Does the Addition of Radial Endobronchial Ultrasound Improve the Diagnostic Yield of Electromagnetic Navigation Bronchoscopy? A Systematic Review

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Keywords
Lung cancer · Diagnostics · Electromagnetic navigation bronchoscopy · Radial endobronchial ultrasound · Systematic review

Abstract

**Background:** Lung cancer is the leading cause of cancer-related death worldwide. Early diagnosis is crucial to increased survival rates. Radial endobronchial ultrasound (rEBUS) and electromagnetic navigation bronchoscopy (ENB) have been developed for the diagnosis of small lung lesions. The aim of this systematic review was to evaluate whether the combination of rEBUS and ENB is superior to ENB alone.

**Method:** A systematic search was performed using MEDLINE, Embase, and Cochrane Library databases on “ENB,” and conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The project was registered with PROSPERO, number CRD42020214682.

**Results:** In total, 2,092 studies were identified through a literature search. Five studies were included in the final review. One study found that the addition of rEBUS increased diagnostic yield, while another concluded the converse. Three studies did not have significant results. Meta-analysis was not feasible due to heterogeneity and the small number of studies.

**Conclusion:** As the current evidence on the topic is sparse and heterogeneous, it is not possible to conclude whether the addition of rEBUS to ENB has a significant impact on diagnostic yield. Further studies are needed to illuminate this question in order to ensure optimal choice of endoscopic technique as well as used time and resources. The project received funding from the Region of Southern Denmark’s PhD fund.

Background

Lung cancer is the current leading cause of cancer-related deaths worldwide [1, 2]. This is partly because a large proportion of patients are diagnosed at late stages [3]. To increase survival, diagnosis must be made in the early stages, when curative treatment is still feasible. Several studies have therefore focused on developing a lung cancer screening program with the aim of early diagnosis [4–6]. However, early diagnosis can be challenging because, at the early stages, the disease is often limited to small lung lesions, making it difficult to obtain a diagnostic tissue sample.
The methods currently available for lung lesion tissue sampling are transthoracic needle biopsies (computed tomography [CT]-guided or ultrasound-guided), surgical biopsies, or endoscopic sampling. When compared to surgery, the endoscopic approach has a low risk of complications [7, 8], at the expense of a lower diagnostic yield.

In recent years, electromagnetic navigation bronchoscopy (ENB) has been developed to guide the operator to the lung lesion [9, 10], using information obtained from (CT) images performed prior to the bronchoscopy. Another method is radial endobronchial ultrasound (rEBUS), in which a radial ultrasound probe is inserted into the working channel of the bronchoscope. rEBUS enables the operator to more accurately identify the lung lesions before obtaining the tissue samples [11]. It may be advantageous to combine ENB with rEBUS in one procedure, allowing the operator to identify the endobronchial pathway to reach the target lesion, using ENB followed by rEBUS to confirm that the lesion has indeed been reached prior to sampling [12]. If the addition of rEBUS to ENB provides a higher diagnostic yield, it is fairly easy to implement, with a low added cost compared to the cost of ENB alone. However, if the addition does not improve diagnostic yield significantly, the increased procedure time and equipment costs for performing the combined procedure should be avoided.

A systematic review was conducted, with the aim as outlined in the following PICO components to specifically assess the value of the combination of ENB and rEBUS:

- **P** – in patients with peripheral lung lesions or solitary lung nodules suspicious for malignancy,
- **I** – is the diagnostic yield of ENB in combination with rEBUS superior
- **C** – compared to ENB alone
- **O** – in establishing a diagnosis?

### Method

A systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [13]. The study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) (registration number: CRD42020214682).

#### Search Strategy

The search strategy was developed with the assistance of a research librarian. A preliminary search identified only a low number of articles on the subject of “ENB.” In consensus with the search librarian, it was then decided to search the literature for “ENB” and synonyms, not limiting the search by adding “rEBUS” or “lung cancer,” see Figure 1. No restrictions were made on the date of publication or language. MEDLINE, Embase, and Cochrane Library were searched for this review.

