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Invasive diagnostic procedures for early-stage lung cancer: the clinical significance of novel navigational techniques in interventional bronchoscopy

Инвазивне дијагностичке процедуре за рак плућа у раном стадијуму: клинички значај нових навигационих техника у интервентној бронхоскопији

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SUMMARY
Long-term statistical data on lung cancer (LC) show an overall 34% reduction in mortality compared to 1991. The primary reasons for this decline include a reduced smoking rate, earlier diagnosis, advancements in invasive diagnostic methods, and the introduction of low-dose computed tomography (LDCT) screening. These factors have contributed to detecting LC at earlier stages of the disease and improving timely treatment. The diagnostic sensitivity of conventional bronchoscopy for peripheral pulmonary lesions (PPL), representing early-stage LC, has historically been relatively low, ranging from 30% to 60%. Over the past two decades, diagnostic sensitivity for PPL has improved with the development of advanced navigational techniques, such as virtual bronchoscopic navigation, electromagnetic navigation bronchoscopy, radial endobronchial ultrasound, cone-beam computed tomography, and ultrathin bronchoscopy. In the past two to three years, robotic-assisted bronchoscopy has further enhanced diagnostic navigation capabilities to their current maximum potential.
Keywords: bronchoscopy; early detection of cancer; lung neoplasms; smoking; video-assisted techniques and procedures

САЖЕТАК
Дугорочни статистички подаци о раку плућа показују укупно смањење морталитета за 34% у поређењу са 1991. годином. Главни разлози за овај пад укључују смањену стопу пушења, ранију дијагнозу, напредак у инвазивним дијагностичким методама и увођење скрининга нискодозном компјутеризованом томографијом. Ови фактори су допринели откривању рака плућа у ранијим фазама болести и побољшању благовременог лечења. Дијагностичка сензитивност за периферне плућне лезије (ППЛ) које репрезентују рани стадијум болести, конвенционалном бронхоскопијом је била релативно мала, између 30% и 60%. Током протекле две деценије, дијагностичка осетљивост за ППЛ се побољшала развојем напредних навигационих техника, као што су виртуелна бронхоскопска навигација, електромагнетна навигациона бронхоскопија, радијални ендобронхијални ултразвук, конусна компјутеризована томографија и ултратанка бронхоскопија. У протекле две до три године, роботски потпомогнута бронхоскопија је додатно побољшала могућности дијагностичке навигације до њиховог тренутног максималног потенцијала.
Кључне речи: бронхоскопија; рано откривање карцинома; неоплазме плућа; пушење; видеоасистиране технике и процедуре

INTRODUCTION

Global data on lung cancer (LC) incidence and mortality have become increasingly refined in recent years and demonstrate significant geographical heterogeneity [1–4]. In the period following the COVID-19 pandemic, studies reported an increase in LC incidence and mortality worldwide, largely due to delayed diagnostic evaluation and detection at more advanced stages, which negatively affected treatment outcomes. Overall cancer incidence in 2020 was 9% lower than in 2019, with the most substantial decrease observed in asymptomatic (in situ and localized) disease, attributable to reductions in screening and incidental detection during routine medical visits [5]. However, when long-term LC statistical data are considered, there

is a continued decrease in mortality, amounting to 34% compared with 1991 (U.S. data). The main reasons for the reduced LC mortality are the decline in the smoking rate, earlier detection, advances in invasive diagnostic modalities, and the implementation of low-dose computed tomography (LDCT) screening, all contributing to earlier-stage diagnosis and timely treatment [6]. Obtaining an adequate bronchial or pulmonary tissue sample is crucial not only for establishing a diagnosis of LC but also for determining the molecular and immunologic profile of the lung tumour [7]. When the objective of invasive pulmonary diagnostics is early-stage diagnosis, sampling typically involves small peripheral pulmonary lesions (PPL), where flexible bronchoscopy has replaced rigid bronchoscopy completely. New image-guided bronchoscopic techniques have increased diagnostic yield and reduced complication rates compared with conventional bronchoscopy. These include virtual bronchoscopic navigation (VBN), electromagnetic navigation bronchoscopy (ENB), radial endobronchial ultrasound (R-EBUS), cone-beam computed tomography (CBCT), ultrathin bronchoscopy, and robotic bronchoscopy (RB) [8]. Advanced bronchoscopic imaging techniques such as autofluorescence imaging (AFI) and narrow-band imaging (NBI) can also detect changes in the bronchial epithelium, including carcinoma in situ (CIS), 40% of which may progress to invasive carcinoma. Early detection allows these lesions to be treated endoscopically, for example, by endobronchial brachytherapy or photodynamic therapy [9].

