Radial-EBUS and virtual bronchoscopy planner for peripheral lung cancer diagnosis: How it became the first-line endoscopic procedure

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Abstract

Background: Various advanced bronchoscopy methods have been developed to reach peripheral lung lesions (PLL). In a large cohort, we aimed to assess a standardized procedure of first-line radial-endobronchial ultrasound (r-EBUS) and virtual bronchoscopy planner for the diagnosis of peripheral lung cancer.

Methods: This retrospective, single center study included patients who had r-EBUS-guided bronchoscopy for the diagnosis of a PLL between 2008 and 2019. Cases without a final diagnosis of cancer or follow-up were excluded.

Results: Between 2008 and 2019, 2735 patients had a r-EBUS procedure, among whom 1627 had a final diagnosis of cancer and were included in the present study. Over the 12-year study period, r-EBUS became the first-line endoscopic procedure to assess PLL (25% as first-line bronchoscopy in 2008 vs. 92% in 2019). The frequency of the bronchus sign decreased from 2009 to 2019 (100% to 80%; *p* = 0.001), whereas US visualization of the lesion remained stable (88%). The median number of biopsies increased from two (2008 to 2014) to four (2015 to 2019) (*p* < 0.0001), with the same diagnostic efficiency (74% total and 80% when a bronchus sign was present). Of the 651 adenocarcinomas, molecular analysis was possible in 86%. PD-L1 expression analysis was possible in 81% of cases. During the study period, the lifetime of the radial probe increased from 57 procedures to 77 procedures/probe.

Conclusion: Because r-EBUS and VB planner is easy to perform under local anesthesia, inexpensive and efficient it can be used as a first-line procedure to assess peripheral lung cancer.

KEYWORDS

bronchoscopy, lung cancer, peripheral pulmonary nodule, radial endobronchial ultrasound, virtual bronchoscopy planner

INTRODUCTION

Lung cancer is the most commonly diagnosed cancer, and the leading cause of cancer-related deaths worldwide, with 18% of cancer deaths in 2018. When detected in the early stages, curative surgical options can be considered, significantly improving survival. Aimed at detecting earlier stages, the National Lung Screening Trial showed a survival advantage in patients screened on a yearly basis with low dose chest computed tomography (CT), despite an increase of incidentally detected solitary pulmonary lesions of unknown origin.
In order to obtain a definitive diagnosis of peripheral pulmonary nodules, tissue sampling is often required. CT-guided percutaneous needle biopsy (CT-PNB) can be performed. However, it is associated with a high rate of pneumothorax, cited between 15% and 43%, as well as a risk of pulmonary hemorrhage, reported between 1.0% and 27%. Standard flexible bronchoscopy has a variable and often poor success rate in sampling peripheral pulmonary lesions during endobronchial examination.

Various advanced bronchoscopy methods have been developed to reach peripheral nodules such as electromagnetic navigation, radial endobronchial ultrasound (r-EBUS), virtual bronchoscopy, and more recently robotic bronchoscopy. Currently, these procedures are often proposed as second attempts after standard bronchoscopy failure, leading to increased cost and time until the diagnosis of a peripheral nodule.

In a large cohort, we aimed to assess a standardized procedure of r-EBUS and virtual bronchoscopy planner as the first-line diagnostic procedure for peripheral lung cancer.

**METHODS**

**Patients**

This retrospective, single-center study included consecutive patients who had r-EBUS-guided bronchoscopy for the diagnosis of a peripheral pulmonary lesion at Rouen University Hospital, France, between April 2008 and December 2019. Patients without a final diagnosis of cancer or who had a previous r-EBUS procedure were excluded.

The study protocol was approved by the Institutional Review Board for noninterventional research of our center: Rouen University Hospital (protocol agreement #E2020-80).