#### Identification of Additional Studies

The systematic database searches were supplemented by reviewing the reference lists of the included articles, together with the reference list of an identified recent systematic review comparing ENB to rEBUS [7].

#### Selection of Studies

**Inclusion criteria**

- Studies comparing ENB to ENB + rEBUS, reporting diagnostic yield for both groups.

**Exclusion criteria**

- Studies in which lung cancer diagnosis was not the objective or part of the objective of the procedures.
- Studies not performed on humans.
- Non-peer-reviewed studies.

Two independent researchers (A.D.J., C.F.) performed both title and abstract screening, along with full text screening. Conflicts were resolved by consensus decision or by a third senior investigator (C.B.L.) if consensus could not be achieved.

Studies investigating the diagnostic yield of only ENB or ENB + rEBUS, and studies comparing ENB + rEBUS to rEBUS were categorized as “wrong combination of procedures” (Fig. 2). To include results from a wide clinical setting, the authors decided to assess retrospective and prospective studies for eligibility, not focusing solely on randomized clinical trials (RCT). Non-peer-reviewed studies, such as conference abstracts, were excluded, although the databases were searched for articles originating from the same studies.

| # Searches | Results |
|------------|---------|
| 1          | EBUS-ENB.mp. | 6 |
| 2          | Electromagnetic navigation guided biopsy.mp. | 0 |
| 3          | Electromagnetic navigation bronchoscopy.mp. | 152 |
| 4          | ENB.mp. | 532 |
| 5          | Electromagnetic navigational bronchoscopy.mp. | 77 |
| 6          | Bronchoscopic navigation system.mp. | 12 |
| 7          | Navigational bronchoscopy.mp. | 119 |
| 8          | Electromagnetic navigation.mp. | 405 |
| 9          | Superdimension.mp. | 30 |
| 10         | EMN.mp. | 139 |
| 11         | ENB-EBUS.mp. | 1 |
| 12         | 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 | 1,031 |

**Fig. 1.** Search string.
**Data Extraction and Quality Assessment**

Data from the included studies were extracted using a predefined data sheet. Information on publication year, country, study design, population, inclusion criteria, exclusion criteria, number of patients, age, funding sources, reported conflicts of interest, prevalence of malignancy in the study population, lesion size, ENB system, rEBUS system, operator level, reference test, additional techniques, reported economic results, intention to treat principles, Enhancing the QUAlity and Transparency Of health Research (EQUATOR) network reporting [14], primary outcome, secondary outcome, adverse effects, diagnostic yield, sensitivity, specificity, positive predictive value, and negative predictive value were recorded. If some of the predefined data were not presented in the original article, online supplementary data (for all online suppl. material, see www.karger.com/doi/10.1159/000524671) were searched and, if still missing, the corresponding authors were contacted. A modified version of the Quality Assessment of Diagnostic Accuracy Studies-2 protocol (QUADAS-2) [15] tool was used to assess the risk of bias (see Table 1: Risk of bias – Modified QUADAS-2 tool).

**Table 1. Risk of bias – modified QUADAS-2 tool**

| Study | Patients selection | Index test | Reference test | Flow and timing |
|-------|-------------------|------------|----------------|-----------------|
| Eberhardt et al.[12] | ☺ | ☻ | ☻ | ☻ |
| Ozgul et al.[17] | ☺ | ☻ | ☻ | ☻ |
| Ost et al.[18] | ☻ | ☻ | ☻ | ☻ |
| Folch et al.[19] | ☻ | ☻ | ☻ | ☻ |
| Bellinger et al.[16] | ☻ | ☻ | ☻ | ☻ |

☺, low risk of bias; ☻, intermediate risk of bias; ☹, high risk of bias.

