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Efficacy and safety of virtual bronchoscopic navigation with fused fluoroscopy and vessel mapping for access of pulmonary lesions

Jiayuan Sun[1] | Gerard J. Criner[2] | David Dibardino[3] | Shiyue Li[4] | Daniel Nader[5] | Bing Lam[6] | Lisa Kopas[7] | Momen M. Wahidi[8] | Adnan Majid[9] | Robert Marron[2] | Steven Verga[2] | Felix J. F. Herth[10]

[1]Department of Respiratory Endoscopy, Department of Respiratory and Critical Care Medicine, Shanghai Engineering Research Center of Respiratory Endoscopy, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China

[2]Department of Thoracic Medicine and Surgery, Lewis Katz School of Medicine at Temple University, Philadelphia, Pennsylvania, USA

[3]Section of Interventional Pulmonology, Pulmonary, Allergy, and Critical Care Division, University of Pennsylvania, Philadelphia, Pennsylvania, USA

[4]State Key Laboratory of Respiratory Disease, Guangzhou Respiratory Institute, Guangzhou, China

[5]Interventional Pulmonology, Cancer Treatment Center of America, Tulsa, Oklahoma, USA

[6]Respiratory Medicine Center, Hong Kong Sanatorium and Hospital, Hong Kong, China

[7]Pulmonary and Critical Care Medicine, Houston Methodist Hospital, Houston, Texas, USA

[8]Department of Pulmonary, Allergy and Critical Care Medicine, Duke University, Durham, North Carolina, USA

[9]Department of Pulmonary and Critical Care Medicine, Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA

[10]Department of Pneumology and Respiratory Care Medicine, Thoraxklinik and Translational Lung Research Center, University of Heidelberg, Heidelberg, Germany

Correspondence
Felix J. F. Herth
Email: felix.herth@med.uni-heidelberg.de

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Abstract

Background and objective: Virtual bronchoscopic navigation (VBN) with fused fluoroscopy and vessel mapping provides a point of entry (POE) for puncturing airway wall to biopsy lesions. The study was designed to evaluate the safety and efficacy of this technology to diagnose peripheral pulmonary lesions.

Methods: It was a prospective, single-arm, multicentre study. Patients underwent lesions biopsy with the Archimedes® VBN System via a POE using one of the two techniques: (1) bronchoscopic transparenchymal nodule access (BTPNA) and (2) guided transbronchial needle aspiration (TBNA). Biopsy yield, sampling yield and diagnostic yield were mainly determined in lesions biopsy attempted.

Results: One hundred and thirty patients underwent anaesthesia and constituted the intention-to-treat population. One hundred and four patients with 114 lesions had biopsy attempted. Mean lesion size was 2.4 ± 1.13 cm. Sufficient tissue samples were obtained from 86 lesions with a biopsy yield of 75.4%. Nevertheless, sufficient samples for diagnosis based on histology ± cytology were obtained from 107 lesions with a sampling yield of 93.9%. Follow-up was conducted for more than 1 year, with a diagnostic yield of 75.4% and 72.8%, respectively, on high and low estimate with consideration of three lesions without follow-up. Two (1.9%) pneumothoraxes and one (1.0%) mild bleeding occurred.

Conclusion: BTPNA and guided TBNA contribute to safe and effective sampling of peripheral pulmonary lesions. A relatively high biopsy yield was obtained independent of the presence or absence of a bronchus sign (BS), and high sampling yield and diagnostic yield were obtained independent of location, lesion size and presence or absence of a BS.

KEYWORDS
bronchoscopic transparenchymal nodule access, point of entry, pulmonary lesion, virtual bronchoscopic navigation

INTRODUCTION

For pulmonary lesions suspected to be malignant, biopsies are obtained by bronchoscopic or transthoracic procedures

This study was previously presented at the 2019 Annual Congress of the European Respiratory Society (ERS).

typically before treatment. Chest computed tomography (CT) scan-guided transthoracic needle aspiration for peripheral lesions reported biopsy yield of 90% but with high pneumothorax rate.[1,2] Transbronchial biopsy (TBB) using fibreoptic bronchoscopy yielded a diagnosis rate of 18%–62%.[3] Navigation bronchoscopy may improve biopsy efficiency. A meta-analysis showed yields of 72% for virtual bronchoscopic navigation (VBN), 67% for electromagnetic navigation bronchoscopy (ENB), 73% with the use of a guide sheath, 70% with ultrathin bronchoscope and 71% with radial probe endobronchial ultrasound (R-EBUS), with substantial variation in yield found across studies.[4] However, the diagnostic yield also varies significantly and is affected by lesion size, distance from the hilum and bronchus sign (BS).[5–7] Diagnostic yield of TBB was reduced to 29%–50% for lesions with no visible bronchus leading to.[6–9]

