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A review of the effectiveness of virtual bronchoscopy in biopsy of lung tumors. Evolution of lung tumor diagnosis

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ABSTRACT

Lung cancer remains the leading cause of cancer-related mortality, emphasizing the need for advanced diagnostic methods. This study reviews modern bronchoscopy navigational techniques, focusing on Virtual Bronchoscopic Navigation (VBN) and Electromagnetic Navigation Bronchoscopy (ENB), assessing their efficacy and safety in biopsying pulmonary lesions. Based on literature from 2000 to 2023, VBN demonstrated superior diagnostic accuracy for smaller nodules, with success rates of 93% vs 89% for ENB, while both methods exhibited low complication rates. Despite higher upfront costs, these technologies may offer long-term savings due to improved outcomes. Further research is warranted to optimize lung cancer diagnostics and enhance patient care.

Aim of the study

This study aims to evaluate the effectiveness and safety of VBN and ENB in diagnosing lung nodules. By comparing diagnostic success rates, complication rates, procedure durations, and cost-effectiveness, we seek to identify the safer and more efficient technique for biopsying neoplastic lesions, ultimately improving patient outcomes.

Materials and methods

We searched the following databases: PubMed, Web of Science, clinical trial registry platforms, using key terms such as *virtual bronchoscopy navigation, navigation system-guided biopsy*, *bronchoscopic lung biopsy*. The results were limited to papers published between 2000 - 2023.

Conclusion

Navigational bronchoscopy techniques like VBN and ENB are safe and effective, with minimal adverse events and no hospitalization needed. They reduce procedure times and patient burden, offering long-term cost-effectiveness despite higher initial costs. Further research is necessary to enhance these technologies for better lung cancer diagnostics.

Key words: *lung biopsy*, *bronchoscopy navigation, lung cancer, bronchoscopic*

Introduction

Despite considerable advancements in our understanding of the risk factors, development, immune response, and treatment options for lung cancer, it continues to be the leading cause of cancer-related deaths. In 2021, lung cancer accounted for the highest number of deaths among men and was the second leading cause of cancer deaths among women. (OECD (2023), Krajowe profile dotyczące nowotworów: Polska 2023, EU Country Cancer Profiles, OECD Publishing, Paris, b.d.).

Among the numerous risk factors, smoking is responsible for approximately 90% of lung cancer cases in men and around 80% in women („Światowy Dzień Raka Płuca - o wyzwaniach związanych z diagnostyką i leczeniem raka płuca", 2023). Moreover, exposure to environmental and occupational hazards, chronic lung diseases, respiratory infections, and certain lifestyle choices all contribute to the development of lung cancer (Bade & Dela Cruz, 2020).

One reason patients often succumb to lung cancer is that it frequently presents no early symptoms, resulting in a diagnosis at an advanced stage. However, by enhancing our understanding of the detailed pathogenesis, improving early detection methods, and employing targeted therapies, we can significantly increase the chances of patient recovery.

Problems of classical through cage biopsy

For pulmonary lesions that are suspected to be malignant, biopsies are typically conducted using bronchoscopic or transthoracic techniques, usually prior to initiating treatment. The precision of localization and the efficiency of sampling are essential for achieving an accurate diagnosis and formulating an optimal treatment plan when biopsying lung nodules. However, traditional biopsy methods can encounter limitations, particularly for nodules that are hard to access or small. These procedures are also associated with a range of potential complications (DiBardino i in., 2015; Wiener i in., 2011). Computed tomography (CT)-guided percutaneous lung biopsy or ultrasound-guided percutaneous lung biopsy has diagnostic efficacy only for peripheral lung lesions, with a success rate of about 75% (Han i in., 2018).

The most common complication of percutaneous lung biopsy is pneumothorax, which can occur in up to 62% of cases. This may lead to the need for chest drainage and unplanned hospitalization in approximately 5.6% of patients. Another frequent complication of the procedure is hemorrhage, which occurs in up to 56% of cases (Heerink i in., 2017; Huo i in., 2020; Zhu i in., 2020).

Biopsy of lung nodules using bronchoscopy

There are several methods of taking a nodule specimen using bronchoscopy: standard bronchoscopy with transbronchial biopsy under fluoroscopy (Lai i in., 1996), ultrasound-guided bronchoscopy (Yamamoto i in., 2004), ultrasound-guided endobronchial radial biopsy (Asano i in., 2006), biopsy under electromagnetic navigation USG and even combinations of these techniques (Ralf Eberhardt, Anantham, Ernst, i in., 2007). Despite the presence of ultrathin bronchoscopes with outer diameters of 3 mm or less, precise localization in the bronchial tree is still extremely difficult. The main reason for the difficulty is the complex and anatomically variable airway structures, especially further away from the first divisions of the bronchial tree (Dolina i in., 2008), resulting in low diagnostic value (Rivera i in., 2007; van ’t Westeinde i in., 2012). The diagnostic efficiency of standard bronchoscopy when collecting material for histopathological examination of peripheral lesions < 2 cm in diameter is only 13.5% (van ’t Westeinde i in., 2012). In this context, virtual bronchoscopy navigation serves as an invaluable tool for the precise guidance and navigation of the bronchoscope within the patient's bronchial tree. Such an innovative method facilitates enhanced opportunities for the detection, localization, and assessment of lung tumors.