**Statistical Analysis**

A meta-analysis of the pooled sensitivity, specificity, and diagnostic yield was planned as part of the systematic review. However, due to heterogeneity and a limited number of studies, it was not feasible to conduct a meta-analysis.
## Table 2. Study characteristics

| Study [ref. No.] | Publication year | Country     | Design                         | Funding sources and reported conflicts of interests | Equipment used ENB/EBUS | Primary outcome               | Secondary outcome                        | Operator level | Reference test                                                                 |
|------------------|------------------|-------------|--------------------------------|----------------------------------------------------|------------------------|--------------------------------|------------------------------------------|----------------|--------------------------------------------------------------------------------|
| Eberhardt et al. [12] | 2007            | Germany/USA | Randomized non-blinded clinical trial – multicenter | Two authors are members of scientific advisory board of superDimension and have received stock options | superDimension/ Olympus | Diagnostic yield               | Yield by lesion size, lobar location, lesion pathology | Not reported | Definite histology from biopsy, otherwise surgical removal |
| Ozgul et al. [17]  | 2015            | Turkey      | Prospective cohort – single center | The authors reported no conflicts of interests | superDimension/ Olympus | Diagnostic yield               | Lesion size, lobar location              | Not reported | Definite histology from biopsy, otherwise CT TTNA or surgery or 6–24 months follow-up |
| Ost et al. [18]   | 2015            | USA         | Prospective cohort – multicenter | The AQuIRE program has been sponsored by the American college of chest physicians (CHEST) | superDimension or Veran/not reported | Diagnostic yield               | Diagnostic yield of each sampling technique, complication, practice patterns | Median number of ENB = 14 per year | Definite histology or 12-month follow-up |
| Folch et al. [19] | 2018            | USA         | Prospective cohort – multicenter | The study was sponsored by Medtronic | superDimension/ not reported | ENB-related pneumothorax requiring intervention or hospitalization | Diagnostic yield | 10 procedure/month = 45%, 5–10 procedures/month = 48%, <5 procedures/month = 8% | Definite histology or 12 months of follow-up or death due to cancer |
| Belliger et al. [16] | 2021            | USA         | Retrospective cohort – single center | The authors reported no conflicts of interests | superDimension/ Olympus | Diagnostic yield by lesion characteristics | Diagnostic yield by Tsuboi classification | Mixed experience levels | Definite histology from biopsy, surgery or 18 months of CT follow-up |
Results

The initial systematic search, performed on November 25, 2020, yielded 3,022 results, including 2,092 unique articles for title abstract screening. Forty-three articles were full-text screened and four articles were included in the review (Fig. 2). Subsequent searches of reference lists of included articles or relevant abstracts revealed no additional studies. An updated search, on May 12, 2021, identified one new study eligible for inclusion [16].

The studies included a total of 1,806 patients undergoing ENB or ENB + rEBUS. The number of cancer cases was not reported separately for all studies. None of the studies reported according to the EQUATOR network guidelines or included information on economical evaluation. In Table 2, characteristics from all included studies are summarized. Table 3 presents an overview of the results from the included studies.

Table 3. Summary of findings

| Study       | Diagnostic yield ENB, % | Diagnostic yield ENB + rEBUS, % | p value | Malignant cases/ patients, n | Adverse events | Size of lesion | Mean age, years (SD) |
|-------------|-------------------------|---------------------------------|---------|------------------------------|----------------|------------------|----------------------|
| Eberhardt et al. [12] | 59                      | 88                              | 0.02    | 60/79                        | Pneumothorax 6% | 26 mm, 13–58 mm | 53 (13)              |
| Ozgul et al. [17]   | 71                      | 73                              | Not reported | 42/56                        | Pneumothorax 1.7% (1 patient) | 30 mm, 23–44 mm | 60 (9.6)             |
| Ost et al. [18]     | 39                      | 47                              | Not reported | Only reported for full study/ 314 patients in the ENB and ENB + rEBUS groups | Pneumothorax, hypoxia, bleeding, respiratory failure, 2.2% in total | 62% < 20 mm, 38% > 20 mm | 67.1 (12.6) |
| Folch et al. [19]   | 76                      | 71                              | 0.04    | 768/1,157                    | Pneumothorax 4.3%, bleeding 2.5% respiratory failure in 0.7% | 20 mm, 14–30 mm | 67.6 (11.3) |
| Bellinger et al. [16] | Not reported            | Not reported                     | –       | 185 malignant lesions/271 lesions | Pneumothorax 3%, bronchospasm and hypoxia 1.9%, pneumonia and COPD exacerbation within 1 week 1.1%, moderate to severe bleeding 0.4% hemoptysis without admission 0.7%, other without admission 0.7% | In total 7.8% | 24.2 mm (12.1 SD) | 67.2 (10.5) |