Bronchoscopic navigation through multiple subsegments is challenging and endobronchial path selection is a major source of error during bronchoscopy.[10] VBN with fused fluoroscopic guidance reconstructs three-dimensional bronchial pathway, as well as virtual image of the lesion based on two-dimensional CT, and highlights the lesion on the fluoroscope screen to facilitate the navigation and diagnostic approach.[11] Vessel mapping is used to avoid large vessels during sampling. Bronchoscopic transparenchymal nodule access (BTPNA) and guided transbronchial needle aspiration (TBNA), both requiring a puncture through the airway wall and creating a point of entry (POE), allow for lesion access regardless of lesion size, proximity of the lesion to the airway, presence of a BS or location in the lung.[12,13] Here, this study examined the value of BTPNA and guided TBNA approaches.

SUMMARY AT A GLANCE

Virtual bronchoscopic navigation with fused fluoroscopy and vessel mapping provides a point of entry (POE) for puncturing airway wall to biopsy lesions. In this study, biopsy yield of 75.4% and sampling yield of 93.9% were obtained independent of bronchus sign from 104 patients with 114 lesions via POE.

METHODS

Study design and patient enrolment

This was a prospective single-arm multicentre interventional study conducted at 10 centres in China, Germany and the United States allowing to enrol up to 200 patients (NCT02867371), aiming to evaluate the safety and efficacy of VBN with fused fluoroscopy and vessel mapping (Archimedes System, Broncus Medical, Inc., San Jose, CA) to facilitate bronchoscopic biopsy of pulmonary lesions. Participants with one or more lesions of ≥8 mm suspicious for lung cancer or metastatic disease and accessible through POE providing written informed consent were enrolled in the study. Physicians could independently select the optimal approach (BTPNA or guided TBNA) based on lesion characteristics.

Study procedure

The Archimedes System reconstructed chest CT images into a 3D model and allowed suspicious lesions to be marked. Several paths were calculated automatically for each lesion, and real-time intraoperative guidance to bronchoscope was realized. A POE was provided through virtual Doppler imaging, which was displayed on both virtual and live bronchoscopic images during the procedure. Therefore, extraluminal lesion was reached in the case of avoiding vascular structures. For a POE and BTPNA tunnel establishment, all procedural tools were contained in the Archimedes Access Kit (Broncus Medical, Inc.): an 18-gauge needle (FleXNeedle®, Broncus Medical, Inc.), a dilatation balloon and a sheath. The two biopsy approaches are described below:

1. BTPNA procedure. The POE location was reached and an 18-gauge needle was inserted through the working channel of a therapy bronchoscope (5.9 mm outer diameter; 2.8 mm/3.0 mm working channel) to puncture the airway wall. Balloon dilation was performed to introduce a radiopaque sheath followed by blunt dissection through lung parenchyma under live fluoroscopic and/or R-EBUS guidance to access a virtual target of the lesion superimposed onto the fluoroscopic image. Multiple airway paths were provided by the software with consideration of vessel location. Tissue samples were collected using biopsy forceps ± needle under fused fluoroscopic guidance.
2. Guided TBNA procedure. Target location was reached utilizing a diagnostic scope (4.0 mm/4.2 mm outer diameter; 2.0 mm working channel) and a needle was inserted to puncture the airway wall at the POE. Operator could also introduce biopsy forceps under live time fluoroscopic visualization and/or R-EBUS guidance.

In addition to forceps ± needles, cytologic sampling method could also be used in both the above-mentioned approaches according to clinical practice.

Cytology assessment was conducted using rapid on-site evaluation (ROSE) when available, followed by regular hospital histopathology process. Sample was clinically qualified for pathological review if abnormal sample was obtained. Normal bronchial mucosa and lung tissue were considered unqualified for pathological review. Meanwhile, if ROSE was not available, hospital histopathology process would be used to determine sample viability. The pathologists were blinded to this trial. Patients were monitored for at least 1 h after the procedure or as per hospital standard of care followed by a chest x-ray to assess for any complications.

Study outcomes

The primary endpoint was biopsy yield, defined as the number of lesions with at least one biopsy sufficient for a tissue diagnosis divided by the number of lesions sampled using the Archimedes System. Sampling yield was defined as the number of lesions with sufficient tissue and/or cytologic samples obtained divided by the number of lesions sampled using the Archimedes System, regardless of sampling instruments. Secondary endpoints included adverse events, procedure planning time, lesion access time, sampling time, fluoroscopy time and registration time. Lesion access time was defined as the time from the start of navigation until the target lesion location confirmed. Technical success rate was calculated and defined as the number of lesions with sufficient tissue and/or cytologic samples obtained divided by the number of lesions with BTPNA/guided TBNA sampling procedure attempted.