Virtual bronchoscopy navigation versus electromagnetic bronchoscopy navigation

Virtual bronchoscopy navigation (VBN) consists of two primary stages. The first stage is the planning phase, wherein the software generates a virtual bronchoscopy tree and maps one or more pathways to the target lesion based on computed tomography (CT) scans and target identification. The utilization of high-quality thin-layer CT scans is critical at this juncture, as the efficacy of the system in rendering accurate maps of the distal airways is directly dependent on the resolution of the scans and the absence of motion artifacts. Subsequently, the bronchoscopist can navigate these pathways to the limits allowed by the bronchoscope and the diameter of the airways.

The first studies on VNB, were conducted mainly by a team of researchers from Hokkaido University in Japan. They showed that the technology not only makes it easier for

operators to navigate the appropriate bronchus to the peripheral lesion but also contributes to diagnostic efficiency. Reports have reported the successful use of virtual bronchoscopy navigation to bar- mark 27/31 lung nodules located at the level to the ninth-generation bronchus prior to them surgical resection (Asano, Matsuno, i in., 2004; Asano, Shindoh, i in., 2004).

These initial studies led to a prospective, multicenter study evaluating the value of VBN in combination with rEBUS for the diagnosis of peripheral lesions up to 30 mm in diameter. One hundred and ninety-nine patients were randomly assigned to the procedure with or without the use of VBN. The sampling sites were checked using EBUS, and fluoroscopy was used to verify the position of the biopsy forceps. The diagnostic success rate was 80% for procedures with VNB and 67% for procedures without. There was also a reduction in procedure time (24 min vs. 26 min, $p = 0.016$) and time to first biopsy (8min vs. 10 min, $p = 0.045$). Researchers reported only one adverse event, pneumothorax, in a group of patients in which VNB was not used (Ishida i in., 2011).

During a prospective, multicenter study conducted at 10 centers in China, Germany and the United States, which included up to 200 patients with one or more lesions ≥8 mm in diameter suspected of lung cancer or metastatic disease that could be accessed via bronchoscopy were biopsied using the Archimedes® VBN system, using one of two techniques: bronchoscopy transparenchymal nodule access (BTPNA) and guided transbronchial aspiration (TBNA). One hundred and four of 114 suspicious lesions were attempted for biopsy material. The mean lesion size was 2.4 ± 1.13 cm. Sufficient tissue samples were obtained from 86 lesions, and the biopsy success rate was 75.4%. There were two cases (1.9%) of pneumothorax and one case (1.0%) of mild bleeding, confirming the low complication rate of VBN procedures (Sun i in., 2022).

Between February 2021 and January 2022, 35 patients underwent VBN treatment during the NAVIGATOR trial. Using the new VBN technique, a diagnostic success rate of 77% was achieved, which is in line with other studies, and enabled the inclusion of treatment in two- thirds of the analyzed patient population. The researchers concluded that without the VBN procedure, almost all patients would have missed a definitive diagnosis. (Hiddinga i in., 2023).

Initial pilot studies using the Archimedes platform to diagnose suspected cancerous lesions in children have demonstrated 100% feasibility of collecting diagnostic material in a child. Inaddition, none of the five children experienced complications, including hemoptysis and

pneumothorax. However, since the sample size was small, the results need to be verified in clinical trials with larger samples (Yang i in., 2023).

Electromagnetic Bronchoscopy Navigation (ENB) is a modern diagnostic method used to obtain samples from peripheral lung lesions in a minimally invasive and patient-safe way. This procedure is characterized by its low invasiveness and allows for the simultaneous sampling of both the peripheral lesion and nearby lymph nodes. ENB enables the creation of a 3D reconstruction of the airway, providing a virtual visualization of the bronchial tree, including subsegments of the lung that are typically inaccessible through conventional bronchoscopic examination. In addition, ENB can be utilized to insert tracers for radiotherapy and catheters for brachytherapy.

ENB similarly to VBN proceeds in two phases: planning and navigation. The first phase uses a pre-executed CT scan to mark and plan paths to targets in the lung. The second stage, or navigation phase, uses previously planned targets and paths. Viewing them allows the bronchoscope to navigate to the inside of the lungs, and once the ENB target is reached, it allows different actions to be taken within the same procedure.

