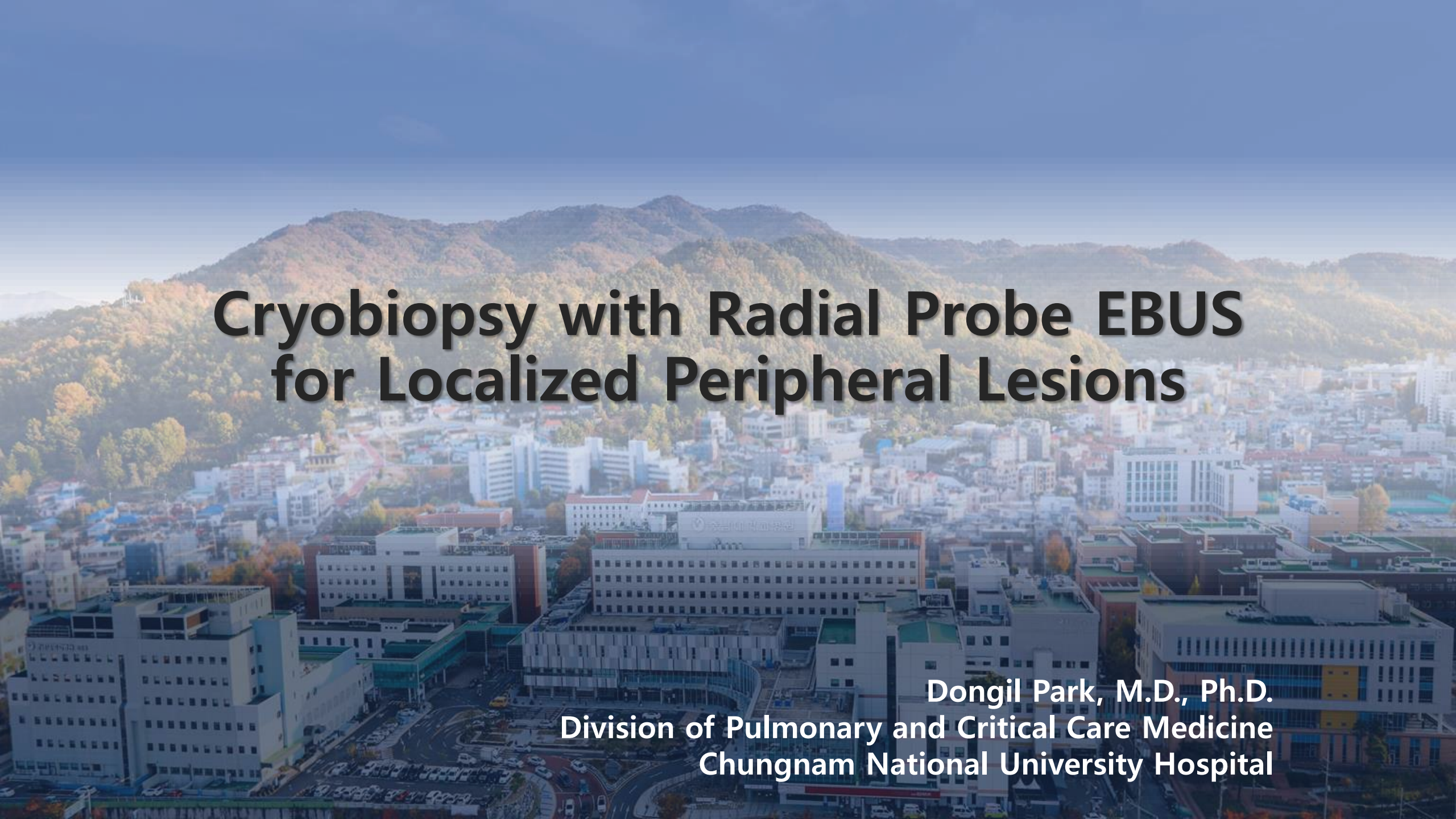


# Cryobiopsy with Radial Probe EBUS for Localized Peripheral Lesions

Dongil Park, M.D., Ph.D.
Division of Pulmonary and Critical Care Medicine
Chungnam National University Hospital

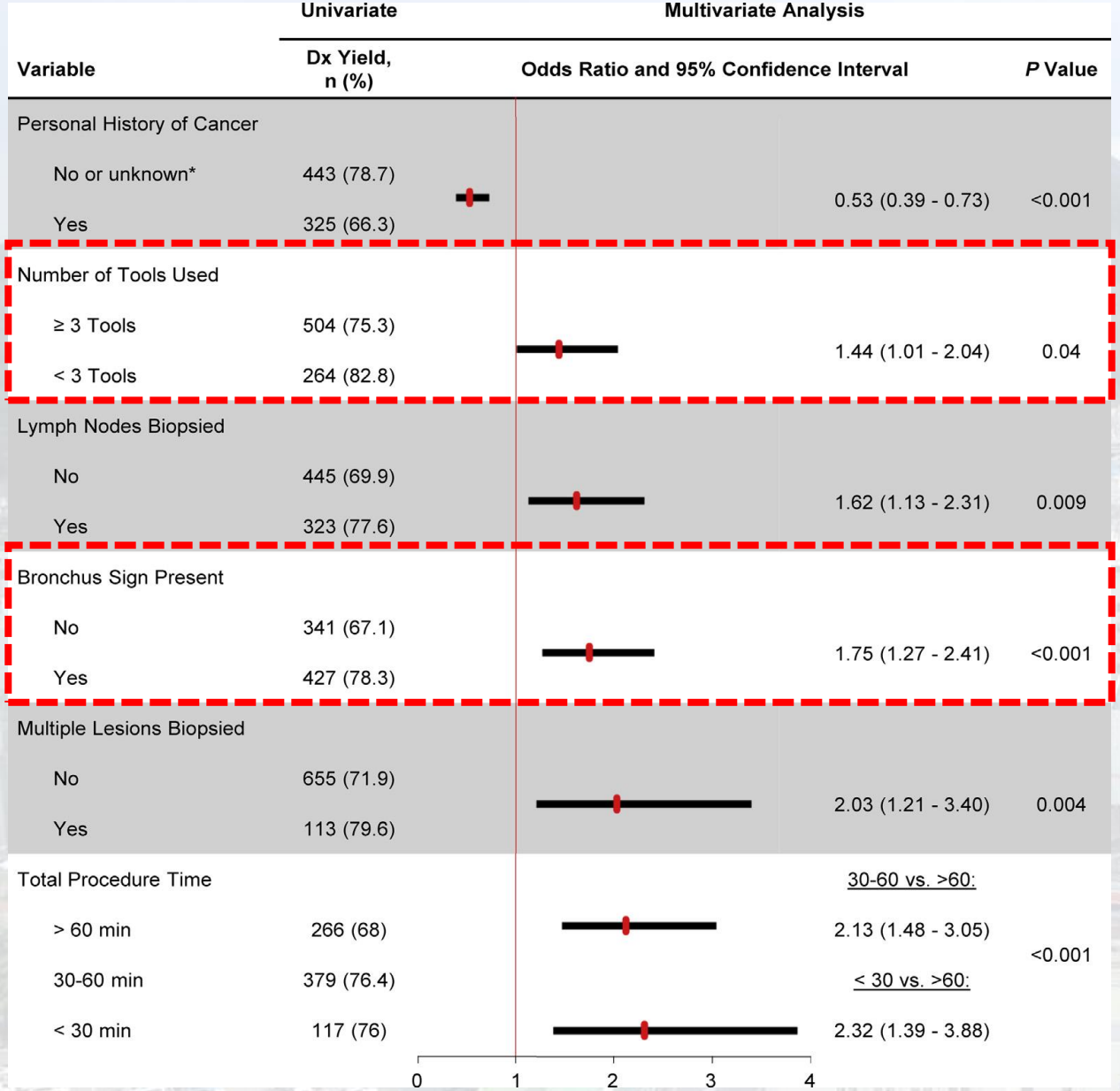
**Table 1** Relative yields, advantages, and shortcomings of currently available diagnostic techniques in the clincal workup of lung cancer

| | Conventional bronchoscopy | ENB | Ultrasound-guided bronchoscopy | EBUS | CT-guided TTNA | Surgery |
|---|---|---|---|---|---|---|
| Sensitivity | + | ++ | ++ | +++ | +++ | +++ |
| Specificity | ++ | ++ | ++ | +++ | ++ | +++ |
| NPV | + | ++ | ++ | +++ | ++ | +++ |
| Safety profile | ++ | +++ | +++ | +++ | ++ | + |
| Cost | + | ++ | ++ | ++ | + | +++ |
| Availability | +++ | + | + | ++ | +++ | ++ |
| Central LC | ++ | ++ | ++ | +++ | – | + |
| Peripheral LC | + | ++ | ++ | – | +++ | +++ |
| Bronchus sign relevance | +++ | +++ | +++ | – | – | – |

**Abberivations:** NPV, negative predictive value; LC, lung cancer; ENB, electromagnetic navigation bronchoscopy; EBUS, endobronchial ultrasonography; CT, computer topography; TTNA, transthoracic needle aspiration

Seijo, L. M. (2016). Lung Cancer (Auckland, N.Z.) 7: 111-118.

# NAVIGATE Study



| Variable | Univariate Dx Yield, n (%) | Multivariate Analysis Odds Ratio and 95% Confidence Interval | *P* Value |
|---|---|---|---|
| Personal History of Cancer | | | |
| No or unknown* | 443 (78.7) | 0.53 (0.39 - 0.73) | <0.001 |
| Yes | 325 (66.3) | | |
| Number of Tools Used | | | |
| ≥ 3 Tools | 504 (75.3) | 1.44 (1.01 - 2.04) | 0.04 |
| < 3 Tools | 264 (82.8) | | |
| Lymph Nodes Biopsied | | | |
| No | 445 (69.9) | 1.62 (1.13 - 2.31) | 0.009 |
| Yes | 323 (77.6) | | |
| Bronchus Sign Present | | | |
| No | 341 (67.1) | 1.75 (1.27 - 2.41) | <0.001 |
| Yes | 427 (78.3) | | |
| Multiple Lesions Biopsied | | | |
| No | 655 (71.9) | 2.03 (1.21 - 3.40) | 0.004 |
| Yes | 113 (79.6) | | |
| Total Procedure Time | | 30-60 vs. >60: | |
| > 60 min | 266 (68) | 2.13 (1.48 - 3.05) | <0.001 |
| 30-60 min | 379 (76.4) | < 30 vs. >60: | |
| < 30 min | 117 (76) | 2.32 (1.39 - 3.88) | |

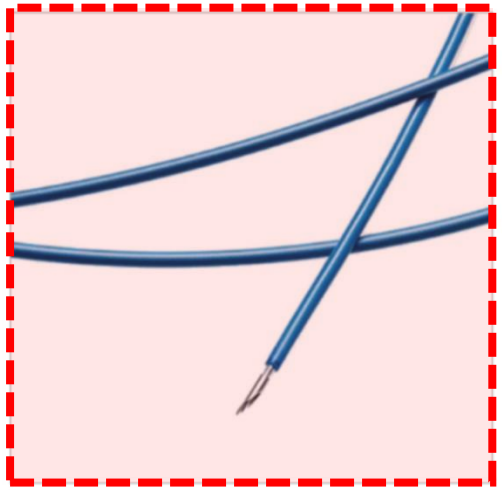


- **Diagnostic yield** according to the presence or absence of a bronchus sign

(+) → 78.3%

(-) → **67.1%**

Folch, E. E., et al. (2019). Journal of Thoracic Oncology 14(3): 445-458.



Arcpoint™ Pulmonary Needle

GenCut™ Core Biopsy System

superDimension™ Aspirating Needles

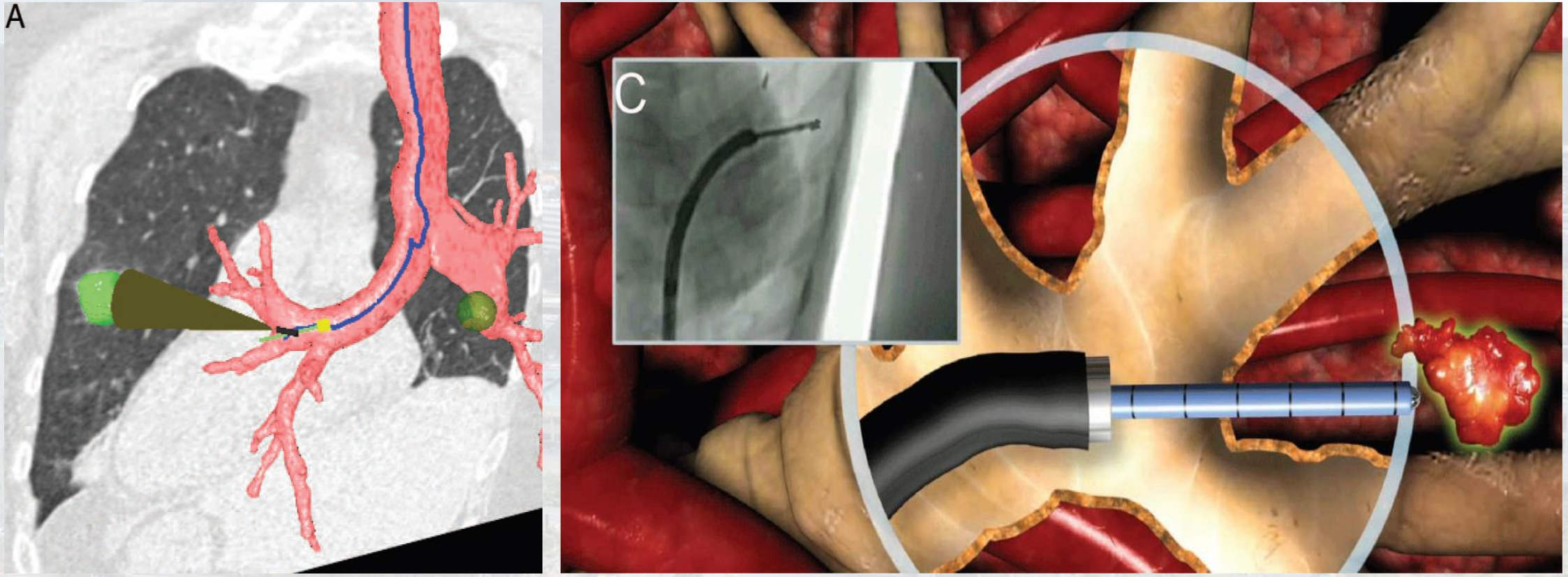
superDimension™ Cytology Brush

superDimension™ Needle-tipped Cytology Brush

superDimension™ Triple Needle Cytology Brush

superDimension™ Biopsy Forceps

# Transparenchymal access (BTPNA)




Herth, F. J., et al. (2015). "Bronchoscopic transparenchymal nodule access (BTPNA): first in human trial of a novel procedure for sampling solitary pulmonary nodules." Thorax 70(4): 326-332.

