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First Human Use of a New Robotic-Assisted Fiber Optic Sensing Navigation System for Small Peripheral Pulmonary Nodules

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Keywords
Lung biopsy · Solitary pulmonary nodule · Robotic bronchoscopy · Lung cancer

Abstract
Background: We tested a new, investigational robotic-assisted bronchoscope system with a remotely controlled catheter to access small peripheral bronchi with real-time driving under live visualization and distal tip articulation of the catheter. The unique catheter remains stationary once located at the biopsy position. ***Objectives:*** The primary objectives of this study were to evaluate the safety and feasibility of a new shape-sensing robotic bronchoscope system to bronchoscopically approach and facilitate the sampling of small peripheral pulmonary nodules of 1–3 cm. Secondary objectives included evaluating procedural characteristics and early performance trends associated with the use of the new robotic bronchoscope system. ***Methods:*** Subjects were enrolled according to study eligibility criteria at a single center. Navigation pathways were semi-automatically created using pre-procedure CT scans. Simultaneous (real-time) viewing of actual and virtual bronchi was used real time during navigation to the displayed target. An endobronchial ultrasound mini-probe was used to confirm lesion location. Flexible 19- to 23-G needles specifically designed to accommodate tight bend radii in transbronchial needle aspiration were used along with conventional biopsy tools. Enrolled subjects completed follow-up visits up to 6 months after the procedure. ***Results:*** The study included 29 subjects with a mean lesion size of 12.2 ± 4.2, 12.3 ± 3.3, and 11.7 ± 4.1 mm in the axial, coronal, and sagittal planes, respectively. The CT bronchus sign was absent in 41.4% of cases. In 96.6% of cases, the target was reached, and samples were obtained. No device-related adverse events and no instances of pneumothorax or excessive bleeding were observed during the procedure. Early performance trends demonstrated an overall diagnostic yield of 79.3% and a diagnostic yield for malignancy of 88%. ***Conclusion:*** This new robotic-assisted bronchoscope system safely navigated to very small peripheral airways under continuous visualization, and through maintenance of a static position, it provides a unique sampling capability for the biopsy of small solitary pulmonary nodules.

Results from this study were presented at the annual CHEST Meeting on November 1, 2017, as an original investigation during the Interventional Pulmonary Procedures Session by D.I.K. Fielding.

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Introduction

Lung cancer remains the most common cause of cancer death in the industrialized world [1]. Recent studies prompted an uptake of CT screening for lung cancer resulting in an increasing incidence of pulmonary nodules [2, 3]. Guidelines recommend tissue diagnosis for lesions ≥8 mm – either bronchoscopically or by CT needle sampling [4]. Bronchoscopic methods for sampling peripheral nodules have improved in terms of diagnosis, progressing from X-ray fluoroscopic guidance to radial endobronchial ultrasound (rEBUS) mini-probe with guide sheath, virtual bronchoscopy, and systems combining specific biopsy instruments aligned to virtual pathways (75–80% yield) [5–7]. Electromagnetic Navigation (ENB) and ultrathin bronchoscopy are important aspects of improvements that address navigation and peripheral access difficulties [8].

Although technology has progressed, the diagnostic yield of bronchoscopic methods remains low (40–60%) compared to CT fine needle aspiration, particularly for lesions <2 cm [7, 9]. Conversely, bronchoscopic methods of sampling small peripheral nodules have an excellent safety profile with negligible pneumothorax and bleeding risk [10]. This compares to higher pneumothorax, chest tube insertion, and admission rates after CT-guided needle sampling. Hence, there is a need for bronchoscopic approaches which improve diagnostic rates with a favorable risk profile.

This first-in-human study evaluated the safety and clinical feasibility of a novel robotic-assisted bronchoscope system designed to mitigate current limitations to sample solitary peripheral nodules. This system combines a robotically controlled catheter, with direct airway visualization, navigated through the airways along a virtual pathway to a target nodule. The robotic components allow controlled advancement of the catheter as well as fine directional movements in all planes at the catheter tip. When not being advanced, the catheter maintains a single position and angulation, with a sufficiently large internal diameter (2 mm) to allow passage of biopsy instruments.