Studies show that ENB is a safe diagnostic method and highly effective regardless of lesion size and lesion location. The efficiency of the procedure was 74% and 100% for peripheral lesions and lymph nodes. The diagnosis was made in 80.3% of the bronchoscopies performed, and a definitive diagnosis of lung cancer was made in 74.4% of the patients examined. Pneumothorax occurred in two patients (Thomas R Gildea i in., 2006). ENB was also shown to have similar efficacy to conventional CT-guided percutaneous methods in the diagnosis of small, deeply located and non-palpable lymph nodes. The study showed a statistically insignificant difference in the effectiveness of localizing the lesion with both methods. However, there was a significant difference in the following parameters – the interval between localization of the lesion and surgery and the incidence of pneumothorax (Shuenn-Wen Kuo i in., 2019).

An important aspect in the introduction of new diagnostic methods is their learning curve. One study on a group of 4 inexperienced operators shows that it can vary from operator to operator. For some, 25-30 operations may be needed to achieve competence, while for others the learning curve will be flatter (Louise L Toennesen i in., 2022)

A group of researchers from the National Defense Medical Center, Taipei City undertook a comparative study between bronchoscopy with electromagnetic navigation (ENB) assistance and bronchoscopy with virtual bronchoscopy navigation (VBN) system assistance. Thirty-five patients who underwent navigation bronchoscopy were included in the study.

There were no differences between groups in terms of characteristics, i.e., age, sex ratio, body mass index, and no significant differences between groups in terms of tumor location, distance from the pleura. During the study, the diagnostic efficacy of ENB was achieved in 89.5% of patients with bronchiectasis on CT imaging, compared to VBN where the biopsy efficacy was 93.8% of patients. The sensitivity and specificity of ENB were 80.0% and 77.8%, respectively. For smaller lung lesions, the success rate of VBN treatment was better compared to ENB (93.8% versus 78.9%). The sensitivity and specificity of VBN were 90.0% and 100.0%, respectively. Moreover, to perform the procedure with ENB transbronchial navigation requires a longer procedure time compared to VBN. Among the available lung biopsy procedures, VBN assisted navigation bronchoscopy is a safe and more effective method for evaluating lung lesions (Tsai i in., 2023).

In another study a comparison was made between ENB and VBN by performing diagnosis in 35 patients - 19 by ENB and 16 by VBN. Based on radiological findings, the mean size of the pulmonary lesion was 36.3 ± 21.9 mm (range: 11-128 mm), and the mean distance from the pleural surface to the lesion in its shortest path was 16.1 ± 11.7 mm (range: 1-41 mm). Tumors were predominantly in the right lower lobe of the lung, followed by the right upper lobe, left upper lobe, right middle lobe and left lower lobe. Most of the tumors had a solid pattern. No pneumothorax, hemorrhage or tracheal injury occurred during the biopsy guided by navigational bronchoscopy. No procedure-related deaths were reported. For transbronchial navigation, Veran ENB requires a longer procedure time compared to Archimedes VBN, but the difference was not significant. Veran ENB was diagnostic in 89.5% of patients with bronchial symptoms on CT imaging, while Archimedes VBN was performed in 93.8% of patients. The sensitivity and specificity of ENB were 80.0% and 77.8%, respectively, with a positive predictive value of 80.0% and
a negative predictive value of 77.8%. For smaller pulmonary lesions, Archimedes VBN had
a better success rate compared to ENB (93.8% versus 78.9%). The sensitivity and specificity of VBN were 90.0% and 100.0%, respectively, with a positive predictive value of 90.0% (9/10) and a negative predictive value of 85.7% (Yuan-Ming Tsai i in., 2023).

Conclusion

The systematic review concluded that navigational bronchoscopy is a safe procedure with potentially high diagnostic efficacy. Both Virtual Bronchoscopy Navigation (VBN) and Electromagnetic Navigation Bronchoscopy (ENB) demonstrate a high safety profile and a low

incidence of adverse events, which typically do not necessitate hospitalization. Additionally, the adoption of modern navigation techniques significantly shortens the duration of the procedure, thereby lessening the burden on the patient. Recent analyses regarding the cost-effectiveness of navigational bronchoscopy indicate that its diagnostic performance is a crucial determinant of its overall cost-effectiveness (*Cone beam CT-guided navigation bronchoscopy: a cost-effective alternative to CT-guided transthoracic biopsy for diagnosis of peripheral pulmonary nodules | BMJ Open Respiratory Research*, b.d.). This means that new navigation techniques, even if they initially involve higher purchase and implementation costs, can be cost-effective.

Disclosures

Author's Contribiutons : Kacper Ziarnik

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Methodology - Kacper Ziarnik, Michał Hofman

Software - Michał Krasowski

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Visualization - Michał Krasowski

Supervision - Kacper Ziarnik

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