# Transparenchymal access (BTPNA)

- **Diagnostic yield: 83% (10/12)**
- **Biopsy yield: 100% (10/10)**

**Table 1** Safety and procedural aspects of Bronchoscopic Transparenchymal Nodule Access (BTPNA) procedure

| | Site | Size (mm) | Visible at fluoroscopy | Procedure planning time (min) | Nodule access time (min) | Fluoroscopy time (min) | Intra-procedural adverse events | Tunnel length (mm) | Pathology | Inspection of resection specimen | TNM | Correlation with resection specimens | Postprocedure adverse events |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | LUL | 40 | Yes | 10 | 40 | 11.6 | None | 10 | Large cell carcinoma | * | T2aN0M0 | Yes | Raised troponin level |
| 2 | Lingula | 20 | Yes | 15 | Data not recorded | 7.09 | None | 50 | Small cell cancer | * | T1aN0M0 | Yes | None reported |
| 3 | LLL | 25 | No | 30 | 30 | 5.18 | None | 60 | Large cell carcinoma | * | T1bN0M0 | | None reported |
| 4 | LUL | 31 | Yes | 18 | No sample taken | 5 | Sheath could not be directed along optimal path | – | N/A | * | T2aN0M0 | | None reported |
| 5 | RML | 22 | No | 15 | 26 | 6.7 | None | 50 | NSCLC | * | T1bN0M0 | | None reported |
| 6 | LLL | 22 | No | 12 | 13 | 3 | None | 30 | NSCLC | * | T1bN0M0 | | None reported |
| 7 | RLL | 30 | No | 25 | 30 | 1.8 | None | 30 | NSCLC | * | T2aN0M0 | | None reported |
| 8 | RLL | 18 | Yes | 15 | 17 | 3.6 | None | 60 | Adenocarcinoma | * | T1aN0M0 | | None reported |
| 9 | RLL | 20 | No | 30 | 12 | 4.2 | None | 90 | NSCLC | * | T1aN0M0 | | None reported |
| 10 | RML | 28 | Yes | 15 | 13 | 9.8 | None | 70 | Adenocarcinoma | * | T1bN0M0 | | None reported |
| 11 | LUL | 17 | No | 14 | No sample taken | N/A | Sheath could not be directed along optimal path | – | N/A | * | T1a N0M0 | N/A | None reported |
| 12 | LUL | 31 | No | 10 | 15 | 2.1 | None | 20 | NSCLC | * | T2aN0M0 | Yes | None reported |

Herth, F. J., et al. (2015). "Bronchoscopic transparenchymal nodule access (BTPNA): first in human trial of a novel procedure for sampling solitary pulmonary nodules." Thorax 70(4): 326-332.

# Cryobiopsy increases the diagnostic yield of endobronchial biopsy: a multicentre trial

J. Hetzel, R. Eberhardt, F.J.F. Herth, C. Petermann, G. Reichle, L. Freitag, I. Dobbertin, K.J. Franke, F. Stanzel, T. Beyer, P. Möller, P. Fritz, G. Ott, P.A. Schnabel, H. Kastendieck, W. Lang, A.T. Morresi-Hauf, M.N. Szyrach, R. Muche, P.L. Shah, A. Babiak and M. Hetzel

ABSTRACT: Forceps, brushes or needles are currently the standard tools used during flexible bronchoscopy when diagnosing endobronchial malignancies. The new biopsy technique of cryobiopsy appears to provide better diagnostic samples. The aim of this study was to evaluate cryobiopsy over conventional endobronchial sampling.

A total of 600 patients in eight centres with suspected endobronchial tumours were included in a prospective, randomised, single-blinded multicentre study. Patients were randomised to either sampling using forceps or the cryoprobe. After obtaining biopsy samples, a blinded histological evaluation was performed. According to the definitive clinical diagnosis, the diagnostic yield for malignancy was evaluated by a Chi-squared test.

A total of 593 patients were randomised, of whom 563 had a final diagnosis of cancer. 281 patients were randomised to receive endobronchial biopsies using forceps and 282 had biopsies performed using a flexible cryoprobe. A definitive diagnosis was achieved in 85.1% of patients randomised to conventional forceps biopsy and 95.0% of patients who underwent cryobiopsy ($p<0.001$). Importantly, there was no difference in the incidence of significant bleeding.

Endobronchial cryobiopsy is a safe technique with superior diagnostic yield in comparison with conventional forceps biopsy.

European Respiratory Journal, (2012), 685-690, 39(3)

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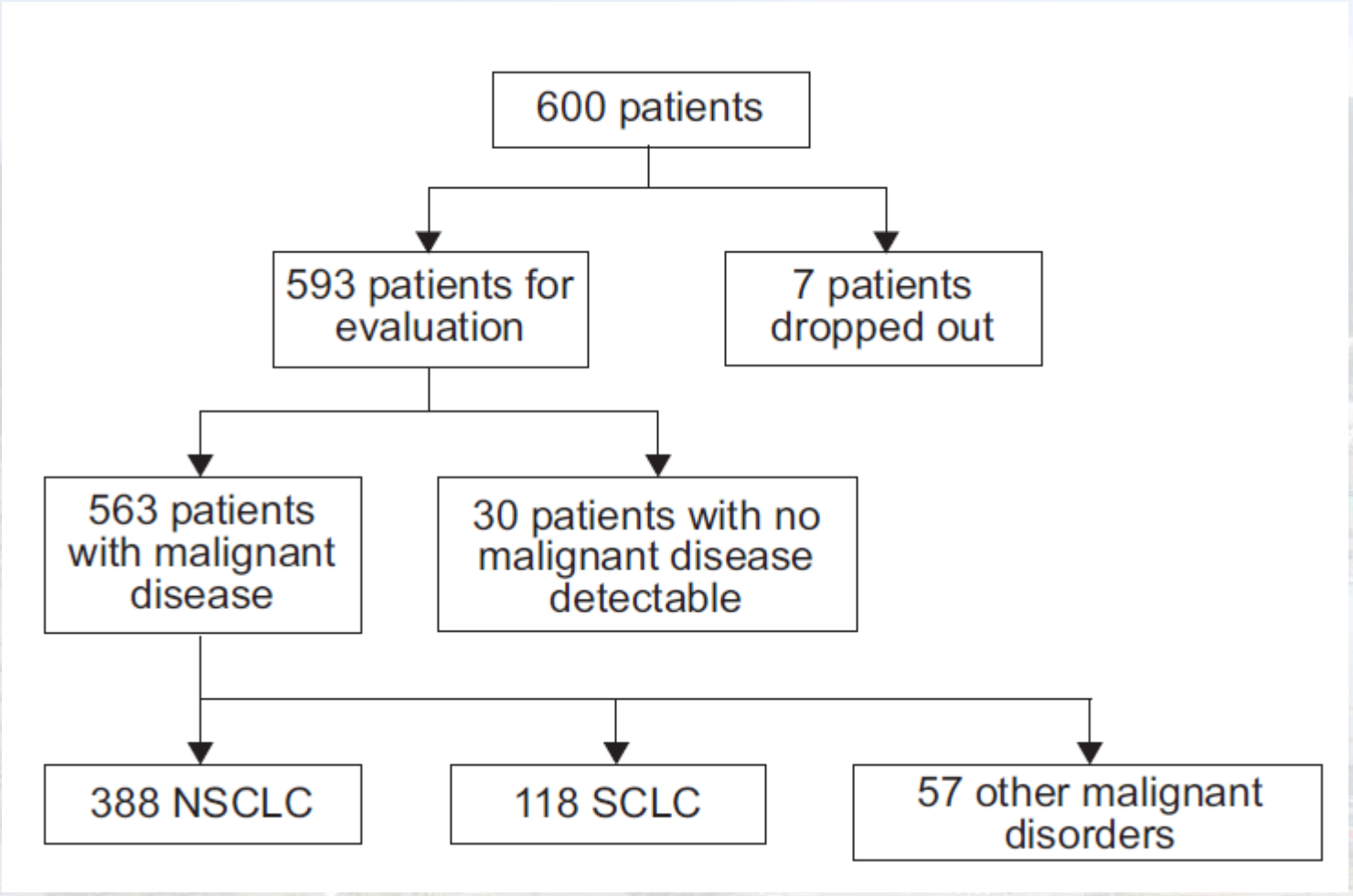


**TABLE 1** Patient characteristics and distribution of the biopsy sites for each biopsy technique

| | Forceps | Cryoprobe | p-value |
|---|---|---|---|
| **Patient characteristics** | | | |
| Patients | 297 | 296 | |
| Age yrs | 65.3±9.9 | 64.8±10.3 | 0.55 |
| Male | 207 (69.6) | 217 (73.4) | 0.36 |
| Body height cm | 170.9±8.5 | 170.2±8.9 | 0.33 |
| Body weight kg | 74.3±14.7 | 72.3±15.0 | 0.10 |
| Aspirin 100 mg·day$^{-1}$ | 25 (8.42) | 27 (9.12) | 0.77 |
| Clopidogrel 75 mg·day$^{-1}$ | 1 (0.34) | 4 (1.35) | 0.22 |
| General anaesthesia | 134 (45.1) | 136 (45.9) | 0.87 |
| Rigid bronchoscopy | 133 (44.8) | 136 (45.9) | 0.80 |
| PT % | 95.1±16.6 | 94.7±16.2 | 0.77 |
| PTT s | 29.8±4.6 | 29.5±4.6 | 0.43 |
| Thrombocyte count $\times 10^3$ cells·μL$^{-1}$ | 331.6±130.9 | 331.0±118.8 | 0.95 |
| NSCLC | 192 | 196 | 0.73 |
| SCLC | 62 | 56 | 0.61 |
| Other malignant disease | 27 | 30 | 0.68 |
| Other disease | 16 | 14 | 0.85 |
| **Distribution of the biopsy sites** | | | |
| Trachea | 18 | 16 | 0.40 |
| Main bronchi | 62 | 57 | |
| Lobe bronchi and intermediate bronchus | 156 | 175 | |
| Segmental bronchi | 61 | 48 | |
| **Lesions in patients with malignancy** | | | |
| Exophytic | 190 | 183 | 0.49 |
| Submucosal | 91 | 99 | |

European Respiratory Journal, (2012), 685-690, 39(3)

**TABLE 2** Diagnostic and nondiagnostic biopsies for each biopsy technique in patients with maligancy

| | Forceps | Cryoprobe | p-value |
|---|---|---|---|
| **Overall** | | | |
| Diagnostic | 239 (85.1) | 268 (95.0) | <0.001 |
| Nondiagnostic | 42 (14.9) | 14 (5.0) | |
| **Exophytic tumour** | | | |
| Diagnostic | 170 (89.5) | 178 (97.3) | 0.003 |
| Nondiagnostic | 20 (10.5) | 5 (2.7) | |
| **Submucosal tumour** | | | |
| Diagnostic | 69 (75.8) | 90 (90.9) | 0.005 |
| Nondiagnostic | 22 (24.2) | 9 (9.1) | |

European Respiratory Journal, (2012), 685-690, 39(3)

Pulmonology xxx (xxxx) xxx–xxx

PULMONOLOGY

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ORIGINAL ARTICLE

# Efficacy of Radial Endobronchial Ultrasound (R-EBUS) guided transbronchial cryobiopsy for peripheral pulmonary lesions (PPL's): A systematic review and meta-analysis

P.B. Sryma[a], S. Mittal[a], N.K. Madan[b], P. Tiwari[a], V. Hadda[a], A. Mohan[a], R. Guleria[a], K. Madan[a,*]

[a] *Department of Pulmonary, Critical Care and Sleep Medicine, All India Institute of Medical Sciences (AIIMS), New Delhi 110029, India*

[b] *Department of Pathology, VMMC and Safdarjung Hospital, New Delhi, India*

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Pulmonology. 2021 Jan 10;S2531-0437(20)30266-X.