Subgroup analyses were performed for biopsy yield and sampling yield based on anatomic and procedure characteristics. BS was defined as a visible airway leading to a lesion on CT and categorized as A–C. CT-BS A was defined as the presence of airway directly leading to, or located within, the lesion, CT-BS B an airway leading to lesion but no visible connection noted on CT imaging and CT-BS C if no airway was seen in the vicinity of the lesion.[9]

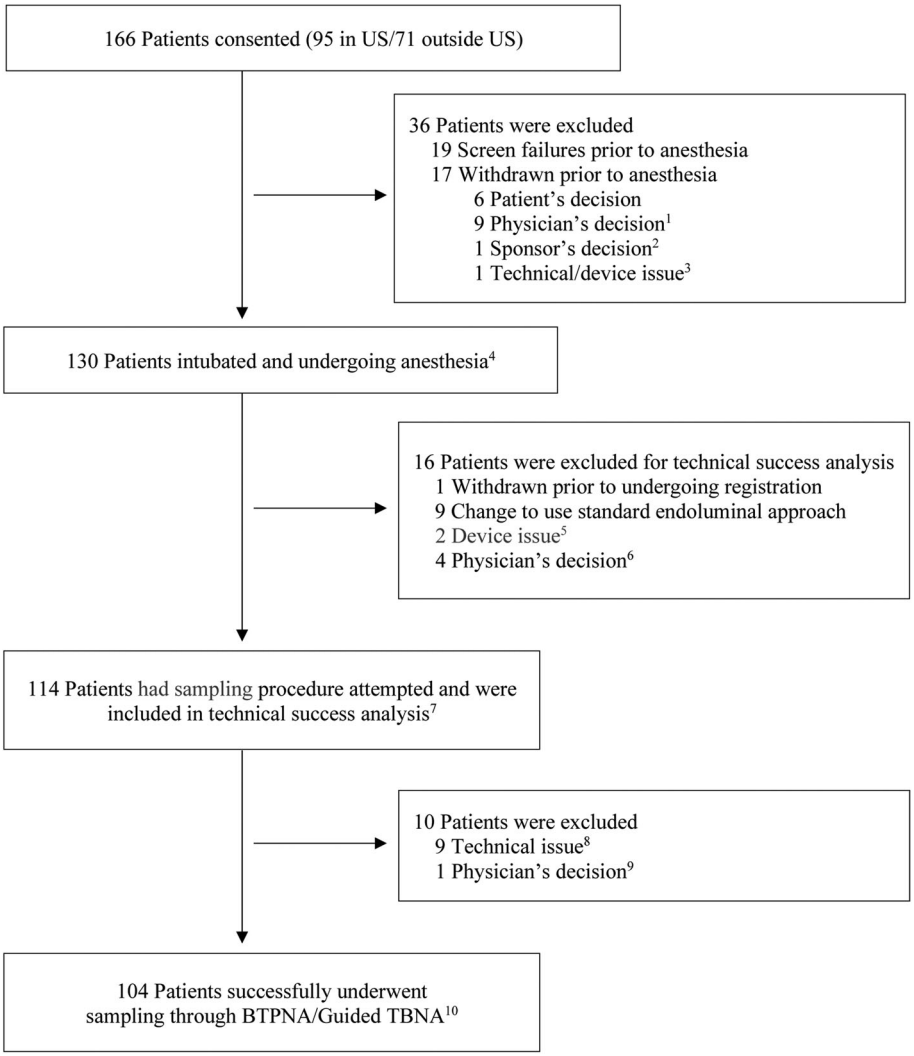

FIGURE 1 The flow chart of patient enrolment. A total of 166 patients were consented, with 130 patients intubated and undergoing anaesthesia. Overall, 114 patients had Archimedes sampling procedure attempted and 104 patients completed the procedure with successful sampling. BTPNA, bronchoscopic transparenchymal nodule access; POE, point of entry; TBNA, transbronchial needle aspiration

[1] One nodule significant size decrease, one physician chose alternative procedure, one cancelled, six no additional comments.
[2] Patient required additional intervention outside study parameters.
[3] Hardware issue.
[4] Intention-to-Treat population.
[5] One case had device malfunction, one equipment was unplugged accidentally.
[6] One bleeding during lymph node biopsy, three cases had anatomic anomaly/pulsating vessels.
[7] Technical success analysis population.
[8] Four cases had registration error, two had fused fluoroscopy image issue, one had difficulty creating POE, one off-target of visual target, one nodule was unable to localize using endobronchial ultrasound-Archimedes.
[9] One bronchoscope unable to articulate to POE.
[10] Safety population.