Materials and Methods

This prospective study was registered (ANZCTR: ACTRN12616001185459) and received Ethics Board approval; it was conducted at the Royal Brisbane and Women's Hospital from September 2016 to July 2017 (HREC/16/QRBW/274). Subject eligibility was based on study criteria (online suppl. 1; for all online suppl. material, see www.karger.com/doi/10.1159/000498951). The Intuitive Robotic Bronchoscope System (Intuitive Surgical, Sunnyvale, CA, USA) evaluated was the first version for human use, and it includes a planning station, a system cart with monitor to display real-time visualization (Fig. 1a), and instruments, including an articulating, flexible catheter instrument (outer diameter ~3.4 mm) (Fig. 1d). The catheter incorporates a shape-sensing fiber along its entire length which provides positional and shape feedback. A video probe is used for live visualization while driving the catheter. A flexible biopsy needle (Fig. 1c), extendable up to 3 cm, was developed for the use within the periphery, and the catheter allows the use of conventional biopsy forceps, biopsy brushes, and mini-lavage compatible with a 2-mm tool channel. Once the vision probe is removed, the operator still receives feedback through the displayed catheter shape in real time confirming non-slippage. The provided distance from the catheter tip to the lesion allows for controlled transbronchial needle aspiration (TBNA) needle stroke length setting and extension distance of biopsy forceps and brush. When close to the pleura, the software provides the optimal angle for fluoroscopy, facilitating an accurate planar view for perpendicular views of needle advancement. The biopsy needle can be visualized along its length, and its length can be set not only to miss the pleura but also to reach the middle of the nodule.

The primary feasibility endpoint evaluated the ability to access pulmonary nodule(s) and retrieve tissue sample(s) from a preplanned location based on CT and identified by the planning station, characterized by a histological or cytological feature other than bronchial epithelial cells or lung parenchyma. The primary safety endpoint included peri-procedure pneumothorax and bleeding requiring intervention. Bleeding was considered mild if suctioning was sufficient, moderate if intervention including wedging of the catheter or saline administration was required, and severe if an intervention including the placement of a balloon blocker, fibrin sealant, or transfusion was required. Complications were reviewed for severity and their potential relationship to the system by an independent physician with an extensive background in interventional pulmonology.

Categorical variables are summarized by percentage; continuous variables are summarized by mean, standard deviation, and range. Early performance trends including yield for malignancy and specificity for follow-ups up to 6 months were evaluated [11, 12]. For the comparison of branch points reached with the study system and conventional bronchoscope during the survey performed, a paired *t* test was used with $p \leq 0.05$ considered significant. The statistical software package SAS® version 9.4 (SAS Institute, Cary, NC, USA) was used.

Procedure

A pre-procedure CT (non-contrast, axial volumetric acquisition with 1-mm reconstruction slices in the lung window) allowed virtual planning through semiautomatic pathway creation using Apollo® software (Vida Diagnostics, Coralville, IA, USA). If the pathway did not reach the target, manual segmentation of all airways in the vicinity of the lesion was performed. The procedures were performed by 2 experienced interventional pulmonologists with 23 and 15 years of experience, respectively. All cases were performed with endotracheal intubation under general anesthesia; in most cases, muscle relaxants were also administered. The size of the endotracheal tube used ranged from 7.5 to 9 mm, with 8 mm being the most common size used. Conventional bronchoscopy (P180; Olympus Medical Systems, To-