Ozgul et al. [17]

This study was conducted as a single-center prospective cohort study. The method of allocating patients to ENB or ENB + rEBUS was not described. If a definitive diagnosis was obtained from the procedure, the diagnosis was considered correct, and no other reference test was used. Other reference tests if a diagnosis was not reached with endoscopy were CT-guided needle biopsy or surgery. If the patient did not wish to undergo additional invasive procedures, radiological follow-up was used as a reference test. No additional techniques were used. Operator skill level was not reported. Seventy-five percent of patients in the cohort were diagnosed with cancer. Although not statistically significant, this study showed a slightly higher diagnostic yield for ENB + rEBUS compared to ENB alone (73% vs. 71.4%). Sensitivity and spec-
In this study, the diagnostic yield for ENB + rEBUS compared to ENB alone was higher, although both yields were lower than for the other studies. The group receiving bronchoscopy without ENB or rEBUS had the highest yield, of 63.7%. The study did not randomize the patients, and there was no description of how patients were selected for each bronchoscopy procedure. If a definitive diagnosis was obtained from the procedure, it was considered correct, and no other reference test was used. Otherwise, the reference test was 12 months of follow-up with CT scans. Bronchoscopy was used in 55 patients, but it is unclear whether it was used alone or in combination with other modalities. The mean number of annual ENB procedures was 14, ranging from 3 to 50. It was not reported how many procedures the operators had performed in total, or if they were considered “experts” or “beginners.” There was no report of the number of cancer cases for patients undergoing ENB or ENB + rEBUS. In the full cohort, 58% of the patients were diagnosed with cancer.

The study had a higher diagnostic yield for ENB + rEBUS compared to ENB alone, although both yields were lower than for the other studies. The group receiving bronchoscopy without ENB or rEBUS had the highest yield, of 63.7%. The study did not report sensitivity or specificity for the two groups of interest. The corresponding author did not reply to our request for additional data.

Folch et al. [19]

The “Clinical Evaluation of superDimension™ Navigation System for Electromagnetic Navigation Bronchoscopy™” (NAVIGATE) study was a prospective multicenter cohort study, evaluating ENB using the superDimension navigation system. The study was funded by Medtronic, the company that owns the superDimension system. The majority of patients (95%) were undergoing examination for lung cancer, but the study also included patients in whom ENB was used for fiducial placement or pleural dye marking. The use of rEBUS was at the operator’s discretion. For all patients, ROSE and fluoroscopy were included as part of the ENB procedure. The procedures were performed by advanced operators. The study included 248 patients with 271 lesions. All results were calculated per lesion instead of per patient. Fifty-nine percent of the lesions were malignant. Diagnostic yield was not reported. Instead, malignant yield (ENB 39%, ENB + rEBUS 41%, p value 0.79), sensitivity (ENB 63%, ENB + rEBUS 54%, p value 0.33) and diagnostic accuracy were reported. Although not statistically significant, diagnostic accuracy was higher in the ENB + rEBUS group at 76%, versus 67% in the ENB group, p value 0.14. Upon request, the corresponding author provided information on operator skill level and the rEBUS system. Diagnostic yield for the two groups was not calculated.