At least 1 year of clinical follow-up was obtained for lesions with an initially non-specific diagnosis. Diagnostic yield was defined as all instances in which the results matched the diagnosis confirmed by pathological and/or bacterial assessment of bronchoscopic samples.[14]

Statistical analysis

Categorical variables were summarized by counts and percentages. Continuous variables were summarized by mean, SD, median, minimum and maximum. Comparisons among groups of categorical data were performed using Fisher's exact or Pearson's chi-square test. Significant variables in univariate analyses and those deemed clinically significant factors were included in logistic regression analyses. A p-value of <0.05 indicated statistical significance. All statistical analyses were

TABLE 1 Demographic and clinical characteristics

Variable	Intention-to-treat population ($N = 130$ subjects)
Sex, *n* (%)	
Male	57 (43.8%)
Female	73 (56.2%)
Age on the procedure date (years)	
Mean (SD)	64.2 (11.22)
Median	65
Minimum, maximum	27, 87
Age group, *n* (%)	
21–54	23 (17.7%)
55–74	85 (65.4%)
≥75	22 (16.9%)
BMI (kg/m^2)	
Mean (SD)	26.4 (5.41)
Median	25.7
Minimum, maximum	15.7, 42.9
Coexisting conditions of interest, *n* (%)	
Heart failure	3 (2.3%)
Myocardial infarction	2 (1.5%)
Chronic obstructive pulmonary disease	15 (11.5%)
Pulmonary fibrosis	1 (0.8%)
Pulmonary hypertension	2 (1.5%)
Prior thoracic surgery	10 (7.7%)
Patients taking antiplatelet or anticoagulation medication	
Anticoagulants	11 (8.5%)
Antiplatelets (prescribed)	10 (7.7%)
Aspirin	32 (24.6%)

TABLE 2 Lesion characteristics

Variable	Lesions sampled ($N = 114$)
No. of samples taken per lesion, *n*	
Mean (SD)	10.4 (5.46)
Median	10
Minimum, maximum	2, 26
Lesion size (cm), *n*	
Mean (SD)	2.4 (1.13)
Median	2.1
Minimum, maximum	0.8, 5.8
<2.0 cm, *n* (%)	45 (39.5%)
≥2.0 cm, *n* (%)	69 (60.5%)
Lesion location, *n* (%)	114
Right upper lobe	23 (20.2%)
Right middle lobe	8 (7.0%)
Right lower lobe	23 (20.2%)
Left upper lobe	41 (36.0%)
Left lower lobe	19 (16.7%)
CT-BS, *n* (%)	112[a]
CT-BS A	64 (57.1%)
CT-BS B	27 (24.1%)
CT-BS C	21 (18.8%)
Distance from the lesion to pleura[b] (mm), *n*	112[a]
Mean (SD)	19.7 (14.47)
Median	17.9
Minimum, maximum	0, 55.8
Procedure techniques, *n* (%)	115[c]
BTPNA	51 (44.3%)
Guided TBNA	64 (55.7%)
Tunnel length of BTPNA technique (cm), *n*	
Mean (SD)	3.3 (1.21)
Median	3.3
Minimum, maximum	0.9, 6
Lesions visible on fluoroscopy, *n* (%)	114
Yes	88 (77.2%)
No	26 (22.8%)
Lesions confirmed with R-EBUS, *n* (%)	114
Yes	68[d] (59.6%)
No	46 (40.4%)

Abbreviations: BS, bronchus sign; BTPNA, bronchoscopic transparenchymal nodule access; CT, computed tomography; CT-BS A, the presence of airway directly leading to, or located within, the lesion, CT-BS B, an airway leading to lesion but no visible connection noted on CT imaging; CT-BS C, if no airway was seen in the vicinity of the lesion; R-EBUS, radial probe endobronchial ultrasound; TBNA, transbronchial needle aspiration.

[a]Missing data in two lesions.

[b]Distance along tunnel/airway path from the back of lesion target to pleura.

[c]One subject had two different procedure techniques (BTPNA and guided TBNA) to access and sampled the same nodule.

[d]R-EBUS was used to confirm the access in 68 of the 114 lesions sampled.

performed in SAS (version 8.2; SAS Institute, Cary, NC) and Microsoft Excel 2010 (Microsoft, Redmond, WA).

RESULTS

Patient population and technical success

Between August 2016 and November 2018, 166 patients were consented, with 130 patients intubated and undergoing anaesthesia (intention-to-treat population). Overall, 114 patients had Archimedes sampling procedure attempted and 104 patients completed the procedure with successful sampling. Enrolment and baseline demographics of eligible patients are shown in Figure 1 and Table 1, respectively. Sufficient histologic and/or cytologic samples were obtained from 107 lesions of 114 patients with 124 lesions having Archimedes sampling procedure attempted, resulting in a technical success rate of 86.3% (107/124).

