax of 2.0% (95% CI, 1.0-3.0), $I^2=45.2%$. In a meta-regression model, they reported a positive relation between the sensitivity and the number of sampling techniques (forceps, needle aspiration, cryoprobe, brush). A negative relation was found between sensitivity and the mean distance between the tip of sensor and center of nodule.

Those data shows that the ENB is a feasible and safety option. However, the diagnostic yield is still lower than transthoracic needle biopsy. Also, the ENB suffer of a lack of visual confirmation of the needle position. That could be a great issue if there is an attempt to ablative procedures. To overcome this, is possible to perform the association between ENB and other navigations technique such as RP-EBUS, conventional fluoroscopy and CBCT.

3. Cone Beam Computed Tomography (CBCT)

Cone beam computed tomography (CBCT) is a recently developed imaging technique. It provides three-dimensional imaging by use of a cone shaped X- ray beam with a single 360° scan. With this set is possible to acquire images in high speed (60 s) and resolution (2-line pair/mm). Also, the applied radiation is considerably lower than regular CT scans. Initially widespread in the practice of maxillo-facial surgery, its availability has been growing thanks to hemodynamic procedures, and can be found in hybrid rooms of specialized centers.

The cone beam CT is generally associated with other navigation methods. The protocol performed in our Institution consists in an association of virtual bronchoscopy, RP-EBUS and cone beam CT¹⁰. During the general anesthesia induction, with a pre-procedure conventional CT-scan, a 3D reconstruction of the airway and lung nodule is performed using an open-source software (3D Slicer)¹¹. That 3D model is used to show the best pathway to achieve the nodule with the RP-EBUS probe (FIGURE 2). Once the nodule is localized, with the RP-EBUS in the best considered position, a cone beam chest-CT is performed, and the position confirmed. With the new image is possible

to generate an off-set with the 3D-radioscopy, a process called augmented fluoroscopy (AF), that aims to supplant the unavailability of a guided sheath kit (FIGURE 3).

In 2018, Pritchett et al published a retrospective cohort of 95 biopsies procedures in 75 patients using CBCT plus AF and ENB¹². They did not use RP-EBUS and the samples was acquired by forceps, needle aspiration, Green cut needle and brush. They reported an overall diagnostic yield of 83.7% (95% confidence interval, 74.8%-89.9%). Sensitivity for malignance varied from 91.3% (95% CI, 82.3%-96.0%) to 95.5% (95% CI, 87.5%-98.4%) depending on malignance population prevalence (minimum of 71.7% (95% CI, 61.8%-79.9%) and maximum of 75.0% (95% CI, 65.3%-82.7%) considering the uncompleted follow-up patients). Verhoeven et al. reported a lower diagnostic yield with a multimodality approach enrolling CBCT, ENB and RP-EBUS (13). In 225 biopsied lesions the overall accuracy was 75.1%. They also analyzed accuracy by different tissue sampling methods (brush, forceps, needle aspiration and cryobiopsy). The most often accurate was forceps (70.6%) followed by 1.1mm cryoprobe (68.4%). However, in a multi-modal sampling approach the most effective combination was forceps plus needle aspiration (91.7%).