Discussion

This systematic review, whose aim was to determine if the combination of ENB and rEBUS is superior to ENB alone, identified only five studies that had addressed our research question. While the identified studies indicate that the diagnostic yield of ENB is possibly improved by the addition of rEBUS, few of the studies reported statisti-
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Due to the significant methodological differences between the studies, a meta-analysis was not performed. The study by Bellinger et al. [16] reported diagnostic accuracy instead of diagnostic yield, but was still included, to illuminate all relevant literature.

The first study on ENB was published in 2003 [20], and in 2005 a pilot study explored the use of ENB for peripheral lung lesions [21]. Since then, a number of articles have reported on the diagnostic yield for ENB alone or ENB + rEBUS. It is therefore surprising to have found only five studies comparing the diagnostic yield of these modalities. A systematic review has been published assessing the diagnostic yield of ENB and rEBUS, but the review did not address the diagnostic yield and added value of combining ENB and rEBUS into a single procedure, but instead chose to compare the two procedures when performed separately [7]. It is possible that the Eberhardt et al. [12] study from 2007 led to the implementation of the combination rEBUS and ENB as standard in some hospitals, whereas other hospitals continued to use ENB alone or in combination with fluoroscopy or ROSE.

Most articles in this review did not randomize patients or provide any indication for when rEBUS was used. In the AQuIRE and NAVIGATE studies, it might have been site-specific, but this is not reported. It is probable that a hospital will employ the same approach for all patients, and this might explain why only five studies have data on both ENB and ENB + rEBUS.

Utilization of ROSE and fluoroscopy are also possible contributing factors in increasing diagnostic yield. Both methods help in the confirmation of correct location during sampling and might dilute the effect of adding rEBUS to ENB. The Eberhardt et al. [12] study did not use either of these methods and showed the greatest difference in favor of ENB + rEBUS.

The diagnostic yield of a given test is typically assessed using a prospective cohort study design, in accordance with "Standards for Reporting Diagnostic Accuracy Studies" (STARD) guidelines, in which the test being assessed is directly compared to a predefined reference test [22]. Prospective cohort studies can be prone to the introduction of selection bias in patient recruitment. Additionally, if a study aims to assess multiple diagnostic tests simultaneously and not all tests are performed in all included patients, additional selection bias might be introduced. Both the NAVIGATE and the AQuIRE studies have the advantage of several inclusion sites with a large number of participants, thus producing results representative of a clinical setting. Unfortunately, none of the cohort studies reported how procedures were selected for each patient, making it impossible to know whether the combination of procedures was selected for the most difficult cases, to optimize tissue sampling. This might explain why ENB performed better than ENB + rEBUS in the NAVIGATE study. In the AQuIRE study, the procedure with the highest diagnostic yield was conventional bronchoscopy, supporting the notion that choice of procedure was dependent on the level of difficulty. Neither the NAVIGATE nor the AQuIRE study reported their results in accordance with the STARD guidelines.

The study by Eberhardt et al. [12] used an RCT design, thus avoiding bias when selecting the procedure for the given patient. This suggests that their results, showing an increase in diagnostic yield using the multimodal approach, are valid. The study had a high proportion of cancer cases and the youngest population of all the studies. This could imply possible significant selection bias for inclusion in the study, with the inclusion of several young individuals with a high clinical suspicion of malignancy prior to the invasive procedure. As such, it is not possible to determine whether the results are reproducible in a general population with a lower cancer incidence, patients in poor health, and a mix of experienced and inexperienced operators. The RCT study was not reported in accordance with the internationally recommended guidelines on the reporting of RCTs (e.g., Consolidated Standards of Reporting Trials [CONSORT] [23]).

None of the studies in this review report using intention-to-treat principles. It is therefore not known if some patients did not receive the intended procedure due to malfunction of medical devices, complication with sedation, etc., and were subsequently excluded or not included in the study. With this approach, one might make conclusions based solely on the patients who tolerated the procedure well and not the patients in which the procedure was not performed or completed, for instance as a consequence of equipment malfunction or clinical deterioration during the procedure. Procedures that are poorly tolerated or with several system malfunctions are less useful in a clinical setting, and studies using intention-to-treat principles will reflect this in their results.