Lesion characteristics

Table 2 describes the key characteristics of the lesions sampled. A total of 114 lesions with a mean lesion size of 2.4 ± 1.13 cm were sampled from 104 patients. R-EBUS was used in 68 (59.6%) lesions. Visualization was noted in 88 (77.2%) lesions on fluoroscopy. Of the lesions biopsied, 57.1% was classified as CT-BS A, with 24.1% as CT-BS B and 18.8% as CT-BS C.

Biopsy yield and sampling yield

The primary endpoint was based on the 104 patients with 114 lesions sampled using the Archimedes System. Sufficient histologic samples were obtained from 86 lesions with a biopsy yield of 75.4% (86/114). Sufficient histologic and/or cytologic samples were obtained from 107 lesions with a sampling yield of 93.9% (107/114). Of them, bronchoscopic

TABLE 3 Subgroup analysis of biopsy yield and sampling yield

Variable	Lesions sampled ($N = 114$)	Lesions with sufficient tissue samples ($N = 86$)	Biopsy yield (%)	*p*	Lesions with sufficient sample for diagnosis ($N = 107$)	Sampling yield (%)[a]	*p*
Lesion size, *n*	114	86			107		
<2.0 cm	45	29	64.4	0.044	42	93.3	1
≥2.0 cm	69	57	82.6		65	94.2	
Lesion location, *n*	114	86		0.95	107		0.634
Right upper lobe	23	16	69.6		21	91.3	
Right middle lobe	8	6	75.0		7	87.5	
Right lower lobe	23	18	78.3		22	95.7	
Left upper lobe	41	32	78.0		40	97.6	
Left lower lobe	19	14	73.7		17	89.5	
CT-BS, *n*	112[b]	85[c]		0.03	105[b]		0.932
CT-BS A	64	54	84.4		60	93.8	
CT-BS B	27	19	70.4		25	92.6	
CT-BS C	21	12	57.1		20	95.2	
Distance from the lesion to pleura[d], *n*	112[b]	85[c]		0.185	105[b]		0.237
<20 mm	63	51	81.0		61	96.8	
≥20 mm	49	34	69.4		44	89.8	
Procedure techniques, *n*	115[e]	87[e]		0.028	108[e]		0.238
BTPNA	51	44	86.3		46	90.2	
Guided TBNA	64	43	67.2		62	96.9	
Tunnel length of BTPNA technique, *n*	51	44		0.40	46		0.335
<30 mm	19	15	78.9		16	84.2	
≥30 mm	32	29	90.6		30	93.8	

Abbreviations: BS, bronchus sign; BTPNA, bronchoscopic transparenchymal nodule access; CT, computed tomography; CT-BS A, the presence of airway directly leading to, or located within, the lesion, CT-BS B, an airway leading to lesion but no visible connection noted on CT imaging; CT-BS C, if no airway was seen in the vicinity of the lesion; TBNA, transbronchial needle aspiration.

[a]Sampling yield was defined as the number of lesions with sufficient tissue and/or cytologic samples obtained divided by the number of lesions sampled using the Archimedes System.

[b]Missing data in two lesions.

[c]Missing data in one lesion.

[d]Distance along tunnel/airway path from the back of lesion target to pleura.

[e]One subject had two different procedure techniques (BTPNA and guided TBNA) to access and sampled the same nodule.

diagnoses for 82 lesions were determined through histologic samples, and bronchoscopic diagnoses for 25 lesions were determined through cytologic samples.

Subgroup analyses (Table 3) showed that lesions with characteristics of size <2.0 cm, CT-BS C sign and using guided TBNA might reduce the biopsy yield. There was no difference in biopsy yield of lesions for their location, distance from lesion to pleura and tunnel length in BTPNA patients. Biopsy yield of BTPNA was much higher than guided TBNA (86.3% vs. 67.2%). Multivariate analysis identified lesion size ($p = 0.019$) and procedure techniques ($p = 0.008$) as independent diagnostic predictors, but BS was not (Table S1 in the Supporting Information). All these factors showed no difference in sampling yield. Both procedural approaches demonstrated sampling yields >90%, even if they are of size <2.0 cm. Notably, for a lesion without an airway directly leading to CT-BS B and CT-BS C, both high biopsy yield (70.4% and 57.1%, respectively) and sampling yield (92.6% and 95.2% reported, respectively) were achieved. More details on procedural and fluoroscopy time are shown in Table S2 in the Supporting Information.

Among the 114 lesions, 61 (53.5%) lesions were characterized as non-specific inflammation/fibrosis/atypia, 34 (29.8%) malignant, 12 (10.5%) definite benign and seven (6.1%) had insufficient sample to make any diagnosis. Table 4 provides the detailed bronchoscopic diagnosis.