## Abstract

*Background:* Transbronchial lung cryobiopsy (TBLC) is frequently described for the diagnosis of diffuse parenchymal lung diseases (DPLD). A few studies have reported transbronchial cryobiopsy for the diagnosis of peripheral pulmonary lesions (PPL's). We aimed to study the utility and safety of transbronchial cryobiopsy for the diagnosis of PPL's.

*Methods:* We performed a systematic search of the PubMed and Embase databases to extract the relevant studies. We then performed a meta-analysis to calculate the diagnostic yields of transbronchial cryobiopsy and bronchoscopic forceps biopsy.

*Results:* Following a systematic search, we identified nine relevant studies (300 patients undergoing cryobiopsy). All used Radial Endobronchial Ultrasound (R-EBUS) for PPL localization. The pooled diagnostic yield of transbronchial cryobiopsy was 77% (95% CI, 71%–84%) ($I\hat{2} = 38.72\%$, $p = 0.11$). The diagnostic yield of forceps biopsy was 72% (95% CI, 60%–83%) ($I\hat{2} = 78.56\%$, $p < 0.01$). The diagnostic yield of cryobiopsy and forceps biopsy was similar (RR 1.05, 95% CI 0.96–1.15), with a 5% risk difference for diagnostic yield (95% CI, −6% to 15%). There was significant heterogeneity ($I\hat{2} = 57.2\%$, $p = 0.017$), and no significant publication bias. One severe bleeding and three pneumothoraxes requiring intercostal drain (ICD) placement (major complication rate 4/122, 1.8%) were reported with transbronchial cryobiopsy.


Pulmonology. 2021 Jan 10;S2531-0437(20)30266-X.

**Table 1** Baseline characteristics of studies describing the utility of transbronchial cryobiopsy for PPLs.

| No. | Author/year | Country | Study design | Total number (number undergoing cryobiopsy) | Inclusion criteria | Comparison with forceps biopsy with cryobiopsy in same patients | Age (years) | Size of PPL (mm) | % Of lesions in upper lobes |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Schuhmann et al./2014[4] | Germany | RCT | 38 (31) | Solid pulmonary lesion of <40 mm | Yes | Median IQR, 68 (37–84) | 29.7 (7.3) | NA |
| 2 | Hibare et al./2017[15] | India | Retrospective | 55(28) | PPL requiring R-EBUS, bronchoscopically invisible | Yes | Mean (SD), 61.8 (7.2) (M), 59.3 (11.2) (F) | Size data for 41 (28 > 3 cm, 13 < 3 cm) | NA |
| 3 | Herath et al./2018[19] | New Zealand | Prospective | 6 (6) | PPL 1 cm or above on CT | Yes | Mean (SD), 56.66 (13.14) | 41 (19–66) | 66.7 |
| 4 | Taton et al./2018[20] | Belgium | Prospective | 32 (29) | Age over 18 years; a CT-detected solid or nonsolid nodule with a diameter from 8 to 20 mm | Yes | Mean (SD), 68(9) | 16 (3) | 51.7 |
| 5 | Arimura et al./2019[18] | Japan | Prospective | 23 (23) | Solid lesions >2 cm away from pleura, bronchoscopically invisible | Yes | Median IQR 69.5 (46–82) | 36 (10–81) | 60.9 |
| 6 | Kho et al./2019[9] | Malaysia | Retrospective | 114 (38) | All adult patients undergoing R-EBUS-guided transbronchial biopsy | No | Median IQR 56 (47.8–64.5) | 34.8 (26.3–45.1) | 23 (60.5) in cry-obiopsy group46 (60.5) in the forceps group |
| 7 | Imabayashi et al./2019[16] | Japan | Retrospective | 38 (36) | Suspected peripheral lung cancer undergoing cryobiopsy | Yes | Median IQR 66.9 (44—81) | 37.2 ± 19.4 | 52.8 |
| 8 | Nasu et al./2019[17] | Japan | Retrospective | 53 (53) | A final diagnosis of lung cancer in PPL who underwent cryobiopsy | Yes | Median IQR 75 (41–90) | 32 (8—85) | 50.9 |
| 9 | Udagawa et al./2020[21] | Japan | Prospective | 121 (57) | Aged 20–80 years with suspected or diagnosed primary lung cancer by chest computed tomography scheduled to undergo TBB by bronchoscopy | Yes | Median IQR 68 (31—79) | 38 (Median) | 40.3 |

Pulmonology. 2021 Jan 10;S2531-0437(20)30266-X.

ANTICANCER RESEARCH *39*: 5683-5688 (2019)
doi:10.21873/anticanres.13766

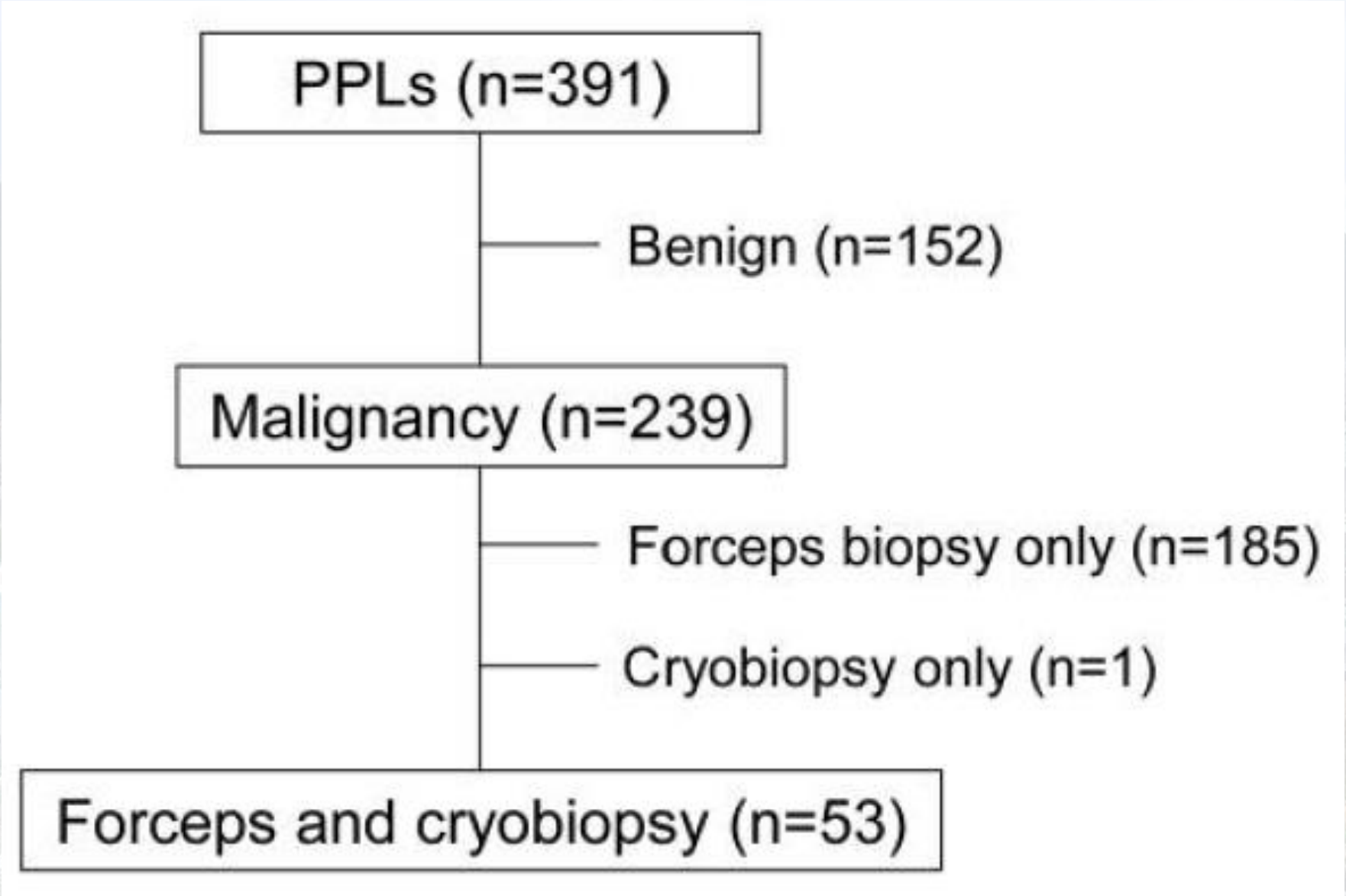
# Comparison of the Utilities of Cryobiopsy and Forceps Biopsy for Peripheral Lung Cancer

SHINGO NASU[1], NORIO OKAMOTO[1], HIDEKAZU SUZUKI[1], TAKAYUKI SHIROYAMA[1], AYAKO TANAKA[1], YUMIKO SAMEJIMA[1], TOMOHIRO KANAI[1], YOSHIMI NODA[1], SATOMU MORITA[1], NAOKO MORISHITA[1], KAYO UEDA[2], KUNIMITSU KAWAHARA[2] and TOMONORI HIRASHIMA[1]

*Departments of [1]Thoracic Oncology, and Pathology, Osaka Prefectural Hospital Organization, Osaka Habikino Medical Center, Osaka, Japan*

**Abstract.** *Background/Aim: This study aimed to compare the efficacies of cryobiopsy and forceps biopsy for peripheral lung cancer detection. Patients and Methods: A retrospective review of peripheral lung cancer cases between December 2017 and April 2019 was conducted. Forceps biopsy was performed followed by cryobiopsy using a guide sheath (GS). Diagnostic yields were compared between cryobiopsy and forceps biopsy. Results: A total of 53 lung cancer lesions were evaluated. The diagnostic yields of forceps biopsy and cryobiopsy were 86.8% and 81.1%, respectively. Univariate and multivariate analyses indicated that cryobiopsy with a GS was significantly associated with increased diagnostic yield (odds ratio(OR)=11.6; p=0.044). Among the four patients who tested positive on cryobiopsy and negative on forceps biopsy, one had diffused pulmonary metastases and the others showed intratumoural air bronchograms. Conclusion: Cryobiopsy using a GS can significantly increase diagnostic yield and help identify lesions with intratumoural air bronchograms and external wall lesions.*

Anticancer Research Oct 2019, 39 (10) 5683-5688




Anticancer Research Oct 2019, 39 (10) 5683-5688

Table I. *Baseline characteristics of patients.*

| Category | Value |
|---|---|
| Age, median (range), year | 75 (41-90) |
| Gender, n (%) | |
| Male | 34 (64) |
| Female | 19 (36) |
| Lesion size, median, (range), mm | 32 (8-85) |
| Lobar location, n (%) | |
| Upper | 26 (49) |
| Middle | 0 |
| Lower | 27 (51) |
| Bronchus sign, n (%) | |
| Positive | 49 (92) |
| Negative | 4 (8) |
| EBUS, n (%) n=52 | |
| Within | 43 (83) |
| Adjacent to | 9 (17) |

Anticancer Research Oct 2019, 39 (10) 5683-5688

Table II. *Histological diagnosis and diagnostic yields.*

| Diagnosis | n | Forceps biopsy | Cryobiopsy | Total yield | *p*-Value |
|---|---|---|---|---|---|
| Lung cancer | | | | | |
| Adenocarcinoma | 39 | 34/39 | 32/39 | 37/39 | |
| Squamous cell carcinoma | 7 | 6/7 | 4/7 | 6/7 | |
| Small cell lung cancer | 1 | 1/1 | 1/1 | 1/1 | |
| Non-small cell carcinoma | 1 | 1/1 | 1/1 | 1/1 | |
| Metastatic lung cancer | 5 | 4/5 | 5/5 | 5/5 | |
| Total (%) | 53 | 46/53 (86.8) | 43/53 (81.1) | 50/53 (94.3) | 0.60 |

Anticancer Research Oct 2019, 39 (10) 5683-5688

Table III. *Factors affecting the diagnostic yield of cryobiopsy.*

| Factor | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| | Diagnostic yield (%) | *p*-Value | OR (95%CI) | *p*-Value |
| Lesion size, mm | | | | |
| ≤30 | 21/26 (80.8) | | | |
| >30 | 22/27 (81.5) | 1 | | |
| Lobar location | | | | |
| Lower | 22/26 (84.6) | | | |
| Upper | 21/27 (77.8) | 0.73 | | |
| Bronchus sign | | | | |
| Negative | 1/4 (25) | | | |
| Positive | 42/49 (85.7) | 0.018 | 21.5 (1.77-798) | 0.034 |
| EBUS image (n=52) | | | | |
| Within | 36/43 (83.7) | | | |
| Adjacent to | 6/9 (66.7) | 0.35 | | |
| EBUS-GS | | | | |
| Without GS | 20/29 (69.0) | | | |
| With GS | 23/24 (95.8) | 0.015 | 11.6 (1.62-298) | 0.044 |

Anticancer Research Oct 2019, 39 (10) 5683-5688

# Performance of transbronchial cryobiopsy in eccentrically and adjacently orientated radial endobronchial ultrasound lesions

Sze Shyang Kho, Swee Kim Chan, Mei Ching Yong and Siew Teck Tie

**Affiliation**: Division of Respiratory Medicine, Dept of Medicine, Sarawak General Hospital, Ministry of Health, Kuching, Malaysia.