**R-EBUS procedure**

Before each procedure, the location of the lesion was analyzed using the planner of the virtual bronchoscopy software (Figure 1a) to identify the optimal bronchial path to the lesion from 2008 to 2011: Superdimension planner (superDimension/Bronchus system, superDimension Ltd.) and since 2011, LungPoint planner (Broncus Medical Inc.), from a millimeter slice chest CT-scan. Bronchoscopy was then carried out using local or general anesthesia with either an MP160F video bronchoscope or a BF-MP60F bronchofiberscope (Olympus), with a 4 mm outer diameter and a 2 mm working channel.

The ultrasonographic probe was the 1.4 mm UM-S20-17S probe (Olympus) (Figure 1b), introduced into the dedicated 1.9 mm-diameter guide catheter (K201, Olympus).

The procedure was performed without navigation or fluoroscopy. After having memorized the endobronchial route from the planning, the operator reached the most distal subsegmental bronchus. The r-EBUS probe, covered with the guide sheath, was then inserted into the working channel and gently pushed until a lesion-specific ultrasonographic image could be obtained, as described elsewhere. R-EBUS views of peripheral lesions were characterized as “centered” when the radial probe appeared within and completely surrounded by the lesion and “tangential” when the probe was adjacent to the lesion, without tissue completely surrounding the probe.

Once the nodule US signal was obtained (Figure 1c), the probe was removed and the guide sheath was left in place in the lesion. The sampling, including cytological brush and forceps biopsies, was then performed.

Rapid on-site evaluation (ROSE) was not used. Systematic chest radiographs were obtained after each procedure to ensure the absence of pneumothorax until 2017, then only in case of chest pain or respiratory symptoms following the procedure.

Specimens were considered diagnostic when a cytological, histological, or microbiological diagnosis was confirmed and consistent with the clinical presentation. Patients in whom the procedures were not diagnostic were referred for other sampling methods or surgery or were followed by surveillance chest CT-scan, when appropriate. Data on the final diagnosis were collected from our center’s electronic medical

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**FIGURE 1** (a) Virtual bronchoscopy planner (LungPoint, Broncus Medical Inc.). (b) A 4 mm scope (MP160F video bronchoscope or a BF-MP60F bronchofiberscope (Olympus). (c) Radial-endobronchial ultrasound (EBUS) image with ultrasonic image of a nodule
records and/or by interviewing the patient’s pulmonologist when clinical follow-up was performed elsewhere.

**Statistical analysis**

Descriptive statistics were performed using Prism (GraphPad) and R Statistical Software (version 4.0.5; R Foundation for Statistical Computing). Comparisons of qualitative and quantitative variables were made using Fisher’s exact test or Mann-Whitney test and chi-squared, respectively. For multivariate analysis, parameters associated with a \( p \)-value < 0.10 in the univariate analysis were integrated in a polynomial logistic regression model. Patients with missing data for tumor size were excluded from this analysis. All tests were two-sided, with a \( p \)-value = 0.05 indicating statistical significance. Missing data are indicated.

**RESULTS**

**Patient characteristics**

Between April 2008 and December 2019, 2735 patients had a r-EBUS procedure (Figure 2). Among them, 695 patients were not included: 210 because the procedure was not the first r-EBUS bronchoscopy and 485 because of the absence of a final diagnosis or follow-up. A further 413 patients were secondarily excluded because the final diagnosis was not a cancer lesion.

Finally, 1627 patients with a definitive diagnosis of lung cancer were included in the study, of which 67% were male, and the mean age was 70 years (min-max = 19–91).

**Characteristics of the lesions**

The median diameter of the lesion was 29 mm in the long axis (IQR = 20–43 mm) and 20 mm in the short axis (IQR = 14–30 mm) (Table 1). The median distance between the nodule and the pleura was 12 mm (IQR = 0–29 mm). A bronchus sign was found on CT-scan in 86% of cases (1399/1627).