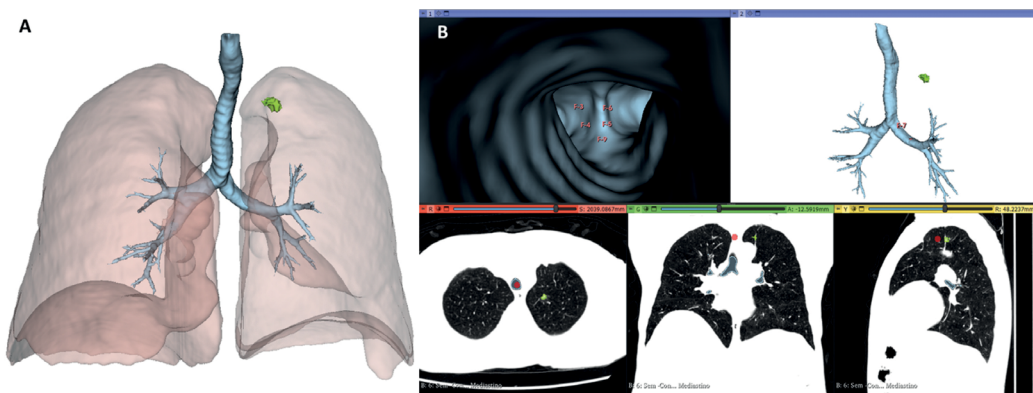


Figura 2. (A): 3D reconstruction of lung, nodule, and airway on 3D Slicer software; (B): Virtual bronchoscopy with airway and nodule pathway in 3D Slicer Software to guide navigation of RP-EBUS.

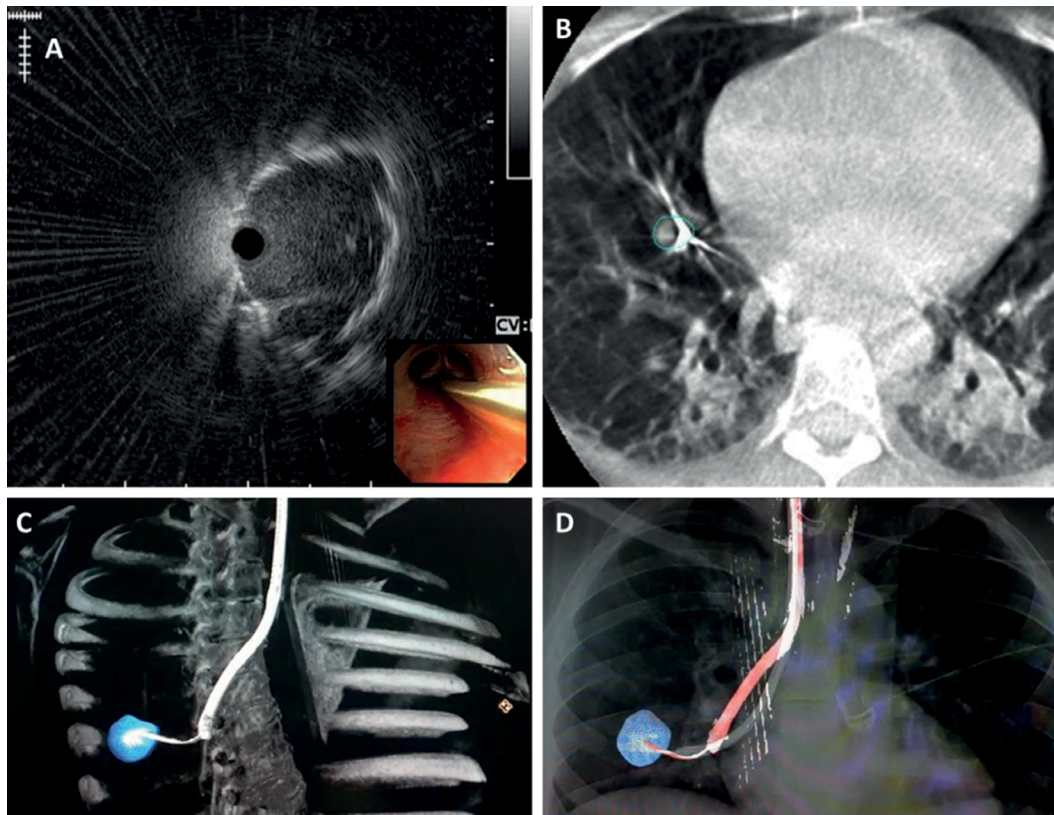


Figura 3. (A) RP-EBUS to identify the correct nodule position; (B) Cone Beam CT to confirm the probe position; (C) 3D reconstruction of cone beam CT to generate a pathway off-set to be used in the 3D radioscopy; (D) 3D radioscopy with augmented fluoroscopy and real-time position confirmation.