**Correspondence**: Sze Shyang Kho, Respiratory Medicine Unit (RCU), Sarawak General Hospital, Jalan Hospital 93586, Kuching, Sarawak, Malaysia. E-mail: bzk99@hotmail.com

ABSTRACT

**Background:** Radial endobronchial ultrasound (R-EBUS) is an effective technique in the diagnosis of peripheral pulmonary lesions (PPL). However, lesion orientation with regards to the radial probe remains an important factor for effective biopsy. "Within" orientation was associated with significantly higher diagnostic yield. Cryobiopsy is a novel technique in obtaining larger tissue samples with the frozen tip allowing biopsy in a 360° direction, thus potentially achieving more effective biopsy in eccentrically and adjacently orientated lesions. We aimed to evaluate the performance and safety of transbronchial cryobiopsy *versus* forceps biopsy in eccentrically and adjacently orientated R-EBUS lesions.

**Methods:** Retrospective review of R-EBUS transbronchial biopsy for PPL over 17 months.

**Results:** 114 R-EBUS scans were included for analysis during the study period. Forceps biopsy was performed in 76 (66.7%) cases and cryobiopsy in 38 (33.3%) cases. Baseline demographics and lesion characteristics did not differ between the two groups. Median (interquartile range) lesion size was 3.48 (2.63–4.51) cm. Overall, 41.2% of lesions were of eccentric orientation and 15.8% adjacent orientation; only 43% were concentric in orientation. Overall diagnostic yield was 67.5% (77 out of 114). Orientation remained an important factor affecting diagnostic yield. Transbronchial cryobiopsy significantly increased the diagnostic yield in eccentrically and adjacently orientated lesions to 75.0% (18 out of 24), compared to 48.8% (20 out of 41) obtained *via* forceps biopsy ($p<0.05$); but not in concentric lesions. Cryobiopsy was associated with more mild and moderate bleeding complications compared to the forceps biopsy group.

**Conclusions:** Transbronchial cryobiopsy under R-EBUS guidance is a safe procedure which potentially increases diagnostic yield in eccentrically and adjacently orientated PPLs.

ERJ Open Res. 2019 Oct 21;5(4):00135-2019

## ABSTRACT

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**Conclusions:** Transbronchial cryobiopsy under R-EBUS guidance is a safe procedure which potentially increases diagnostic yield in eccentrically and adjacently orientated PPLs.


ERJ Open Res. 2019 Oct 21;5(4):00135-2019

- Concentric - the probe was within and completely surrounded by the lesion
- Eccentric - the probe was within but largely biased toward one side at the edge of the lesion
- Adjacent - the probe was not within the lesion and only placed next to the lesion

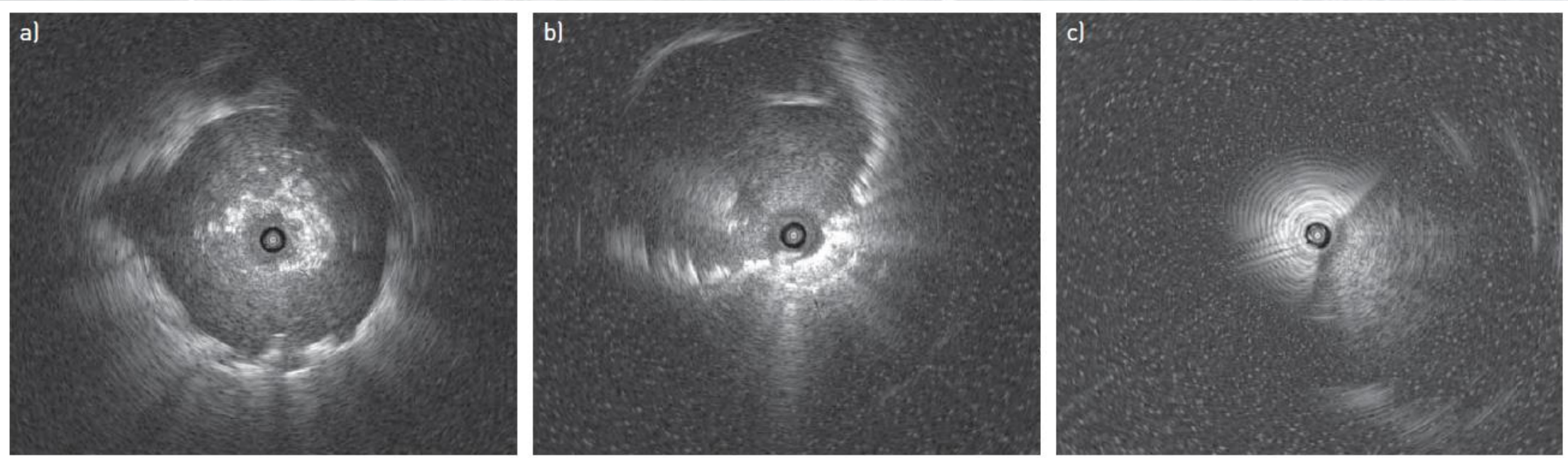
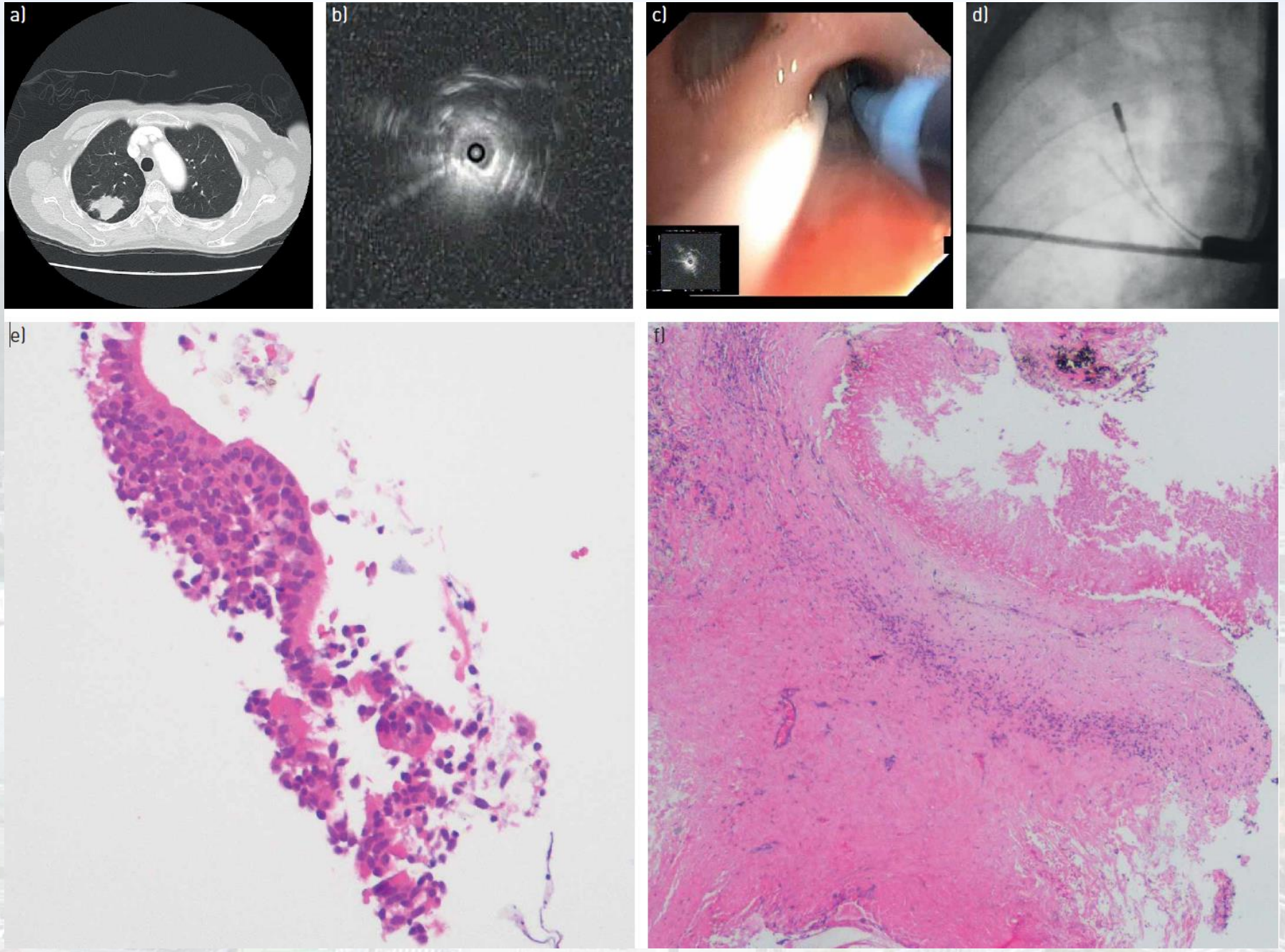



FIGURE 1 Radial endobronchial ultrasound orientation. a) Concentric orientation; b) eccentric orientation; c) adjacent orientation.

ERJ Open Res. 2019 Oct 21;5(4):00135-2019

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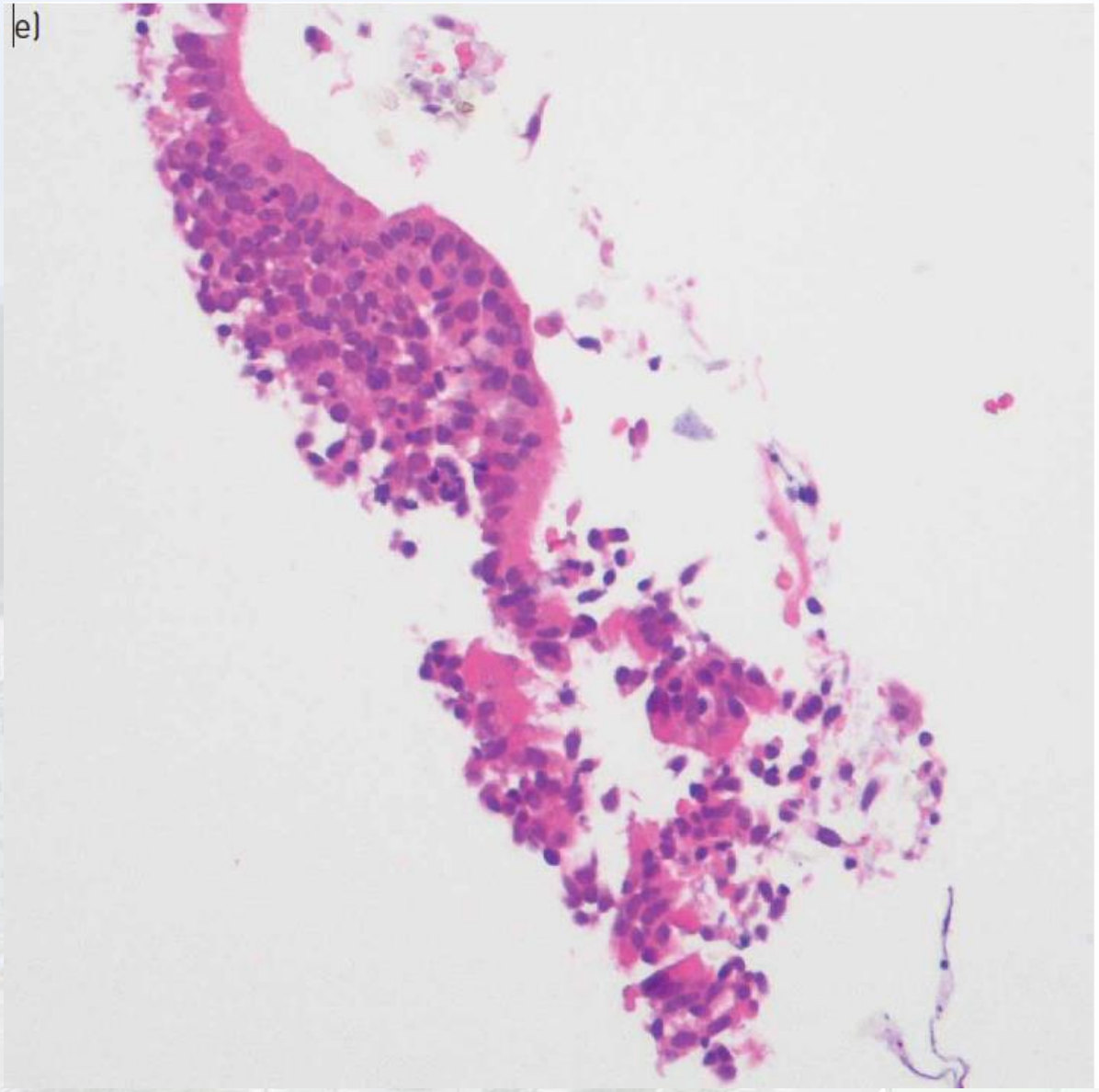