In the AQuIRE article, the authors discuss how patient selection and the prevalence of a disease may affect diagnostic yield, noting that the cancer prevalence in their population is lower than in previous studies. If a tissue sample reveals malignancy, it is easy to conclude that the sampling was done correctly. It is far more difficult to draw the same conclusion if histology shows, e.g., "unde-
terminated inflammation,” despite the fact that it might be the correct diagnosis. In a cohort with low cancer prevalence, there will be an increase in cases in which it is difficult for the clinician to draw conclusions from the tissue sample, thus lowering the diagnostic yield. The Eberhardt et al. [12] study had a cancer prevalence of 76%, Ozgul et al. [17] 75%, NAVIGATE 66%, Bellinger et al. [16] 59% (of lesions), and AQuIRE 58%. These numbers are quite high, when considering that the purpose of ENB is to reach peripheral and difficult lesions and not easily accessible tumors near the mediastinum. One could argue that proper selection of patients for invasive procedures is good clinical practice, but in the daily setting it is difficult to rule out malignancy based on CT imaging. With the possibility of a future lung cancer screening program being implemented, we need to prepare for a rise in false positive CT scans and a lower cancer prevalence than previously observed. It is important to consider how this shift will affect diagnostic yield and the capacity to rule out malignancy using these procedures.

Knowing the competence level of the operator is important, when evaluating a new diagnostic tool or procedure. Studies comprised solely of experts ensure the equipment is tested in an optimal setting. However, the results may not be representative of a clinical setting if there are varying levels of operator experience. Reporting on this subject is not uniform in the included studies but is an important consideration for future studies.

Limitations
The main limitation of this review is, first and foremost, the limited number of included studies. EQUATOR network reporting was another notable omission in all included studies, which should be standardized. Most studies had a high prevalence of cancer cases, possibly increasing diagnostic yield. The results from this study are limited by the lack of a meta-analysis. The study design only included peer-reviewed articles, which means some non-published studies could have been missed.

Clinical Perspectives
In spite of ENB and rEBUS being two very commonly used tools in lung cancer diagnostics, very few studies actually explore the added value of using both in the same procedure. As a vast number of patients undergo these diagnostic procedures for lung cancer every day, the lack of evidence on the topic is concerning seen from both a patient and organizational perspective. Hence, further prospective studies either as diagnostic accuracy studies or preferable randomized clinical trials assessing the clinical impact, resources used (e.g., procedure time, procedure costs, total costs for obtaining a diagnosis), and any relevant patient preferences are warranted.

Conclusion
Very few studies on the subject exist, some of which reported an increase in diagnostic yield by adding rEBUS to ENB. However, it was not possible to explore these conclusions statistically through meta-analysis. Further studies assessing the diagnostic yield of ENB and rEBUS should be performed and reported in accordance with EQUATOR guidelines, to ensure correct methodology, reporting, and to provide data which can be used for subsequent reviews and meta-analysis.

Statement of Ethics
An ethics statement is not applicable because this study is based exclusively on published literature.

Conflict of Interest Statement
Christian Laursen received honoraria from AstraZeneca A/S: Lecture at the 6th Nordic Respiratory Science Forum on February 11, 2021 and Royalties for educational materials (books, web-based learning platforms) in Munksgaard, Denmark. All the authors had full access to all data and the corresponding author had final responsibility of submission for publication.

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Author Contributions
Contributors Amanda Juul designed the study in consultation with Christian Laursen, Ole Hilberg, Torben Riis Rasmussen, Arman Arshad, and Niels Jacobsen. Amanda Juul and Niels Jacobsen designed the article search with the assistance of a research librarian. Amanda Juul and Casper Falster did the study selection, data.
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A Data Availability Statement

A preprint version of this publication can be accessed at www.zeno.org, DOI: 10.5281/zenodo.6223895 [24]. Data can be requested from the corresponding author.

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