**Abbreviation**: US, ultrasound.
Histological results of r-EBUS procedures

R-EBUS + virtual bronchoscopy planner (VB) was the first bronchoscopy examination performed for 1114 patients (68%), whereas 513 (32%) had standard bronchoscopy with negative results before r-EBUS. Procedures were performed under local anesthesia in 1259 cases (77%). No severe complication was reported. One case of pneumothorax was reported, with no need for chest tube placement (0.06%). A total of 88% of the lesions (1429/1627) could be visualized by r-EBUS, of which 89% (1272/1429) with a centered signal and 11% (157/1429) with a tangential signal.

A lung cancer diagnosis was obtained in 1200 patients (74%), including 1110 (93%) primary lung cancers (adenocarcinomas: 710 [64%], squamous carcinoma: 272, other: 131) and 90 secondary malignancies. In 223 cases (18% of the 1200 cancer cases), a lung cancer diagnosis was obtained on the cytological brush sample only (biopsy sample not contributive).

Factors influencing the diagnostic efficiency

R-EBUS positivity for a malignant nodule was 74%, increasing to 80% (1113/1399) when a bronchus sign was found on CT-scan and 82% (1154/1429) when an ultrasound image of the lesion was obtained. R-EBUS positivity was 83% (1058/1272) when the r-EBUS image was centered and 61% (96/157) when the image was tangential. The positivity of the procedure decreased to 5% (11/198) when no characteristic r-EBUS image was obtained.

The positivity was 59% for lesions of <20 mm (203/343) and 75% for lesions of >20 mm \( (n = 674/897) \). In 385 cases, data were missing on the size.

In univariate analysis, bronchus sign, nodule diameter and US visualization were associated with a higher positivity of the procedure (Table 2). When r-EBUS was the first-line examination, the positivity of the procedure was lower (65% vs. 72%, \( p = 0.026 \) in univariate analysis). However, in multivariate analysis only bronchus sign, nodule diameter and US visualization were predictive factors of diagnostic efficiency. The performance of r-EBUS as a first-line examination was not associated with a lower positivity of the procedure (OR 0.862, 95% CI: 0.639;1.1, \( p = 0.033 \)).

Changes in r-EBUS strategy and performances over time

R-EBUS procedures and results between 2008 and 2019 are summarized in Figure 4. The number of r-EBUS procedures performed per year increased progressively to 220 and became the first-line examination in 2012 (25% in 2008 vs. 92% in 2019). The mean size of sampled lesions remained stable during this period (29 ± 2 mm). The frequency of bronchus sign decreased from 2009 to 2019.
DISCUSSION

In this large single center cohort of more than 1500 r-EBUS + VB planner procedures for peripheral lung cancer diagnosis, the positivity of the procedure was 74%, similar to other series. Also, despite the small size of biopsy samples, molecular analysis and immunohistochemistry analysis for the assessment of PDL1 expression were possible in more than 80% of nonsquamous NSCLC cases, a success rate similar to that of previous reports. This high diagnostic efficiency has remained stable since it was introduced in our center, indicating a short learning curve, as reported previously. Moreover, as in other reports, complications of the procedure were also extremely rare.

Over the last 12 years, r-EBUS associated with VB has become the first-line endoscopic procedure for peripheral lung nodule diagnosis, increasing from 25% at the implementation of the procedure to more than 90% during the last 3 years. Several reasons explain why the r-EBUS VB procedure has become the first endoscopic procedure over time. First, the r-EBUS technique we used is simplified, using virtual bronchoscopy planning without fluoroscopy, a 4 mm bronchoscope and the guide sheath procedure. As a result, the endoscopy was performed as an outpatient procedure under local anesthesia in nearly 80% of the cases, with more than 200 procedures a year during the last 4 years. In most studies, including metanalyses, the majority of cases were performed under general anesthesia or sedation. Here, we show that a simplified r-EBUS procedure performed under local anesthesia does not decrease the diagnostic yield. Along the same line, we chose to use VB planning alone without the endoscopic navigation component of VB in order to simplify the procedure and decrease its length and cost. Moreover, if the combination of electromagnetic navigation with r-EBUS has been shown to slightly increase the