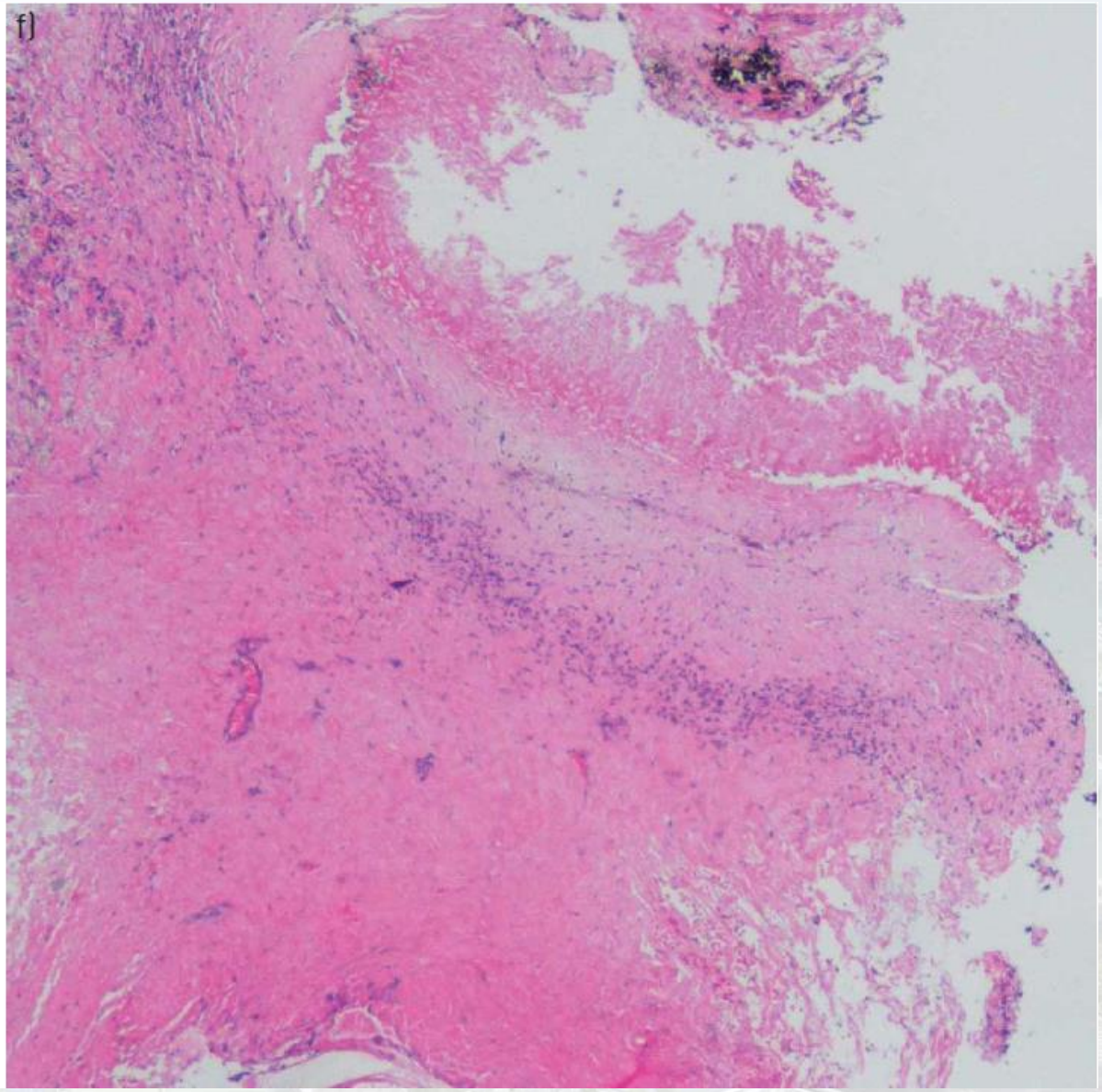


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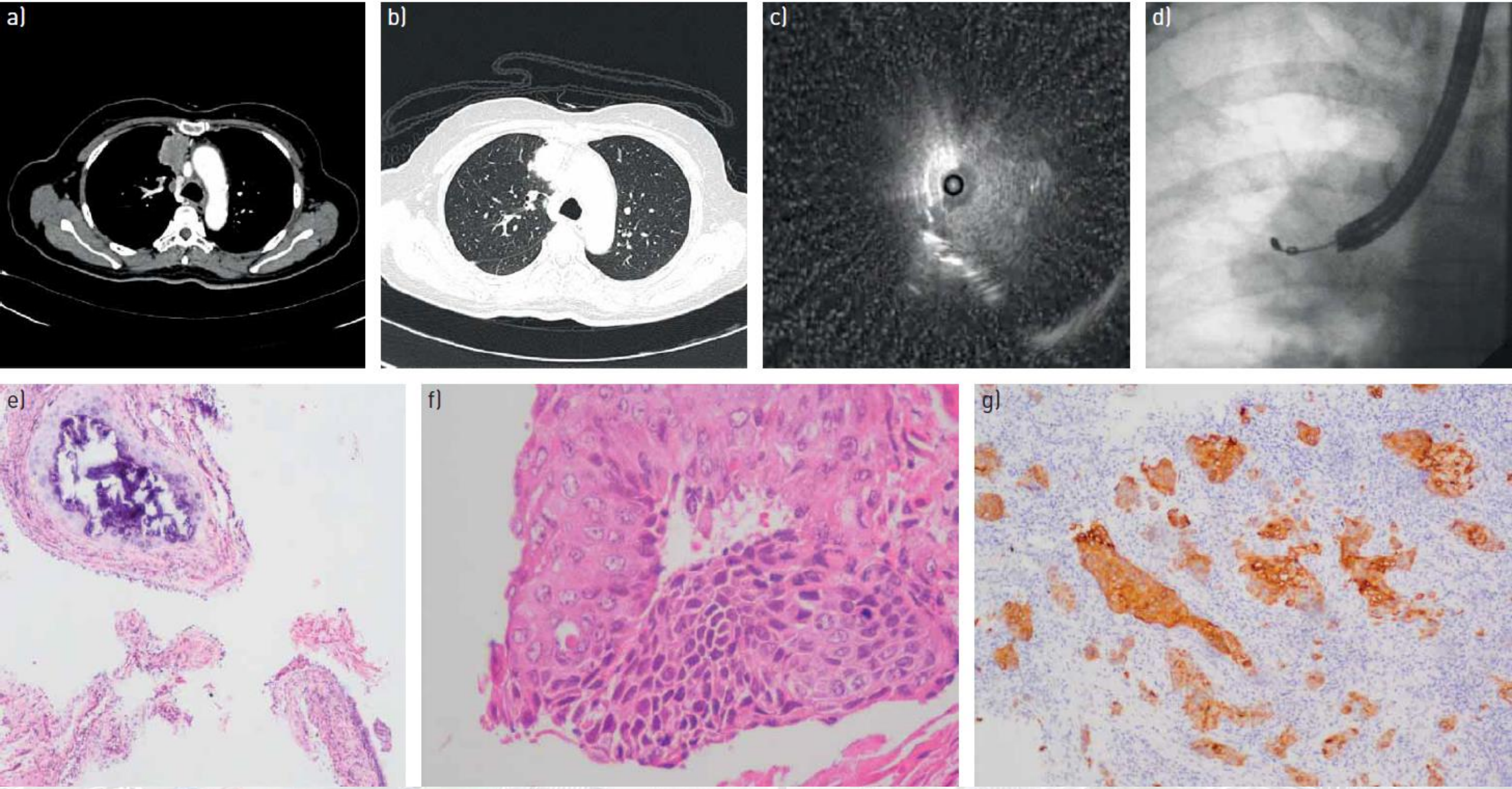
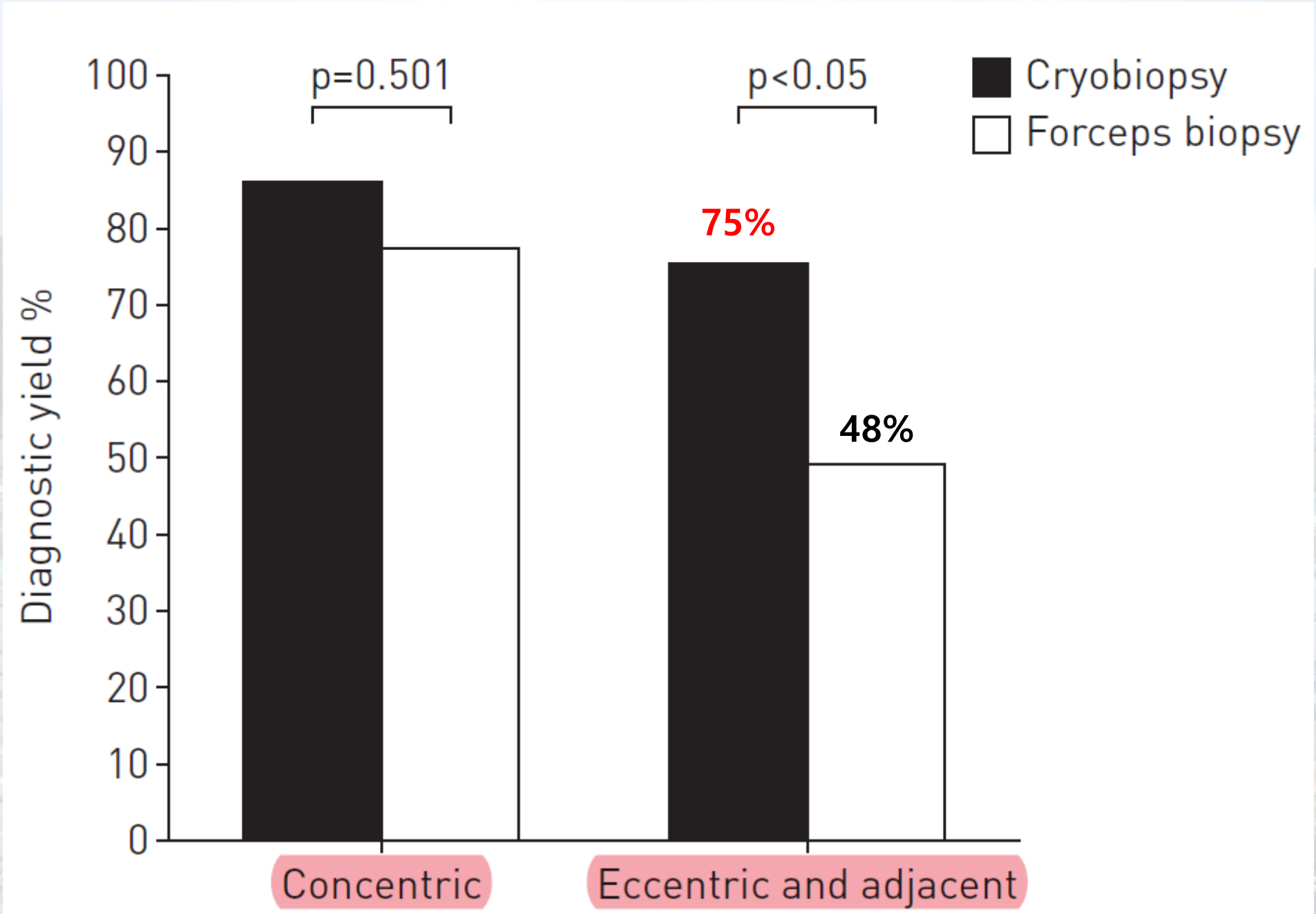



ERJ Open Res. 2019 Oct 21;5(4):00135-2019

| | Overall | Forceps biopsy | Cryobiopsy | p-value |
|---|---|---|---|---|
| **Subjects** | 114 | 76 | 38 | |
| **Patient characteristics** | | | | |
| Age years | 58.5 (49.8–68.3) | 60 (50–70) | 56 (47.8–64.5) | 0.210 |
| Sex | | | | |
| Male | 78 (68.4) | 53 (69.7) | 25 (65.8) | 0.669 |
| Female | 36 (31.6) | 23 (30.3) | 13 (34.2) | |
| **Target lesion characteristics** | | | | |
| Size cm | 3.48 (2.63–4.51) | 3.50 (2.65–4.81) | 3.39 (2.59–4.19) | 0.637 |
| Lobe | | | | |
| Upper lobe | 69 (60.5) | 46 (60.5) | 23 (60.5) | 0.976 |
| Middle lobe/lingular | 16 (14.1) | 11 (14.5) | 5 (13.2) | |
| Lower lobe | 29 (25.4) | 19 (25.0) | 10 (26.3) | |
| Location | | | | |
| Inner third | 20 (17.5) | 15 (19.7) | 5 (13.2) | 0.172 |
| Middle third | 45 (39.5) | 33 (43.4) | 12 (31.6) | |
| Outer third | 49 (43.0) | 28 (36.8) | 21 (55.3) | |
| Orientation | | | | |
| Concentric | 49 (43.0) | 35 (46.1) | 14 (36.8) | 0.248 |
| Eccentric | 47 (41.2) | 32 (42.1) | 15 (39.5) | |
| Adjacent | 18 (15.8) | 9 (11.8) | 9 (23.7) | |
| **Procedure characteristics** | | | | |
| Time min | 45 (35.8–60) | 40.5 (35–51.5) | 50.0 (45–60) | **<0.01** |
| Airway | | | | |
| Transnasal | 91 (79.8) | 69 (90.8) | 22 (57.9) | **<0.001** |
| Advanced airway | 23 (20.2) | 7 (9.2) | 16 (42.1) | |
| Fluoroscopy | 91 (79.8) | 56 (73.7) | 35 (92.1) | **<0.05** |
| Guide sheath | 94 (82.5) | 72 (94.7) | 22 (57.9) | **<0.001** |

ERJ Open Res. 2019 Oct 21;5(4):00135-2019




ERJ Open Res. 2019 Oct 21;5(4):00135-2019

TABLE 2 Factors influencing diagnostic yield in eccentric and adjacent lesions

| | Diagnostic yield | p-value |
|---|---|---|
| **Biopsy method** | | |
| Forceps biopsy | 48.8 (20/41) | **<0.05** |
| Cryobiopsy | 75.0 (18/24) | |
| **Lesion size** | | |
| <3 cm | 56.7 (17/30) | 0.786 |
| ⩾3 cm | 60.0 (21/35) | |
| **Airway** | | |
| Transnasal | 54.9 (28/51) | 0.266 |
| Advanced airway | 71.4 (10/14) | |
| **Fluoroscopy** | | |
| With | 59.6 (31/52) | 0.706 |
| Without | 53.8 (7/13) | |
| **Guide sheath** | | |
| With | 54.7 (29/53) | 0.198 |
| Without | 75.0 (9/12) | |