As observed, the accuracy of CBCT guided procedures may randomly vary in different reports. One of the main factors for that is prolonged learning curve for expertise acquisition in peripheral nodule biopsy. The process involves not only the bronchoscope manipulation expertise but also the best performance in minor procedure details such as ventilation technique to avoid atelectasis, accuracy of pathologist in the rapid onset evaluation (ROSE) and case selection. Recently, Bhadra et al. reported the results of a ventilation protocol to reduce the atelectasis issue during imaging acquisition and biopsy guided by CBCT confirmation¹⁴. The diagnostic yield was 70% for conventional ventilation and 92% for the study group ($P=0.08$) showing that the anesthesia procedure may have a great importance in the accuracy rate.

The development and implementation of robotic assisted bronchoscopy arrives as great new improvement for peripheral lung nodule biopsy and ablation. The refined movements, longer reach of robotic endoscope, greater stability, and association with navigation software make the robotic platform the future of more complex endoscopic procedures working to reduce the learning curve and quality procedure variability among institutions. However, there is still a limitation regarding the real-time confirmation of biopsy device. The PRECISION – 1 study reported the comparative results between ultrathin bronchoscope with radial RP-EBUS, ENB and robotic bronchoscopy in a human cadaver model for biopsy of PLL < 2 cm¹⁵. In the 60 procedures performed the robotic platforms had the best performance with the higher rate of need-

le puncture (80%, $p=0.022$) using the CBCT to guide real-time position. Thus, even with robotic assistance, CBCT occupies a critical position for being able to visualize in real time, confirming the correct position of the puncture or ablation instrument.

»» CONCLUSION

Technology advanced is providing a new armamentarium for endoscopic biopsy of peri-

pheral lung nodules. The nodule localization and endobronchial navigation are winning a great improvement with the RP-EBUS, ENB and the brand-new robotic bronchoscopy. The CBCT stands as a facilitating technology in real-time confirmation of sample acquisition of ablation probe position. The multimodal use of these technologies currently seems to be the best way to improve the performance of these procedures.