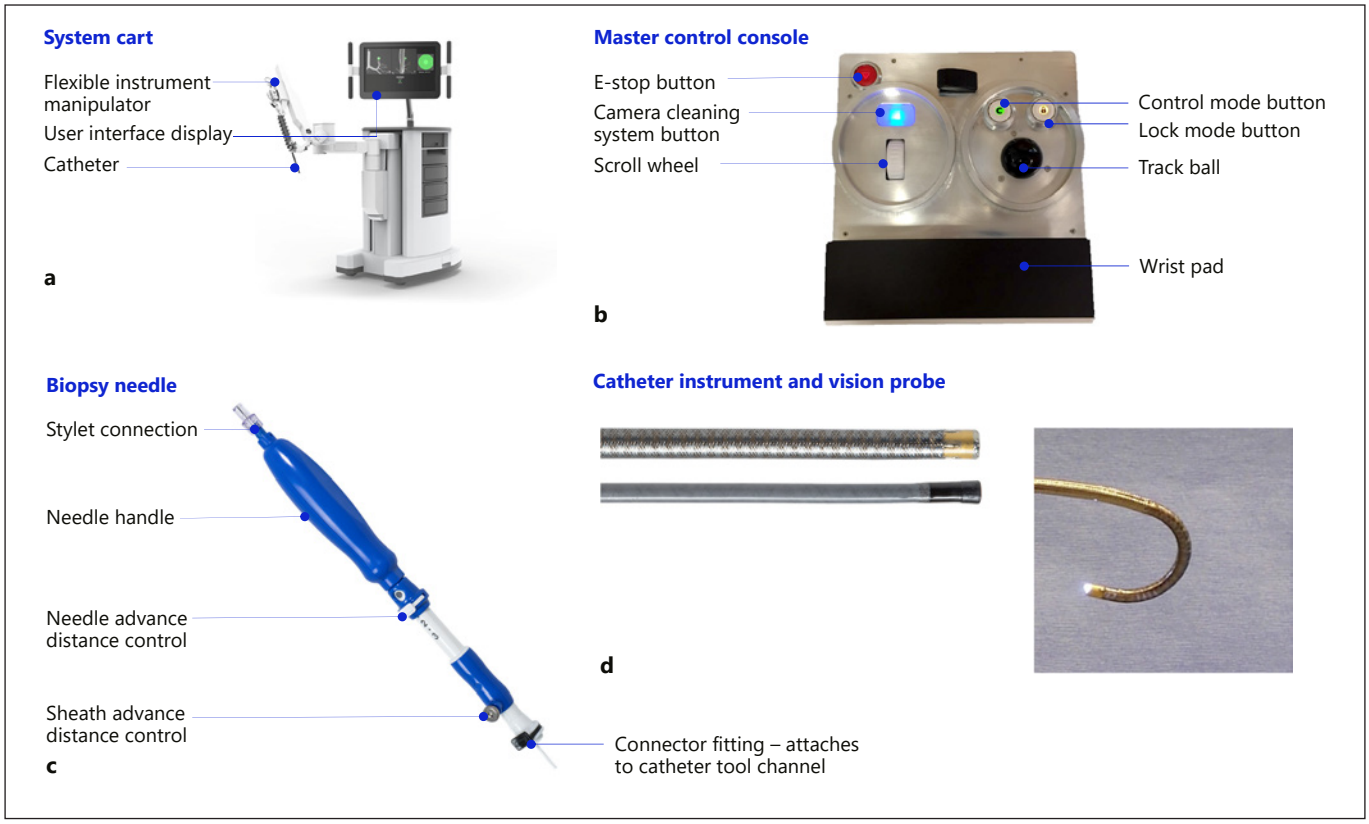

Fig. 1. a IROB study system. **b** Master control console with trackball/scroll wheel interface. **c** Vision probe and catheter instrument with catheter instrument in articulated position. **d** Study-specific flexible biopsy needle.

kyo, Japan; 4.4 mm) was performed prior to catheter insertion to inspect airways and clear secretions. The system was docked on the housing of a swivel connector connected to a conventional endotracheal tube. The catheter passed through the swivel connector and endotracheal tube into the trachea. The robotic catheter was manipulated with a trackball/scroll wheel user interface. To align actual and virtual bronchi, registration was performed by driving the catheter through segments of both bronchial tree sides. Navigation followed the virtual pathway using live visualization of the airways, which was simultaneously displayed next to the virtual pathway on the system cart monitor (Fig. 2a). Prior to sampling, the catheter was locked in a stationary position, and the optic was removed; a 1.7-mm rEBUS miniprobe (Olympus Australia Pty Ltd, Victoria, Australia) was deployed after navigation was completed to refine biopsy positioning. Sampling at the discretion of the physician included TBNA using system-specific needles as well as conventional biopsy tools. ROSE was available for TBNA, forceps, and brush samples [13]. Catheter tip redirection enabled directed sampling from different parts of the lesion as shown by the virtual view (Fig. 2b, c).

Fluoroscopy was used during biopsies and to assess for pneumothorax during and at the end of the procedure. Prior to extubation, the airways were visually inspected for bleeding or injury. A chest X-ray was performed at least 2 h after the procedure to assess delayed pneumothorax. All subjects were required to complete 3 pre-specified follow-up visits (7 days, 3 months and 6 months) unless a subsequent diagnostic or therapeutic intervention was performed. Disease assessment used pathology from the sample obtained through the study procedure and confirmed through up to 6 months per standard of care.