ERJ Open Res. 2019 Oct 21;5(4):00135-2019

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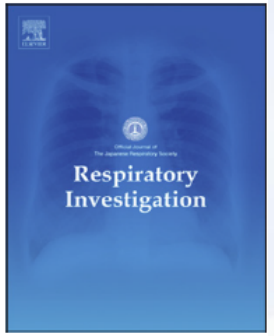



Original article

# Cryobiopsy with endobronchial ultrasonography using a guide sheath for peripheral pulmonary lesions and DNA analysis by next generation sequencing and rapid on-site evaluation ☆

*Ken Arimura*[a,b,*], *Etsuko Tagaya*[a], *Hiroyuki Akagawa*[c], *Yoji Nagashima*[d], *Satoru Shimizu*[e], *Yoshihide Atsumi*[a], *Akitoshi Sato*[a], *Masato Kanzaki*[f], *Mitsuko Kondo*[a], *Kiyoshi Takeyama*[a], *Pierre P. Massion*[b], *Jun Tamaoki*[a]

[a]*Department of Respiratory Medicine, Tokyo Women's Medical University, Tokyo, Japan*
[b]*Division of Allergy, Pulmonary and Critical Care Medicine, Vanderbilt University School of Medicine, Nashville, TN, USA*
[c]*Tokyo Women's Medical University Institute for Integrated Medical Sciences, Tokyo, Japan*
[d]*Department of Surgical Pathology, Tokyo Women's Medical University, Tokyo, Japan*
[e]*Department of Medical Education, Tokyo Women's Medical University School of Medicine, Tokyo, Japan*
[f]*Department of Thoracic Surgery, Tokyo Women's Medical University, Tokyo, Japan*

## ABSTRACT

*Background:* The purpose of this study was to evaluate the diagnostic accuracy of Cryo with endobronchial ultrasonography using a guide sheath (EBUS-GS) for peripheral pulmonary lesions (PPLs) to assess the volume of specimen, determine DNA sequencing analysis, and evaluate the utility of rapid on-site evaluation (ROSE).

*Methods:* Out of 30 patients assessed for eligibility, 23 were enrolled in this prospective study. The histological diagnostic yield of Cryo was evaluated and the volume was compared to that of trans-bronchial biopsy (TBB). DNA analysis of Cryo was performed using next generation sequencing (NGS). ROSE was compared with the final diagnosis.

*Results:* The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy rate was 85%, 100%, 100%, 50%, 87% for Cryo and 80%, 100%, 100%, 42.9%, 82.6% for TBB, respectively. The mean volume was 0.078 $cm^3$ for Cryo and 0.003 $cm^3$ for TBB ($p < 0.0001$). All Cryo specimens provided sufficient quantity and quality of DNA for analysis by NGS. ROSE had a high sensitivity (70%), specificity (100%), PPV (100%), and diagnostic accuracy (73.9%). There were no clinically serious adverse events except mild bleeding in 4 cases.

*Conclusions:* Cryo with EBUS-GS for PPLs is a safe and potentially useful diagnostic strategy.


Respir Investig. 2019 Mar;57(2):150-156

[ Thoracic Oncology Original Research ]

CHEST

# Diagnostic Outcomes and Safety of Cryobiopsy Added to Conventional Sampling Methods

## An Observational Study



*Yuji Matsumoto, MD; Toshiyuki Nakai, MD; Midori Tanaka, MD; Tatsuya Imabayashi, MD; Takaaki Tsuchida, MD; and Yuichiro Ohe, MD*

Chest. 2021 Nov;160(5):1890-1901.

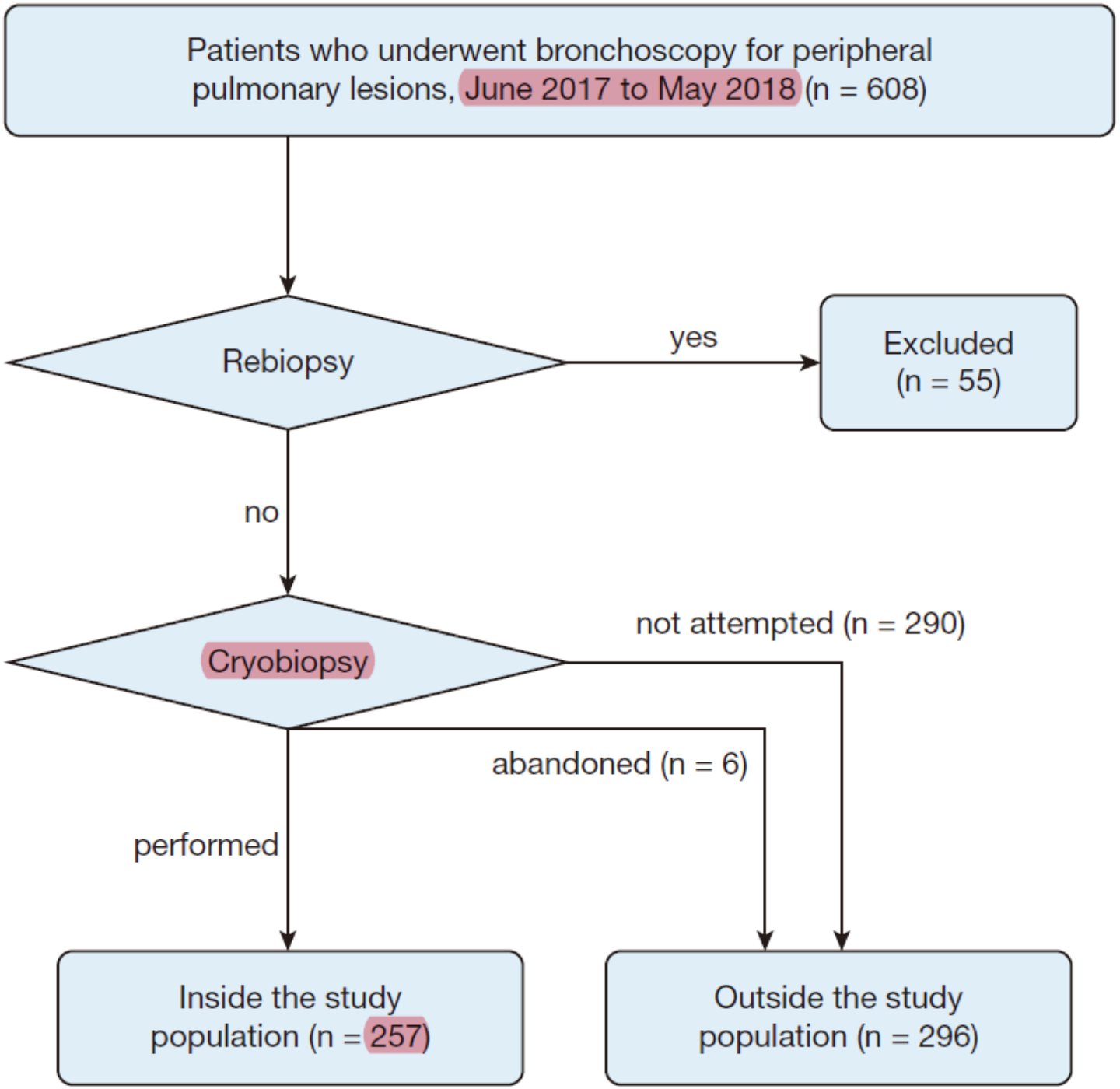
**BACKGROUND:** Cryobiopsy enables specialists to perform high-quality, large, entirely circumferential biopsies; therefore, it may improve the diagnostic yield of peripheral pulmonary lesions (PPLs), as has been previously observed regarding endobronchial tumors and interstitial lung diseases.

**RESEARCH QUESTION:** How do the diagnostic accuracy and safety change by cryobiopsy when performed alongside conventional biopsy for PPLs?

**STUDY DESIGN AND METHODS:** Consecutive patients who underwent cryobiopsy in addition to conventional biopsies for PPL diagnosis at our institution between June 2017 and May 2018 were reviewed retrospectively. The target location was estimated and sampling was performed using conventional devices (ie, forceps, brush, aspiration needle), and cryobiopsy was performed at the same location. Diagnostic outcomes and cryobiopsy safety when performed in addition to conventional sampling methods were analyzed in this observational study.

**RESULTS:** In total, 257 patients were analyzed, and the overall diagnostic yield was 89.9%. Among them, 22 lesions were diagnosable by cryobiopsy exclusively, which improved the rate of diagnosis by 8.6%. Advantages of the use of cryobiopsy were the most apparent when lesions were adjacent to areas assessed via radial endobronchial ultrasound (69.4% vs 84.3%). Multivariable analysis identified bronchus sign (positive/negative, $P = .001$), lobe (other lobes/right upper lobe and left upper segment, $P = .028$), and visibility on radiograph (visible/invisible, $P = .047$) as factors that significantly affected diagnostic yield. On the other hand, three instances of severe hemorrhage (1.2%) and two of pneumothorax (0.8%) occurred. Although most complications were minor, two patients required hospitalization because of cerebral infarction and lung abscess.

**INTERPRETATION:** Cryobiopsy improves the diagnostic yield of PPLs when combined with other conventional sampling methods; however, caution is required because of the possibility of complications.




Chest. 2021 Nov;160(5):1890-1901.

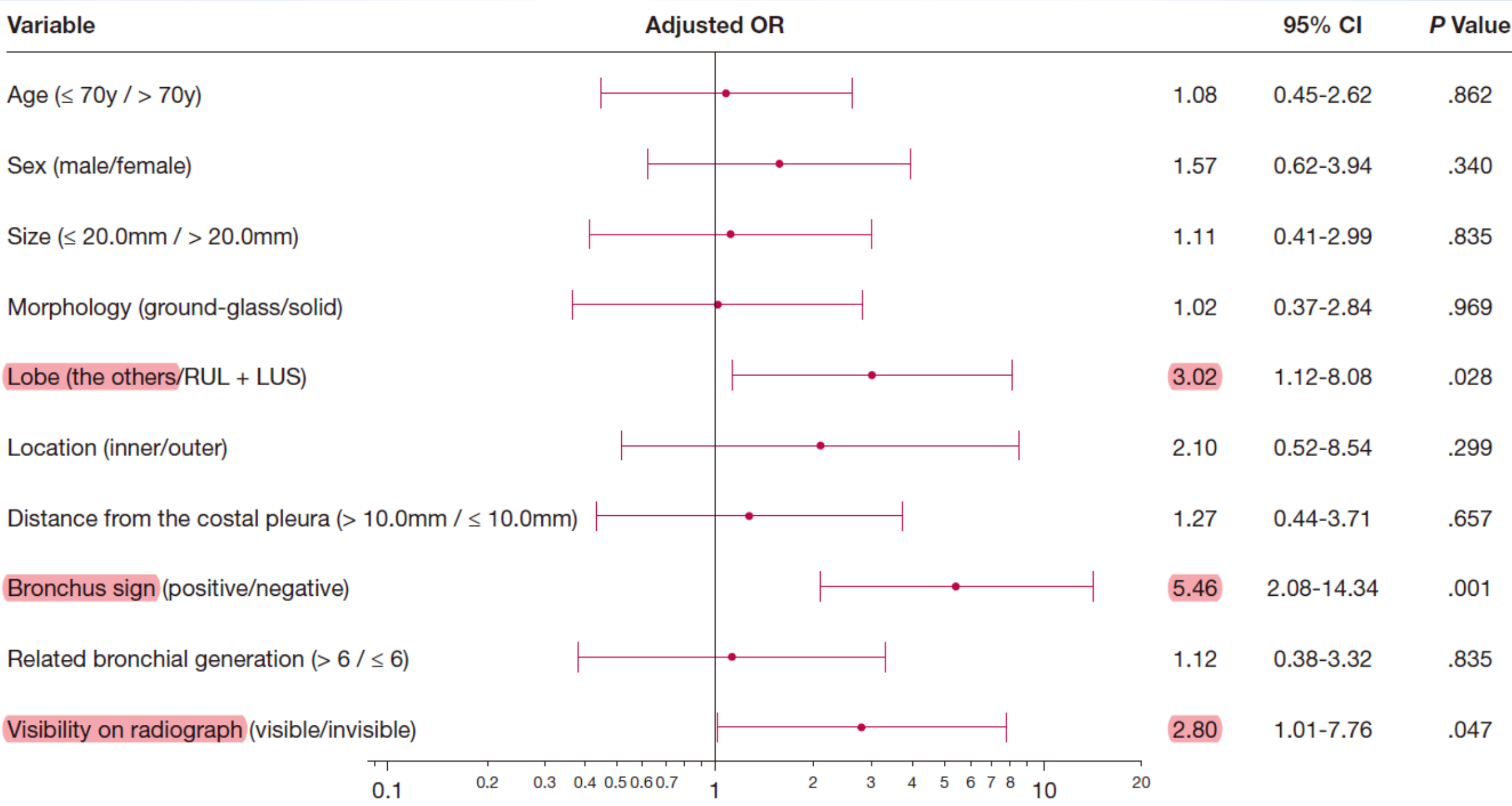
| Variable | With Cryobiopsy (Inside the Study) | Without Cryobiopsy (Outside the Study) |
|---|---|---|
| Age, y | 70 (33-86) | 70 (29-88) |
| ≤ 70 | 130 (50.6) | 158 (53.4) |
| > 70 | 127 (49.4) | 138 (46.6) |
| Sex | | |
| Male | 134 (52.1) | 191 (64.5) |
| Female | 123 (47.9) | 105 (35.5) |
| Size, mm | 22.9 (7.1-115.4) | 24.9 (6.4-103.6) |
| ≤ 20.0 | 98 (38.1) | 109 (36.8) |
| > 20.0 | 159 (61.9) | 187 (63.2) |
| Morphology | | |
| Solid | 152 (59.1) | 245 (82.8) |
| Part-solid | 92 (35.8) | 44 (14.8) |
| Pure ground-glass | 13 (5.1) | 7 (2.4) |
| Lobe | | |
| RUL and LUS | 132 (51.3) | 151 (51.0) |
| RML and lingula | 39 (15.2) | 27 (9.1) |
| RLL and LLL | 86 (33.5) | 118 (39.9) |