»» REFERÊNCIAS

1. Kalanjeri S, Holladay RC, Gildea TR. State-of-the-Art Modalities for Peripheral Lung Nodule Biopsy. *Clin Chest Med*. 2018 Mar;39(1):125-138. doi: 10.1016/j.ccm.2017.11.007.
2. Ost DE, Ernst A, Lei X, Kovitz KL, Benzaquen S, Diaz-Mendoza J, et al. Diagnostic yield and complications of bronchoscopy for peripheral lung lesions. Results of the AQUIRE registry. *Am J Respir Crit Care Med*. 2016; 193:68-77. doi: 10.1164/rccm.201507-1332OC.
3. DiBardino DM, Yarmus LB, Semaan RW. Transthoracic needle biopsy of the lung. *J Thorac Dis* 2015;7: S304-16. doi: 10.3978/j.issn.2072-1439.2015.12.16.
4. Heerink WJ, de Bock GH, de Jonge GJ, Groen HJM, Vliegthart R, Oudkerk M. Complication rates of CT-guided transthoracic lung biopsy: meta-analysis. *Eur Radiol* 2017; 27:138-48. doi: 10.1007/s00330-016-4357-8.
5. Anayama T, Hirohashi K, Miyazaki R, Okada H, Kawamoto N, Yamamoto M, Sato T, Orihashi K. Near-infrared dye marking for thoracoscopic resection of small-sized pulmonary nodules: comparison of percutaneous and bronchoscopic injection techniques. *J Cardiothorac Surg*. 2018 Jan 12;13(1):5. doi: 10.1186/s13019-018-0697-6.
6. Sato M, Omasa M, Chen F, Sato T, Sonobe M, Bando T, Date H. Use of virtual assisted lung mapping (VAL-MAP), a bronchoscopic multispot dye-marking technique using virtual images, for precise navigation of thoracoscopic sublobar lung resection. *J Thorac Cardiovasc Surg*. 2014 Jun;147(6):1813-9. doi: 10.1016/j.jtcvs.2013.11.046.
7. Jacomelli M, Demarzo SE, Cardoso PF, Palomino AL, Figueiredo VR. Radial-probe EBUS for the diagnosis of peripheral pulmonary lesions. *J Bras Pneumol*. 2016 Jul-Aug;42(4):248-253. doi: 10.1590/S1806-37562015000000079. Erratum in: *J Bras Pneumol*. 2017 Jan-Feb;43(1):78.
8. Ali MS, Trick W, Mba BI, Mohananey D, Sethi J, Musani AI. Radial endobronchial ultrasound for the diagnosis of peripheral pulmonary lesions: A systematic review and meta-analysis. *Respirology*. 2017 Apr;22(3):443-453. doi: 10.1111/resp.12980.
9. Folch EE, Bowling MR, Pritchett MA, Murgu SD, Nead MA, Flandes J, et al. NAVIGATE 24-Month Results: Electromagnetic Navigation Bronchoscopy for Peripheral Pulmonary Lesions at 37 Centers in Europe and the United States. *J Thorac Oncol*. 2022 Apr;17(4):519-531. doi: 10.1016/j.jtho.2021.12.008.
10. Gilberto GM, Falsarella PM, Rocha Júnior E, Terra RM, Jacomelli M, Garcia RG. New endobronchial ultrasound (EBUS) techniques. *einstein (São Paulo)*. 2022;20:eCE0159. https://doi.org/10.31744/einstein_journal/2022CE0159

11. Fedorov A, Beichel R, Kalpathy-Cramer J, Finet J, Fillion-Robin J-C., Pujol S, et al. 3D Slicer as an Image Computing Platform for the Quantitative Imaging Network. *Magnetic Resonance Imaging*. 2012 Nov;30(9):1323-41. doi: 10.1016/j.mri.2012.05.001.
12. Pritchett MA, Schampaert S, de Groot JAH, Schirmer CC, van der Bom I. Cone-Beam CT With Augmented Fluoroscopy Combined With Electromagnetic Navigation Bronchoscopy for Biopsy of Pulmonary Nodules. *J Bronchology Interv Pulmonol*. 2018 Oct;25(4):274-282. doi: 10.1097/LBR.0000000000000536. PMID: 30179922; PMCID: PMC6166698.
13. Verhoeven RLJ, Fütterer JJ, Hoefsloot W, van der Heijden EHF. Cone-Beam CT Image Guidance With and Without Electromagnetic Navigation Bronchoscopy for Biopsy of Peripheral Pulmonary Lesions. *J Bronchology Interv Pulmonol*. 2021 Jan 1;28(1):60-69. doi: 10.1097/LBR.0000000000000697. PMID: 32649327; PMCID: PMC7742216.
14. Bhadra K, Setser RM, Condra W, Pritchett MA. Lung Navigation Ventilation Protocol to Optimize Biopsy of Peripheral Lung Lesions. *J Bronchology Interv Pulmonol*. 2022 Jan 1;29(1):7-17. doi: 10.1097/LBR.0000000000000756. PMID: 33734150.
15. Yarmus L, Akulian J, Wahidi M, Chen A, Steltz JP, Solomon SL, et al. Interventional Pulmonary Outcomes Group (IPOG). A Prospective Randomized Comparative Study of Three Guided Bronchoscopic Approaches for Investigating Pulmonary Nodules: The PRECISION-1 Study. *Chest*. 2020 Mar;157(3):694-701. doi: 10.1016/j.chest.2019.10.016.