Results

Thirty subjects underwent a biopsy attempt; 1 subject was later found to be ineligible due to previous radiotherapy and was excluded from the analysis. The mean patient age was 63.2 years ± 9.7 years, with an almost even distribution of gender. The most commonly reported comorbidities included chronic obstructive pulmonary disease, prior history of extrapulmonary malignancy, and hypertension. Eleven subjects (36.7%) had previously undergone biopsy attempts (Table 1).

Characteristics of target solitary peripheral nodules are provided in Table 2; notably, in the axial dimension, 23 nodules (79.3%) were <2 cm in the largest diameter.

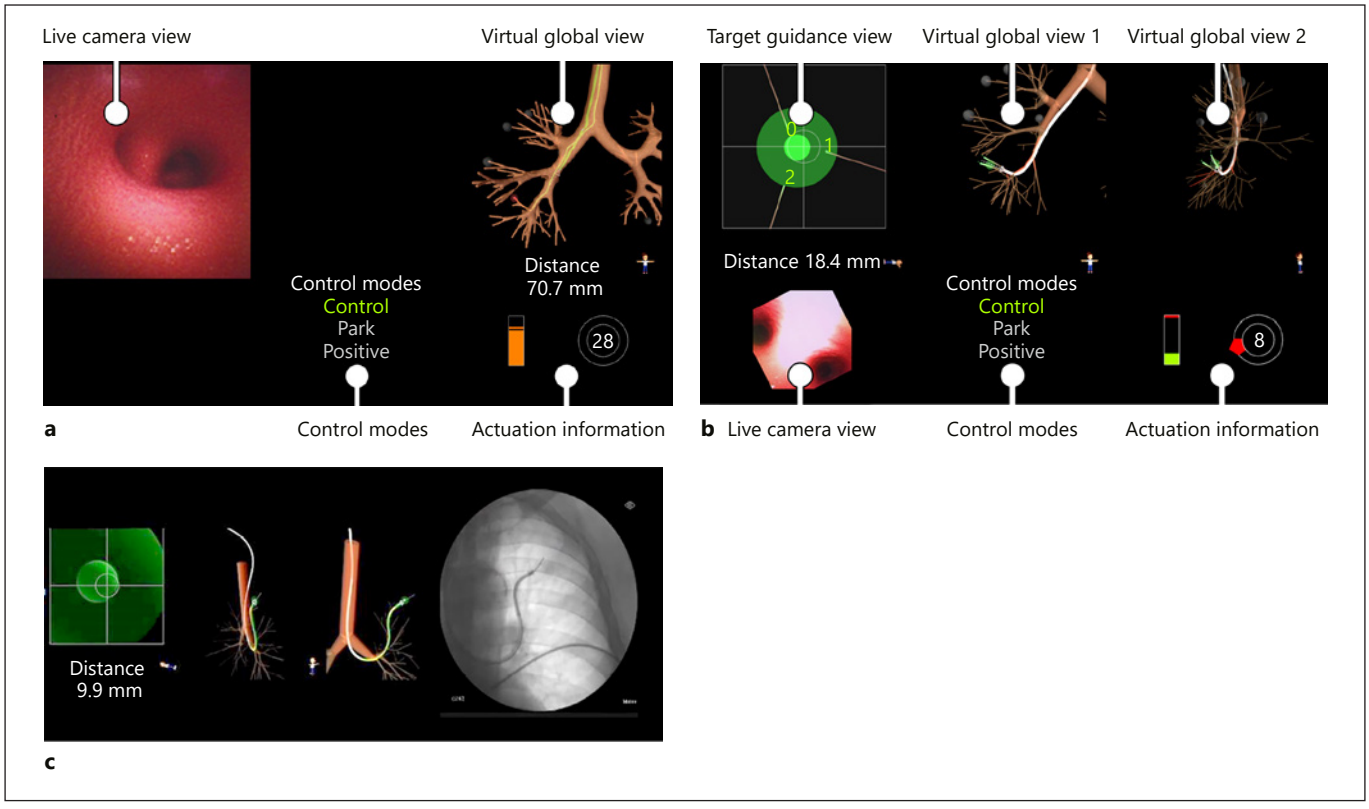

Fig. 2. a Clinician view – real-time visualization of the airways from the vision probe and simultaneous global view with shape-sensing fiber displaying the position of the catheter moving towards the target location. **b** Clinician display during the biopsy attempt. **c** Visualization of the target and simultaneous global view with shape-sensing fiber displaying the position of the catheter in the airways. Real-time fluoroscopy view demonstrates the catheter position through tortuous airways with a system-specific biopsy needle extended during the biopsy attempt.