Transthoracic needle aspiration and biopsy (TTNA/TTNB)

TTNA/TTNB are well-established and safe diagnostic techniques for obtaining cytologic or histologic samples from PPL. Over time, several imaging modalities have been used to guide needle placement, including plain radiography, fluoroscopy, computed tomography, ultrasound, and electromagnetic-navigated TTNA [10]. These TTNA/TTNB methods have

become procedures of choice for diagnosing peripheral pulmonary nodules due to their high diagnostic yield. A sample can be obtained via needle biopsy or fine needle aspiration for cytology and cell-block preparation, and both sample types are suitable for molecular analysis. The CT-guided TTNA and TTNB demonstrate diagnostic yields ranging from 64% to 97% [11]. The most common complications include pneumothorax (39% prevalence) and bleeding (5% prevalence) [12]. Thoracic oncologists generally avoid TTNA/TTNB for PPL because these lesions are potentially resectable. However, this approach is preferred for suspected small cell lung carcinoma, for which surgery is not indicated. When surgery is contraindicated for any reason, TTNA/TTNB method is strongly recommended.

Bronchoscopy – New Diagnostic Procedures

Interventional pulmonology has expanded rapidly since the first groundbreaking studies in 2004 which demonstrated the usefulness of radial and linear endobronchial ultrasound (R/L-EBUS) for diagnosing pulmonary lesions and LC staging. The development of interventional pulmonology has significantly improved the management of LC, particularly early-stage non-small cell lung cancer (NSCLC) [12,13].

Radial endobronchial ultrasound with and without guide sheath

Although conventional flexible bronchoscopy can be used for diagnosing PPL, its diagnostic sensitivity is variable and generally lower than that of CT-guided TTNA/TTNB. This limitation facilitated the development of newer bronchoscopic techniques, such as radial and linear endobronchial ultrasound R-EBUS [14]. Several studies have confirmed that a multimodal approach that combines R-EBUS with VBN or ENB has an improved diagnostic yield when

compared to using only R-EBUS, as navigational systems compensate for instances in which R-EBUS fails to reach the lesion [15]. The key limitation of R-EBUS is the lack of real-time tissue sampling, as the radial probe (RP) must be removed from the bronchoscope's working channel before biopsy instruments are introduced. Maintaining a consistent position of the radial probe withdrawal and instrument insertion is challenging (Figure 1) [16]. Guide sheath (GS) use can partly help mitigate this issue. Diagnostic sensitivity of R-EBUS for PPL depends on lesion size, location, presence of a bronchus sign, lesion type, and the availability of rapid on-site evaluation (ROSE) [17]. Diagnostic sensitivity is reduced for upper lobe lesions because the radial probe cannot navigate sharply angled segments. The diagnostic sensitivity is greatly influenced by the position of PPL when compared to RP, with the highest diagnostic sensitivity when the R-EBUS probe is centrally positioned within the lesion (82.6%), lower when in the adjacent position (56.8%), and the lowest when the probe is outside the lesion (17.3%) (24). A meta-analysis of 46 studies (2002–2022) included 7,252 patients with PPL, out of which 5,173 patients were successfully diagnosed by R-EBUS with an overall diagnostic sensitivity of 73.4% (95% CI: 69.9–76.7%) [18].

Ultrathin bronchoscopy in the diagnosis of PPL

Ultrathin bronchoscopy (UTB) uses bronchoscopes with a working channel diameter of 1.8–2.2 mm, enabling navigation into smaller bronchi and facilitating access and biopsy of PPL. When combined with R-EBUS, UTB demonstrates better diagnostic sensitivity compared with thin bronchoscopy (TB), particularly for lesions in the upper segments of the lower lobes and the upper lobes [19, 20].

Multiple studies have shown higher sensitivity with UTB compared to TB (70.1% vs. 58.7%) (27,28). In Nishii's study, patients first underwent TB with R-EBUS; if the probe did not enter

the lesion, TB was replaced with UTB. Positive or negative bronchus sign presence or absence had an impact on statistically significant difference between diagnostic and nondiagnostic bronchoscopies, and both procedures were performed with VBN assistance [21].

New navigational techniques in bronchoscopy of PPL

Electromagnetic Navigation Bronchoscopy (ENB) is a type of bronchoscopic navigation that enables guided sampling of PPL using electromagnetic field–based reconstruction of a three-dimensional pathway (3D) to the target lesion [22]. During the procedure, the bronchoscope is navigated through the airways using real-time electromagnetic navigation. Virtual 3D mapping laid over the live bronchoscopic imaging allows the operator to lead the bronchoscope with precision to the lesion. Biopsy instruments are then introduced into the working channel to obtain diagnostic biopsy samples (Figure 2) [23].