Final diagnosis in 58 of the 61 lesions characterized as non-specific diagnosis was determined based on subsequent standard clinical follow-up, with confirmed benign in 37 (60.7%) lesions and false negative in 21 (34.4%) lesions, which were confirmed as malignant. The remaining three (4.9%) lesions had no follow-up reported, but were calculated as both true negative and false negative. The average follow-up period was 437 days, and the overall results are available in Figure 2. The diagnostic yield would be 75.4% (86/114) on the high estimate or 72.8% (83/114) on the low estimate. Meanwhile, diagnostic yields of 74.1% (20/27) and 71.4% (15/21) were obtained for CT-BS B and CT-BS C, respectively.

TABLE 4 Detailed bronchoscopic diagnosis

Variable	Lesions diagnosed through histologic samples ($N = 82$)	Lesions diagnosed though cytologic samples ($N = 25$)	Lesions sampled ($N = 114$)
Malignant, *n* (%)	29 (35.4%)	5 (20.0%)	34 (29.8%)
Non-small cell lung cancer	24 (29.3%)	2 (8.0%)	26 (22.8%)
Adenocarcinoma	20 (24.4%)	1 (4.0%)	21 (18.4%)
Squamous cell carcinoma	4 (4.9%)	0 (0%)	4 (3.5%)
Not otherwise specified	0 (0%)	1 (4.0%)	1 (0.9%)
Neuroendocrine tumour	1 (1.2%)	0 (0%)	1 (0.9%)
Carcinoid tumour	1 (1.2%)	0 (0%)	1 (0.9%)
Precursor neoplastic lesion	4 (4.9%)	3 (12.0%)	7 (6.1%)
Atypical adenomatous hyperplasia	2 (2.4%)	0 (0%)	2 (1.8%)
Atypical cells[a]	2 (2.4%)	2 (8.0%)	4 (3.5%)
Squamous metaplasia	0 (0%)	1 (4.0%)	1 (0.9%)
Benign, *n* (%)	10 (12.2%)	2 (8.0%)	12 (10.5%)
Pulmonary hamartoma	1 (1.2%)	0 (0%)	1 (0.9%)
Organizing pneumonia	4 (4.9%)	0 (0%)	4 (3.5%)
Pulmonary abscess	1 (1.2%)	0 (0%)	1 (0.9%)
Mycobacterium avium complex	1 (1.2%)	1 (4.0%)	2 (1.8%)
Cryptococcosis	2 (2.4%)	0 (0%)	2 (1.8%)
Granulomatous lesion	1 (1.2%)	1 (4.0%)	2 (1.8%)
Non-specific inflammation/fibrosis/atypia, *n* (%)	43 (52.4%)	18 (72.0%)	61 (53.5%)
Fibroelastosis	1 (1.2%)	0 (0%)	1 (0.9%)
Non-specific inflammation	22 (26.8%)	1 (4.0%)	23 (20.2%)
Non-specific fibrosis	6 (7.3%)	0 (0%)	6 (5.3%)
Non-specific fibrosis with inflammation	3 (3.7%)	0 (0%)	3 (2.6%)
Atypical cells[b]	2 (2.4%)	1 (4.0%)	3 (2.6%)
Reactive bronchial cells	9 (11.0%)	16 (64.0%)	25 (21.9%)
Insufficient, *n* (%)[c]	—	—	7 (6.1%)

[a]Atypical cells were suspicious and confirmed as malignant.
[b]Atypical cells with indeterminate diagnosis.
[c]Neither sufficient histologic samples nor cytologic samples were obtained for these seven lesions.