| Variable | With Cryobiopsy (Inside the Study) | Without Cryobiopsy (Outside the Study) |
|---|---|---|
| Location | | |
| Outer | 192 (74.7) | 210 (70.9) |
| Inner | 65 (25.3) | 86 (29.1) |
| Distance from the costal pleura, mm | 8.2 (0-52.1) | 5.9 (0-55.2) |
| ≤ 10.0 | 147 (57.2) | 178 (60.1) |
| > 10.0 | 110 (42.8) | 118 (39.9) |
| Bronchus sign | | |
| Positive | 192 (74.7) | 251 (84.8) |
| Negative | 65 (25.3) | 45 (15.2) |
| Related bronchial generation | 7 (3-12) | 7 (2-13) |
| ≤ 6 | 111 (43.2) | 147 (49.7) |
| > 6 | 146 (56.8) | 149 (50.3) |
| Visibility on radiograph | | |
| Visible | 187 (72.8) | 243 (82.1) |
| Invisible | 70 (27.2) | 53 (17.9) |
| Total | 257 (100) | 296 (100) |

Chest. 2021 Nov;160(5):1890-1901.

| Final Diagnosis | Diagnostic Cases | Nondiagnostic Cases |
|---|---|---|
| Adenocarcinoma | 151 (12[a]) | 9 |
| Minimally invasive adenocarcinoma | 2 (1[a]) | 1 |
| Squamous cell carcinoma | 23 (1[a]) | 3 |
| Adenosquamous carcinoma | 5 (1[a]) | 0 |
| Non-small cell carcinoma | 1 | 0 |
| Pleomorphic carcinoma | 5 (1[a]) | 0 |
| Large cell carcinoma | 1 | 1 |
| Small cell carcinoma[b] | 4 | 0 |
| Large cell neuroendocrine carcinoma | 2 | 1 |
| Metastatic tumor | 12 (4[a]) | 0 |
| Malignant mesothelioma | 0 | 1 |
| Carcinoid | 1 (1[a]) | 1 |
| Thymoma | 1 | 0 |
| Hamartoma | 4 | 1 |
| Granuloma | 2 | 0 |
| Mycobacterial infection | 3 | 0 |
| Organizing pneumonia | 4 (1[a]) | 0 |
| Pneumonia | 2 | 0 |
| Chronic inflammation | 5 | 2 |
| Other benignity | 3 | 0 |
| Unknown[c] | 0 | 6 |
| Total | 231 (22[a]) | 26 |

Chest. 2021 Nov;160(5):1890-1901.

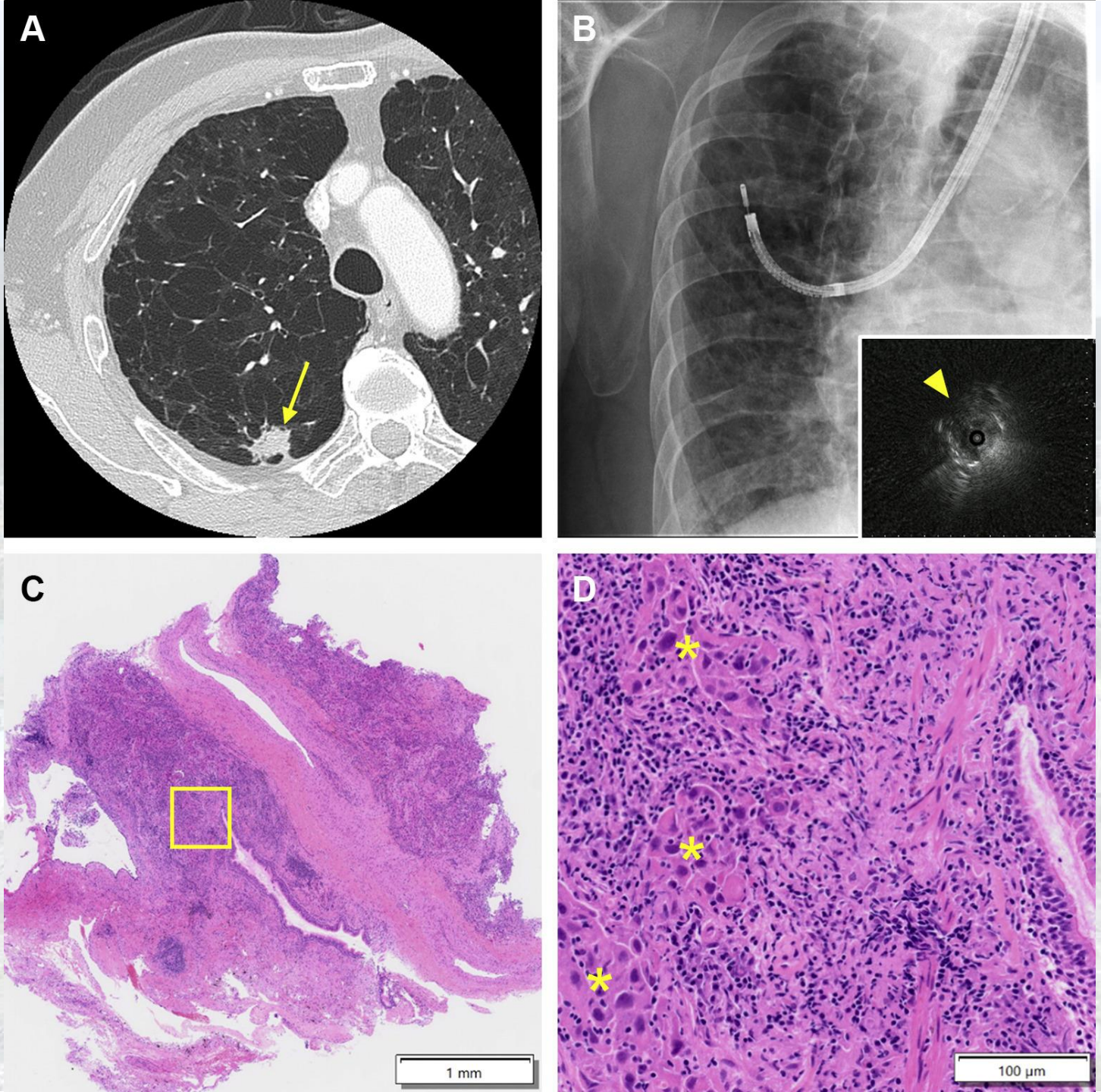



Chest. 2021 Nov;160(5):1890-1901.

TABLE 4 ] Transition of Diagnostic Outcomes With Cryobiopsy for Each Variable

| Variable | Additional Diagnosable Cases by Cryobiopsy | Conventional Diagnosable Cases | *P* Value |
|---|---|---|---|
| Age, y | | | .263 |
| ≤ 70 | 14 (10.8) | 103 (79.2) | |
| > 70 | 8 (6.3) | 106 (83.5) | |
| Sex | | | .825 |
| Male | 11 (8.2) | 111 (82.8) | |
| Female | 11 (8.9) | 98 (79.7) | |
| Size, mm | | | .102 |
| ≤ 20.0 | 12 (12.2) | 73 (74.5) | |
| > 20.0 | 10 (6.3) | 136 (85.5) | |
| Morphology | | | .463 |
| Solid | 14 (9.2) | 123 (80.9) | |
| Part-solid | 6 (6.5) | 77 (83.7) | |
| Pure ground-glass | 2 (15.4) | 9 (69.2) | |
| Lobe | | | .524 |
| RUL and LUS | 9 (6.8) | 105 (79.6) | |
| RML and lingula | 3 (7.7) | 34 (87.2) | |
| RLL and LLL | 10 (11.6) | 70 (81.4) | |
| Location | | | .803 |
| Outer | 17 (8.8) | 153 (79.7) | |
| Inner | 5 (7.7) | 56 (86.2) | |
| Distance from the costal pleura, mm | | | .269 |
| ≤ 10.0 | 10 (6.8) | 121 (82.3) | |
| > 10.0 | 12 (10.9) | 88 (80.0) | |
| Bronchus sign | | | .011 |
| Positive | 12 (6.3) | 169 (88.0) | |
| Negative | 10 (15.4) | 40 (61.5) | |
| Related bronchial generation | | | .502 |
| ≤ 6 | 8 (7.2) | 95 (85.6) | |
| > 6 | 14 (9.6) | 114 (78.1) | |
| Visibility on radiograph | | | .120 |
| Visible | 13 (7.0) | 159 (85.0) | |
| Invisible | 9 (12.9) | 50 (71.4) | |
| R-EBUS finding | | | .001 |
| Within | 4 (3.0) | 124 (92.5) | |
| Adjacent to | 18 (14.9) | 84 (69.4) | |
| Invisible | 0 (0) | 1 (50.0) | |
| Aspiration needle | | | .003 |
| With | 13 (16.1) | 59 (72.8) | |
| Without | 9 (5.1) | 150 (85.2) | |
| ROSE | | | .344 |
| With | 17 (7.8) | 179 (81.7) | |
| Without | 5 (13.2) | 30 (78.9) | |
| Total | 22 (8.6) | 209 (81.3) | ... |

Chest. 2021 Nov;160(5):1890-1901.




Chest. 2021 Nov;160(5):1890-1901.

| Grade | Findings at Bronchoscopy | Rationale |
|---|---|---|
| 1 | Suctioning of blood required for less than 1 minute | Minimal bleeding of no clinical consequence to the patient or the provider. |
| 2 | Suctioning more than 1 minute required or repeat wedging of the bronchoscope for persistent bleeding or instillation of cold saline, diluted vasoactive substances or thrombin | Requirement of one or more tools to control or prevent further bleeding. |
| 3 | Selective intubation with ETT or balloon/bronchial blocker for less than 20 minutes.<br>Or premature interruption of the procedure. | Meaningful but short-term change in the clinical status of the patient involving more invasive procedures and causing interruption of the planned procedure. |
| 4 | Persistent selective intubation > 20 minutes or new admission to the ICU or PRBC transfusion or need for bronchial artery embolization or resuscitation. | Change in level of care and requiring advanced ventilatory support and/or transfusion of PRBC. |

Chest. 2020 Jul; 158(1): 393–400.

**TABLE 5** ] Complications

| Adverse Event | Cases |
|---|---|
| Bleeding | |
| Mild | 101 (39.3) |
| Moderate | 100 (38.9) |
| Severe | 3 (1.2) |
| Life-threatening | 0 (0) |
| Hypoxemia | 11 (4.3) |
| Pneumothorax | 2 (0.8) |
| Lung abscess | 2 (0.8) |
| Cerebral infarction | 1 (0.4) |

Chest. 2021 Nov;160(5):1890-1901.

Nakai *et al. BMC Pulmonary Medicine* (2022) 22:20
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BMC Pulmonary Medicine

RESEARCH

Open Access

# Safety profile and risk factors for bleeding in transbronchial cryobiopsy using a two-scope technique for peripheral pulmonary lesions

Toshiyuki Nakai[1*], Tetsuya Watanabe[1], Yuto Kaimi[2], Koichi Ogawa[1], Yoshiya Matsumoto[1], Kenji Sawa[1], Atsuko Okamoto[1], Kanako Sato[1], Kazuhisa Asai[1], Yuji Matsumoto[3,4], Masahiko Ohsawa[2] and Tomoya Kawaguchi[1]

## Abstract

**Background:** A balloon occlusion technique is suggested for use in cryobiopsy for interstitial lung diseases because of the bleeding risk. However, it may interfere with selection of the involved bronchus for peripheral pulmonary lesions (PPLs). A two-scope technique, in which two scopes are prepared and hemostasis is started using the second scope immediately after cryobiopsy, has also been reported. This study aimed to evaluate the safety and diagnostic utility of transbronchial cryobiopsy using the two-scope technique for PPLs.