In the multicentre NAVIGATE study, ENB achieved a diagnostic yield of 73%, with the R-EBUS-assisted group demonstrating superior sensitivity compared with the fluoroscopy group [24].

Cone-beam computed tomography (CBCT) in bronchoscopy

CBCT provides real-time airway imaging and confirms navigational accuracy through specialised software. This enables the bronchologist to localize with PPL that are difficult or impossible to reach using conventional bronchoscopy and would require fluoroscopy to guide the instruments into the lesion [25]. The use of radiation or fluoroscopy is highly reduced or completely absent since the fluoroscopic lung imaging is often not needed. Limitations of the

procedure are the following: the need for specialized equipment and infrastructure, including a complete CBCT system. The interpretation of CBCT also requires advanced operator training, and there are also significant system and maintenance costs. All this makes CBCT less accessible for institutions with limited resources [25, 26].

Bhadra et al. published a study of 200 patients who underwent CBCT bronchoscopy with a multimodal approach which incorporated both conventional and ultrathin bronchoscopy, and with a smaller group of patients also underwent cryobiopsy. The diagnostic sensitivity was 90%, with 60% malign lung lesions, 30% benign lung lesions and 10% undiagnosed. By using the cryoprobe, the authors increased the diagnostic sensitivity from 86.4% to 90.1% [27].

Robotic-Assisted Bronchoscopy (RAB)

Robotic-assisted bronchoscopy enables the bronchologist to visualise and access previously unreachable peripheral lung regions. Although system cost remains a significant barrier for RAB (Figure 3), it currently offers the highest diagnostic yield for PPL [28]. This method integrates three navigational modalities—electromagnetic guidance, optical pattern recognition, and robotic kinematic feedback—providing highly accurate localization on high-resolution monitors. Initially, target lesions are mapped on CT, imported into planning software, and then via robotic platform the target lesions are accessed with precision by guiding the bronchoscope through the airways [29].

The robotic platform includes an innovative telescoping endoscope mounted on flexible robotic arms, enabling superior manoeuvrability, reach, and stability. Combining advanced imaging, improved biopsy tools, and robotic precision has enabled diagnostic sensitivity for small PPL to exceed 90% [30]. These results are comparable to CT-guided transthoracic needle

aspiration/biopsy (TTNA), which has proven sensibility of 84–96%. However, RAB has a better safety profile, with the 2.3% pneumothorax rate and 0.6% bleeding risk [31]. Current evidence suggests that, with appropriate expertise and technology, bronchoscopy-based biopsy of PPL can be recommended as preferrable method with minimal selection bias.

CONCLUSION

Bronchoscopy has undergone profound transformation since its inception, evolving from a simple tool for removing foreign bodies into a sophisticated diagnostic and therapeutic platform. Modern navigational technologies have markedly improved the safety and accuracy of diagnosing PPL. Robotic-assisted bronchoscopy (RAB) represents the most advanced development to date and is poised to become a standard diagnostic modality. As these technologies continue to evolve, they hold promise not only for improving peripheral lesion diagnosis but also for enabling future bronchoscopic therapeutic interventions in peripheral lung malignancies.

Ethics: The authors declare that the article was written in accordance with the ethical standards of the Serbian Archives of Medicine as well as the ethical standards of medical facilities for each author involved.

Conflict of interest: None declared.