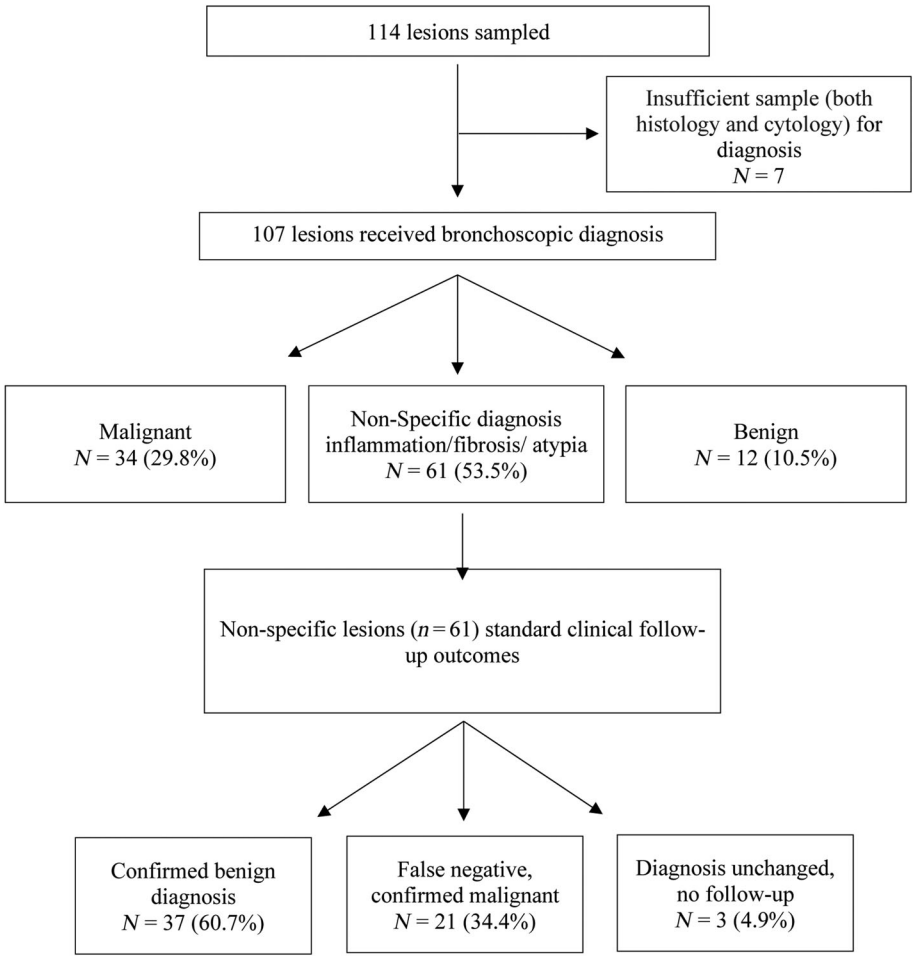

FIGURE 2 Diagnosis summary of sampled lesions. Among the 114 lesions sampled, seven had insufficient sample to make any diagnosis, 34 were positive for a malignant diagnosis, 12 were positive for a definite benign diagnosis and 61 were characterized as non-specific inflammation/fibrosis/atypia. Final diagnosis of the 61 non-specific lesions was determined based on subsequent standard clinical follow-up, with confirmed benign in 37 lesions and malignant in 21 lesions. The remaining three lesions had no follow-up reported

Adverse events

Three adverse events (2.9%) were documented. There were two pneumothoraxes (1.9%), but neither required intervention with a chest tube. One patient who had mild bleeding (1.0%) required clearing with suction and instillation of epinephrine.

DISCUSSION

This was a global multicentre study in a real-world setting, evaluating VBN with fused fluoroscopy and vessel mapping technology's contribution to safe and effective sampling of pulmonary lesions via BTPNA and guided TBNA. We reported a biopsy yield of 75.4% and a sampling yield of 93.9% in the study.

Diagnostic yield of different modalities of bronchoscopy has been widely studied. A diagnostic yield of 38.5%–80% was reported when using alone or combination of different guided bronchoscopy, which depended on lesion size, lesion location and the presence of a CT-BS.[15–19] In a randomized trial, a 3-mm ultrathin bronchoscope showed a higher yield of 70.1% versus 58.7% with thin bronchoscope (4 mm) combined with R-EBUS, VBN and fluoroscopy.[20] Recently, robotic bronchoscopy has shown promise, with a retrospective review revealing successful navigation yield of 88.6%, diagnostic yield of 69.1%–77%, tissue obtained in 98.8% of cases and a 3.6% pneumothorax rate.[18,21,22]

Despite the development of new technologies to improve the bronchoscopic diagnosis,[23] they were limited to the presence of airway leading to the lesion. Only 59.1% and 22.6% of positive rates were achieved for conventional TBNA and TBB, respectively, when the EBUS probe was adjacent to lesions,[24] and reduced to 31% even using ENB in lesions with no discernible BS.[6] The first-in-human trial using BTPNA was reported to yield accurate diagnostic biopsies in 10 of 12 patients.[12] An early case series of BTPNA reported that all five patients had adequate biopsies.[25] For this large-scale study, the diagnostic yield was 75.4% on the high estimate or 72.8% on the low estimate independent of the presence of CT-BS, with diagnostic yields of 74.1% and 71.4% for CT-BS B and CT-BS C, respectively. This significantly improved the diagnostic yield in lesions with absence of CT-BS.

Subgroup analysis and multivariate analysis identified lesion size and procedure techniques as independent diagnostic predictors, but BS was not due to smaller lesion size in CT-BS C group than the other two groups (Table S3 in the Supporting Information), which demonstrated the diagnostic value of BTPNA and guided TBNA. Moreover, all these factors showed no difference on sampling yield.