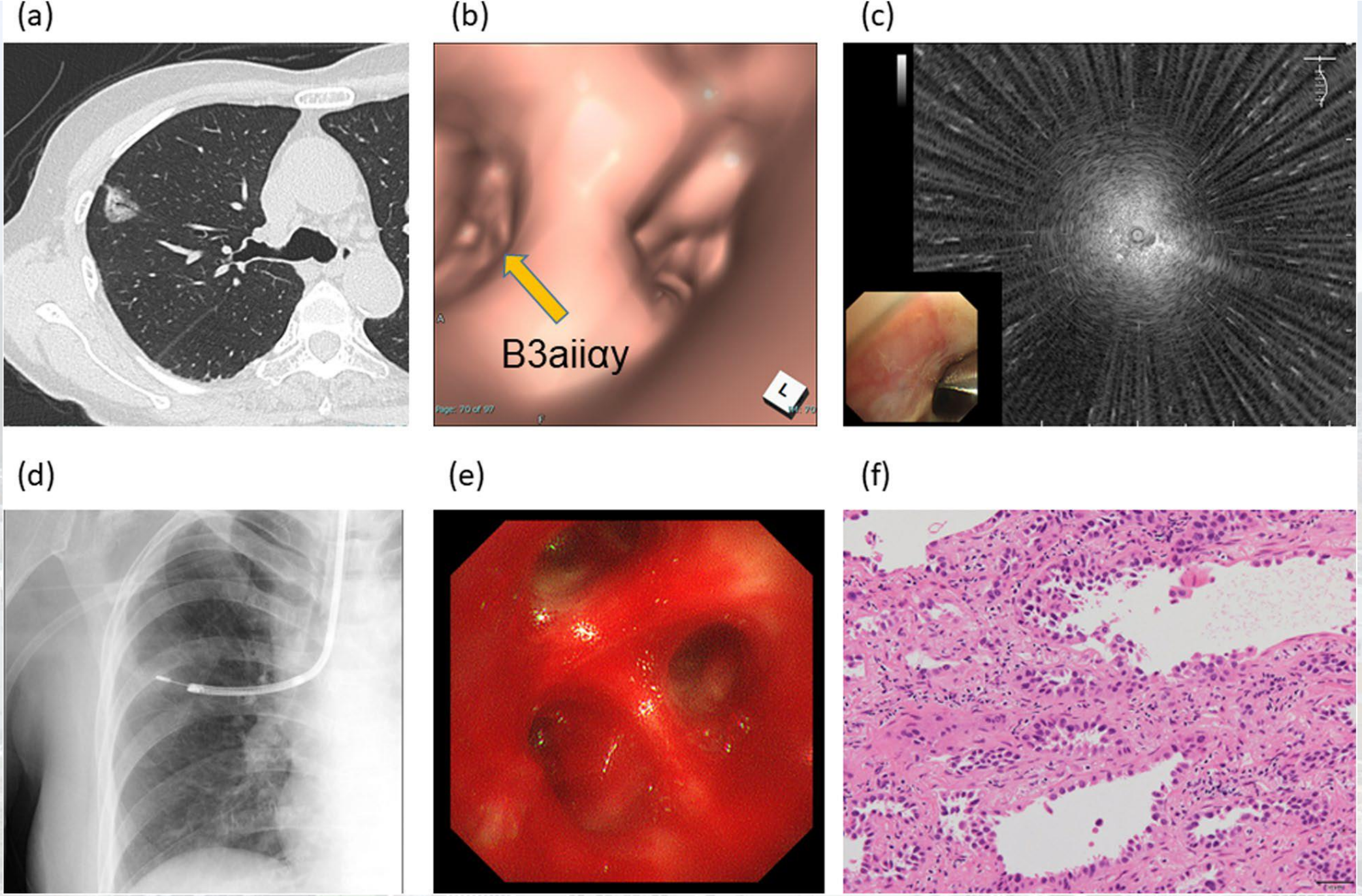
**Methods:** Data of patients who underwent conventional biopsy followed by cryobiopsy using the two-scope technique for PPLs from November 2019 to March 2021 were collected. The incidence of complications and risk factors for clinically significant bleeding (moderate to life-threatening) were investigated. Diagnostic yields were also compared among conventional biopsy, cryobiopsy, and the combination of them.

**Results:** A total of 139 patients were analyzed. Moderate bleeding occurred in 25 (18.0%) patients without severe/life-threatening bleeding. Although five cases required transbronchial instillation of thrombin, all bleeding was completely controlled using the two-scope technique. Other complications included two pneumothoraces and one asthmatic attack. On multivariable analysis, only ground-glass features ($P < 0.001$, odds ratio: 9.30) were associated with clinically significant bleeding. The diagnostic yields of conventional biopsy and cryobiopsy were 76.3% and 81.3%, respectively ($P = 0.28$). The total diagnostic yield was 89.9%, significantly higher than conventional biopsy alone ($P < 0.001$).

**Conclusions:** The two-scope technique provides useful hemostasis for safe cryobiopsy for PPLs, with a careful decision needed for ground-glass lesions.

**Keywords:** Bronchoscopy, Peripheral pulmonary lesion, Lung cancer, Cryobiopsy, Two-scope technique


BMC Pulm Med. 2022 Jan 10;22(1):20.




BMC Pulm Med. 2022 Jan 10;22(1):20.

**Table 2** Results of bronchoscopy

| | N = 139 |
|---|---|
| Procedure time (min) | 28.2 (9.9–55.5) |
| Bronchial generation of bronchoscope inserted, generations | 4 (2–7) |
| EBUS images | |
| Within | 52 (37.4) |
| Adjacent to | 83 (59.7) |
| Invisible | 4 (2.9) |
| Total diagnostic yield | 125 (89.9%) |

BMC Pulm Med. 2022 Jan 10;22(1):20.

**Table 4** Logistic regression analysis of clinical factors for clinically significant bleeding occurring with transbronchial cryobiopsy

| Variable | Univariable analysis | | Multivariable analysis | |
|---|---|---|---|---|
| | Incidence rate (%) | *P* value | OR (95% CI) | *P* value |
| Age (years) | | | | |
| ≤ 70 | 8/57 (14.0) | 0.37 | | |
| > 70 | 17/82 (20.7) | | | |
| Sex | | | | |
| Male | 13/88 (14.8) | 0.25 | | |
| Female | 12/51 (23.5) | | | |
| Body height (cm) | | | | |
| ≤ 170 | 24/121 (19.8) | 0.20 | 2.58 (0.29–23.30) | 0.40 |
| > 170 | 1/18 (5.6) | | | |
| Body mass index (kg/m$^2$) | | | | |
| ≤ 25 | 22/103 (21.4) | 0.13 | 2.63 (0.62–11.10) | 0.19 |
| > 25 | 3/36 (8.3) | | | |
| Diameter of the lesion (mm) | | | | |
| ≤ 20 | 10/47 (21.3) | 0.49 | | |
| > 20 | 15/92 (16.3) | | | |
| Lobar position | | | | |
| Right upper lobe/left upper segment | 13/70 (18.6) | 1 | | |
| Right middle/left lingula | 3/17 (17.6) | | | |
| Lower | 9/52 (17.3) | | | |
| Location area | | | | |
| Inner area | 9/53 (17.0) | 1 | | |
| Outer area | 16/86 (18.6) | | | |
| Lesion appearance on CT | | | | |
| GGN | 17/36 (47.2) | < 0.001 | 9.30 (3.40–25.40) | < 0.001 |
| Solid nodule | 8/103 (7.8) | | | |
| Bronchus sign | | | | |
| Positive | 18/104 (17.3) | 0.8 | | |
| Negative | 7/35 (20.0) | | | |
| R-EBUS image | | | | |
| Within | 7/52 (13.5) | 0.41 | | |
| Adjacent to | 17/83 (20.5) | | | |
| Invisible | 1/4 (25.0) | | | |
| Chronic obstructive pulmonary disease | | | | |
| Present | 2/16 (12.5) | 0.74 | | |
| Absent | 23/123 (18.7) | | | |
| Interstitial lung disease | | | | |
| Present | 1/6 (16.7) | 1 | | |
| Absent | 24/133 (18.0) | | | |
| Bronchial asthma | | | | |
| Present | 1/6 (16.7) | 1 | | |
| Absent | 24/133 (18.0) | | | |
| Using bridging anticoagulation therapy | | | | |
| Present | 1/5 (20.0) | 1 | | |
| Absent | 24/134 (17.9) | | | |
| Cryoprobe size (mm) | | | | |
| 1.9 | 24/129 (18.6) | 0.69 | | |
| 2.4 | 1/10 (10.0) | | | |

BMC Pulm Med. 2022 Jan 10;22(1):20.

| | | | | |
|---|---|---|---|---|
| Location area | | | | |
| Inner area | 9/53 (17.0) | 1 | | |
| Outer area | 16/86 (18.6) | | | |
| Lesion appearance on CT | | | | |
| GGN | 17/36 (47.2) | < 0.001 | 9.30 (3.40–25.40) | < 0.001 |
| Solid nodule | 8/103 (7.8) | | | |
| Bronchus sign | | | | |
| Positive | 18/104 (17.3) | 0.8 | | |
| Negative | 7/35 (20.0) | | | |
| R-EBUS image | | | | |
| Within | 7/52 (13.5) | 0.41 | | |
| Adjacent to | 17/83 (20.5) | | | |
| Invisible | 1/4 (25.0) | | | |
| Chronic obstructive pulmonary disease | | | | |
| Present | 2/16 (12.5) | 0.74 | | |
| Absent | 23/123 (18.7) | | | |
| Interstitial lung disease | | | | |
| Present | 1/6 (16.7) | 1 | | |
| Absent | 24/133 (18.0) | | | |
| Bronchial asthma | | | | |
| Present | 1/6 (16.7) | 1 | | |
| Absent | 24/133 (18.0) | | | |
| Using bridging anticoagulation therapy | | | | |
| Present | 1/5 (20.0) | 1 | | |
| Absent | 24/134 (17.9) | | | |
| Cryoprobe size (mm) | | | | |
| 1.9 | 24/129 (18.6) | 0.69 | | |
| 2.4 | 1/10 (10.0) | | | |
| Number of cryobiopsies taken | | | | |
| 1 biopsy | 24/120 (20.0) | 0.20 | 0.29 (0.032–2.69) | 0.28 |
| ≥ 2 biopsies | 1/19 (5.3) | | | |
| Freezing time of cryobiopsy (s) | | | | |
| ≤ 5 | 12/59 (20.3) | 0.66 | | |
| > 5 | 13/80 (16.3) | | | |
| Sample size ($mm^2$) | | | | |
| ≤ 15 | 15/103 (14.6) | 0.084 | 0.5 (0.17–1.46) | 0.21 |
| > 15 | 10/36 (27.8) | | | |

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**Table 3** Complications during cryobiopsy using a two-scope technique for PPLs (N = 139)

| Complication | Conventional biopsy | Cryobiopsy |
|---|---|---|
| Pneumothorax | 0 | 2 (1.4%) |
| Bleeding | | |
| Mild | 0 | 59 (42.4%) |
| Moderate | 0 | 25 (18.0%) |
| Severe/life-threatening | 0 | 0 (0%) |
| Asthma attack | 0 | 1 (0.7%) |
| Hypoxemia | 0 | 3 (2.2%) |

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**Table 5** Histological diagnoses and diagnostic yield

| | n | Conventional biopsy | Cryobiopsy | Total yield | *P* value |
|---|---|---|---|---|---|
| Malignant n = 127 117/127 = 92.1% | | 100/127 = 78.7% | 105/127 = 82.7% | | |
| Adenocarcinoma | 85 | 69/85 | 71/85 | 80/85 | |
| Minimally invasive adenocarcinoma | 1 | 0/1 | 1/1 | 1/1 | |
| Adenocarcinoma in situ | 2 | 0/2 | 1/2 | 1/2 | |
| Adenosquamous carcinoma lung | 1 | 1/1 | 1/1 | 1/1 | |
| Non-small cell carcinoma | 1 | 0/1 | 1/1 | 1/1 | |
| Squamous cell carcinoma | 21 | 17/21 | 17/21 | 19/21 | |
| Small cell lung carcinoma | 6 | 6/6 | 6/6 | 6/6 | |
| Pleomorphic carcinoma | 3 | 2/3 | 2/3 | 3/3 | |
| Large cell neuroendocrine carcinoma | 5 | 4/5 | 4/5 | 4/5 | |
| Metastatic tumor | 2 | 1/2 | 1/2 | 1/2 | |
| Benign n = 8 | | | | | |
| Screlosing hemangioma | 1 | 0/1 | 1/1 | 1/1 | |
| Organizing pneumonia | 1 | 1/1 | 1/1 | 1/1 | |
| Lung abscess | 1 | 1/1 | 1/1 | 1/1 | |
| Nontuberculous mycobacteria | 2 | 2/2 | 2/2 | 2/2 | |
| Chronic inflammation | 2 | 1/2 | 2/2 | 2/2 | |
| Cryptococcus | 1 | 1/1 | 1/1 | 1/1 | |
| Unknown[a] | 4 | 0/4 | 0/4 | 0/4 | |
| Total | 139 | 106/139 (76.3%) | 113/139 (81.3%) | 125/139 (89.9%) | 0.28 |

[a] These 4 cases are being followed-up by CT

# Summary

- **Diagnostic yield**
  - Cryo > Forcep (except Anticancer Research Oct 2019, 39 (10) 5683-5688)
  - Eccentric/Adjacent: cryo > Forcep
  - With GS > Without GS
  - Bronchus sign: positive > negative
  - Non-RUL/RUL, Visible on radiograph, Aspiration needle (Chest. 2021 Nov;160(5):1890-1901.)

- **Significant bleeding**
  - Total: Severe (1.2%), life-threatening (0%) (n=257) (Chest. 2021 Nov;160(5):1890-1901.)
  - Cryo: Severe/life-threatening (0%) (n=139) (BMC Pulm Med. 2022 Jan 10;22(1):20.)
  - Cryo > Forcep
  - GGN > Solid (BMC Pulm Med. 2022 Jan 10;22(1):20.)


Thanks for your attention