**TABLE 2**  
Influencing factors of positivity of the procedure

|                      | R-EBUS negative (n = 365) | R-EBUS positive (n = 877) | p-value | OR     | CI95     | p-value |
|----------------------|---------------------------|---------------------------|---------|--------|---------|---------|
| First-line           | 261 (72%)                 | 570 (65%)                 | 0.026   | 0.862  | [0.639; 1.16] | 0.33   |
| BS                   | 248 (68%)                 | 797 (91%)                 | <0.001  | 2.09   | [1.43; 3.03] | <0.001 |
| Diameter             | 27.5 (±15.8)              | 35.8 (±19.5)              | <0.001  | 1.19   | [1.09; 1.30] | <0.001 |
| US signal            | 236 (65%)                 | 841 (96%)                 | <0.001  | 8.56   | [5.69; 13.2] | <0.001 |

Abbreviations: BS, bronchus sign; US, ultrasound.

**FIGURE 4**  
Evolution of radial-endobronchial ultrasound (r-EBUS) diagnostic strategy and performances over time.
diagnostic yield, this appears time consuming, expensive, and complex to implement. For the same reason we did not use fluoroscopy, even if it has shown a slight benefit in the accuracy of sample collection. Furthermore, fluoroscopy cannot visualize nodules with a diameter under 20 mm, and is probably not helpful in these cases.

Second, as previously published, VB plus r-EBUS appears cost effective when compared to transthoracic biopsies (TTB), mainly in reducing the risk of complications and therefore shortening the in-patient hospitalization time. Moreover, even if the vulnerability of the r-EBUS probe is well known, it can be used for 50–100 procedures, in our experience, the median durability of the probe was 74 procedures per probe and improved over the study period.

Third, it is now accepted in the pulmonology community that standard bronchoscopy (i.e., without navigational bronchoscopy) is of marginal value for the diagnosis of peripheral nodules, with a low yield in most series.

Last, we systematically performed brush sampling in all procedures. Indeed, we believe that performing brush sampling for cytological analysis may also increase the positivity of the procedure. In our series, brush sampling provided the only positive sample in 18% of cases. However, the sensitivity of brush sampling could not be evaluated in our study because the brush samples were not analyzed when the biopsy samples were positive. Moreover, if some studies report excellent results by using needle (especially for adjacent lesion to r-EBUS), we never use it because this procedure needs to be performed under fluoroscopy.

Therefore, with the development of the r-EBUS technique in our center, a large majority of patients are now referred only a few days after the initial chest CT, without previous endoscopic exploration, a strategy that appears to be able to save resources and shorten the time to diagnosis, and therefore to treatment.

The strength of our study relies on its large size, and standardized procedure throughout the study period. In addition to its retrospective and single center nature, our study presents some limitations. As many as 86% of the patients in our series harbored a bronchus sign on CT scan, a situation that was associated with a r-EBUS yield of more than 80%. This may suggest a selection bias either by the bronchoscopist who performed the procedure or the physicians who referred the patient, whereas other patients may have been preferentially referred to TTNA or surgery. Of note, the proportion of bronchus sign positive nodules but also the size of the nodules decreased over time in our series, with only a small decrease in the diagnostic rate of the procedure.

In future, new robotic bronchoscopy associated with r-EBUS could be used in the most difficult cases such as pure ground-glass opacities or nodules without bronchus signs. However, the cost and the availability of this high-level technology suggest that this new technique may not replace the simple r-EBUS + VB planner procedure in the large majority of cases.

In conclusion, R-EBUS and VB planner is an easy to perform and inexpensive procedure for the diagnosis of peripheral lung cancer that can be performed under local anesthesia. It has a high diagnostic efficiency and can be easily implemented in bronchoscopy units as a first-line procedure, allowing histology, immunohistochemistry and molecular analysis.

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CONFLICT OF INTEREST
MS and SL have received fees for consulting and training from Olympus. LP, DG, MDM, LT, HMP, ED, SB, NP, FG declare no conflict of interest related to the submitted work.

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