Guided TBNA with fluoroscopy has been shown to have a higher yield than TBB and even yields when a CT-BS was present, lesions were larger (>3 cm) and lesions were malignant.[26] Theoretically, guided TBNA yields better than biopsy forceps when the lesion is adjacent to the R-EBUS probe because it can penetrate into the bronchial wall and sample the peribronchial tissues.[24,27] We reported biopsy yields of 67.2% and 86.3%, and sampling yields of 96.9% and 90.2%, when using guided TBNA or BTPNA with Archimedes system, respectively. In lesions with a tunnel length ≥ 30 mm, both biopsy yield and sampling yield exceeded 90%. BTPNA had a relatively higher biopsy yield compared to guided TBNA, which may be due to the ability of BTPNA to create a tunnel directly to the lesion, but at the same time, a longer average lesion access time was taken for BTPNA procedure than guided TBNA. Meanwhile, the sampling yield was not reduced in scenarios which may typically lower the yield of conventional bronchoscopy, such as the absence of a CT-BS, the lesion being <20 mm in size, distance from the pleura <20 mm or an upper lobe location.

The complication rate was low with 2 (1.9%) pneumothorax rate in the sampling population especially when considering that 51 (44.3%) lesions were sampled via BTPNA, including 32 lesions that required a tunnel length of ≥30 mm. Our study shows a significantly lower pneumothorax rate in patients receiving BTPNA than previous study.[25] Additionally, three lesions had sampling cessation due to anatomic anomaly/pulsating vessels revealed by Archimedes, which showed the safety of the technology.

Several limitations are considered. First, pre-sample size calculation was not conducted due to a real-world study setting and the expected enrolment sample size was not reached. Further studies will be more rigorous in sample size calculation based on the results of the current study. Second, specialized operators, centres and the need for specialized technology may limit its generalizability to conventional clinical practice. Third, many lesions got non-specific inflammatory diagnosis, which may hinder accurate evaluation of this study, although the patients were followed up for approximately 1 year. Meanwhile, some lesions with an airway directly leading to that can be sampled through conventional bronchoscopy were enrolled in this study. Because it is not always easy to predict, such lesions will be confirmed at conventional bronchoscopy therefore obviating the need for more complex procedures. Studies excluding such lesions can be conducted to further evaluate the value of this technology.

The study demonstrates that VBN with fused fluoroscopy and vessel mapping can safely achieve a relatively high biopsy yield with multiple techniques and acceptable procedure durations. A relatively high biopsy yield was obtained independent of the presence or absence of a BS, and high sampling yield and diagnostic yield were obtained independent of location, lesion size and presence or absence of a BS.

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CONFLICT OF INTEREST

The trial was sponsored by Broncus Medical.

AUTHOR CONTRIBUTION

Gerard J. Criner: Formal analysis (equal); investigation (equal); methodology (equal); resources (equal); validation (supporting); writing – review and editing (equal). **David Dibardino:** Resources (equal); validation (equal); writing – review and editing (equal). **Shiyue Li:** Resources (equal); validation (equal); writing – review and editing (equal). **Daniel Nader:** Resources (equal); validation (equal); writing – review and editing (equal). **Bing Lam:** Resources (equal); validation (equal); writing – review and editing (equal). **Lisa Kopas:** Resources (equal); validation (equal); writing – review and editing (equal). **Momen M. Wahidi:** Resources (equal); validation (equal); writing – review and editing (equal). **Adnan Majid:** Resources (equal); validation (equal); writing – review and editing (equal). **Robert Marron:** Resources (equal); validation (equal); writing – review and editing (equal). **Steven Verga:** Resources (equal); validation (equal); writing – review and editing (equal). **Jiayuan Sun:** Formal analysis (equal); resources (lead); validation (equal); writing – original draft (lead); writing – review and editing (equal). **Felix F. J. Herth:** Conceptualization (lead); data curation (lead); formal analysis (lead); methodology (lead); project administration (lead); resources (equal); supervision (lead); validation (equal); writing – review and editing (equal).

DATA AVAILABILITY STATEMENT

Individual participant data (including text, tables, figures and appendices) that underlie the results reported in this article after deidentification are available. Meanwhile, the study protocol is available at https://clinicaltrials.gov/ct2/show/NCT02867371. The data would be available immediately following publication and with no end date. Researchers who provide a methodologically sound proposal and make data analysis to achieve aims in the approved proposal would be shared these data. Proposals should be directed to felix.herth@med.uni-heidelberg.de.

HUMAN ETHICS APPROVAL STATEMENT

The study was approved by the Human Research Ethics Committees and Institutional Review Boards of all participating study sites. All participants provided written informed consent prior to enrolment. Clinical trial registration: NCT02867371 at clinicaltrials.gov.

ORCID

Jiayuan Sun https://orcid.org/0000-0003-3158-3256
David Dibardino https://orcid.org/0000-0003-2524-1348

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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