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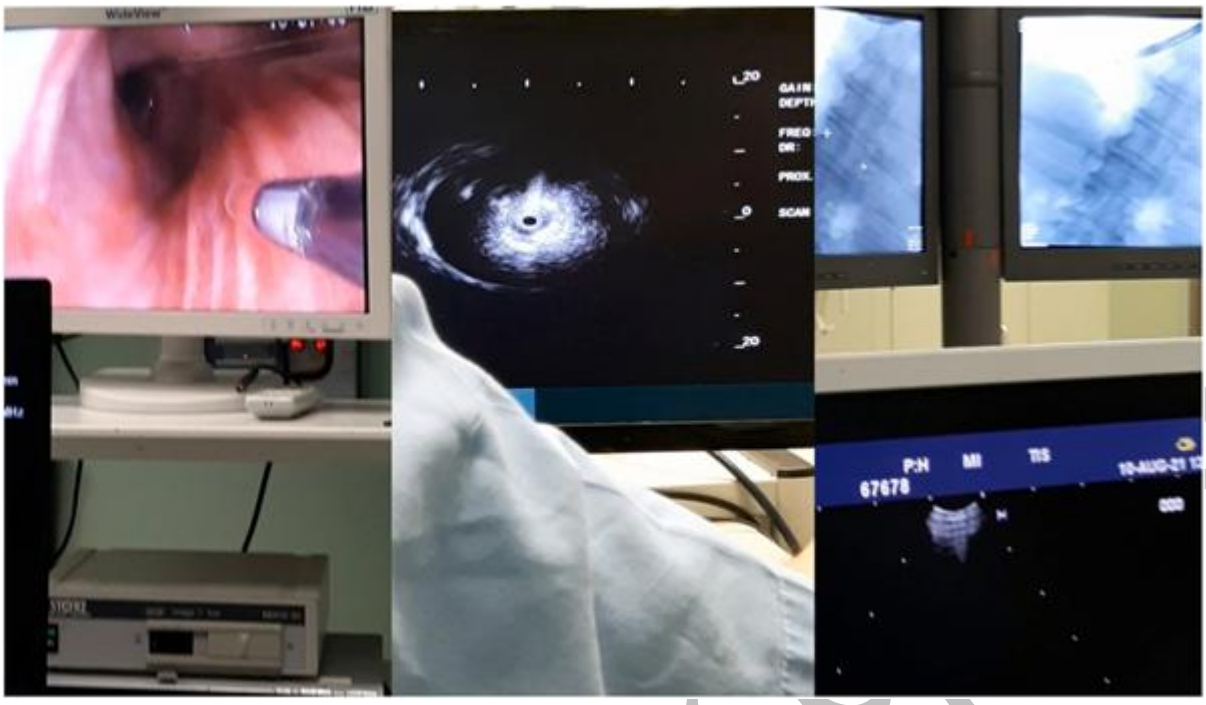

Figure 1. Radial endobronchial ultrasound (R-EBUS) [16]

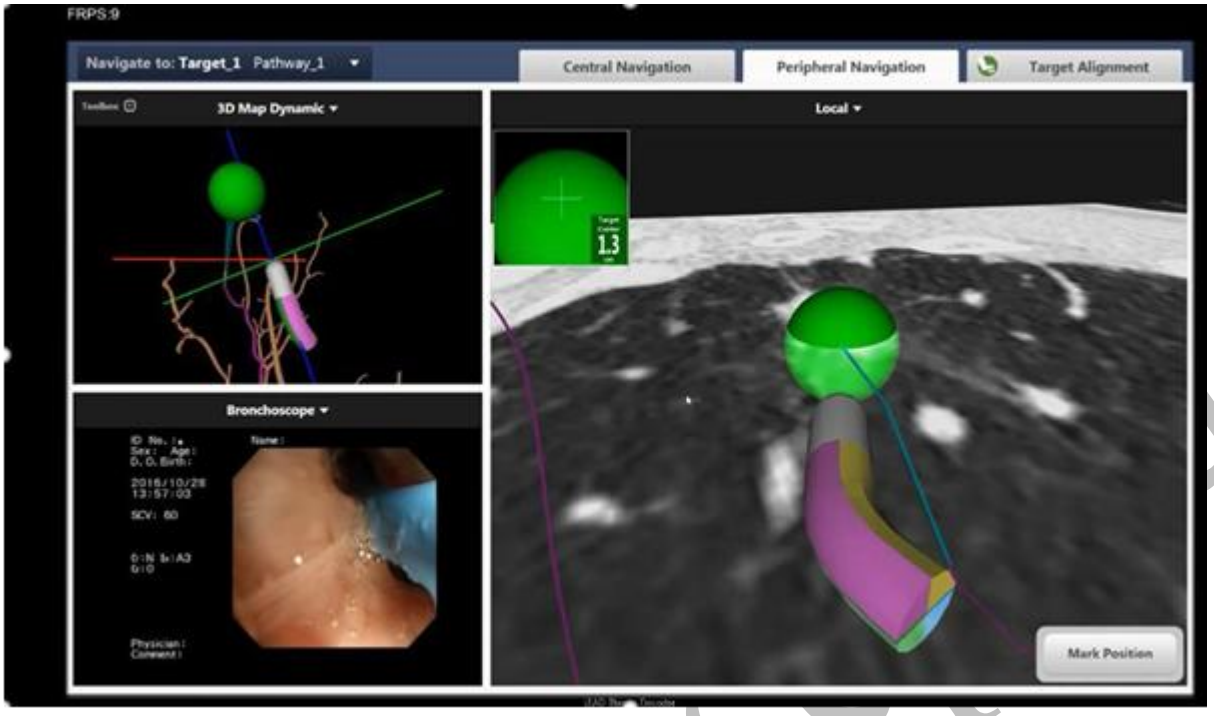

Figure 2. Electromagnetic navigation bronchoscopy [23]

Figure 3. Application of robotic assisted bronchoscopy; the bronchologist guides the procedure via the display; on the left in the image of the monitor is a real-time bronchoscopic procedure, the right side shows a virtual bronchoscopic view [28]