The majority of nodules were in the upper lobes (69%) (online suppl. Fig. 1). rEBUS visualization was reported for 27 (93.1%) subjects with 1 additional subject visualized on rEBUS; however, the image pattern was not recorded. Only 17 (58.6%) lesions had a bronchus sign visible on CT, and approximately half of the cases had an eccentric rEBUS image. When catheter advancement was challenging in very small peripheral airways in a small number of cases and the target was reachable per virtual distance, the rEBUS probe was extended, and the best angle of the catheter giving the best rEBUS image was held.

Procedure characteristics are provided in Table 3. Procedure time, defined as catheter insertion to removal, was 63.9 ± 24.4 min; mean procedure time of the first and last 5 cases was approximately 95 and 61 min, respectively. The mean number of biopsy attempts, characterized by a series of tool passes and subsequent repositioning of the catheter, was 2.6 ± 1.8. The most common needles sizes were 21 + 23 G (24.1%) and 19 + 21 G (24.1%). Furthermore, the catheter instrument reached significantly further than the standard bronchoscope used; a comparison of branch points reached yielded a mean difference of 2.21 ± 1.2 (95% confidence interval, CI: 1.76–2.67, $p < 0.001$).

There were no instances of pneumothorax or bleeding requiring intervention observed (95% CI: 0.0–11.9%), and no airway injury was reported. No instances of unexpected bleeding, which included any type of bleeding that required prolonged or continuous suction, were reported. Although the vision probe is removed to facilitate the introduction of biopsy tools through the catheter, there were no concerns regarding the absence of live visualization during the biopsy as fluoroscopy provided feedback over the tool-tissue and tool-catheter interaction. No complications were related to the study system; 2 subjects experienced procedure-related complications (CTCAE >2): 1 subject experienced an adverse reaction

Table 1. Subject demographics (n = 29)

Age (mean ± SD), years	63.2±9.7
Range	41.0–79.0
BMI (mean ± SD), kg/m²	26.7±6.6
Range	16.3–41.1
Gender	
Male:female ratio	14:15
ECOG performance status	
Grade 0	16 (55.2)
Grade 1	12 (43.3)
Grade 2	1 (3.3)
American Society of Anesthesiologists	
Class 2	21 (72.4)
Class 3	8 (27.6)
Subjects with comorbidities	29 (100.0)
COPD	13 (44.8)
Prior cancer/history of other malignancy	13 (44.8)
Hypertension	12 (41.4)
Emphysema	9 (31.0)
Cardiovascular disease	7 (24.1)
Diabetes	4 (13.8)
Family history of lung cancer	2 (6.9)
Esophageal stricture	1 (3.4)
Other nonrespiratory comorbidities	11 (36.7)
Other respiratory comorbidities	5 (16.6)
Smoking status	
Current smokers	11 (37.9)
Previous smokers	15 (51.7)
No history of smoking	3 (10.3)
Likelihood of SPN (mean ± SD)	24.8±17.4

Data are numbers (%) unless indicated otherwise. The ECOG performance status describes, on a scale from 0 to 5, a patient's activity level in terms of their ability to care for themselves, daily activity, and physical ability [25]. Comorbidities are not mutually exclusive as subjects may have had >1 comorbidity. COPD, chronic obstructive pulmonary disease; SPN, solitary peripheral nodules

to a muscle relaxant resulting in delayed re-paralysis, which resolved with additional administration of a muscle relaxant reversal agent and overnight observation. After being discharged, another subject developed contralateral bronchopneumonia the day following the procedure, which resolved after hospital admission and standard treatment including intravenous antibiotics, nebulized bronchodilators, oral steroids, and physiotherapy (Table 3). Most subjects (86.2%) were discharged the same day with a mean length of stay of 5.2 ± 0.6 h; with regard to the 4 overnight hospital admissions, only 1 was for a clinical observation of the muscle relaxant complication, while the other 3 admissions were preplanned.

The primary feasibility endpoint (Table 4) was achieved in 28 (96.6%) cases where the target nodule was reached with a tissue sample supportive of a histological or cytological assessment with feature(s) other than bronchial epithelial cells or lung parenchyma obtained. The nodule in the first case (11.1 mm in diameter in the apical segment of the right upper lobe) was not reached, likely due to system acclimation and a challenging nodule location. Early performance trends through the 6-month follow-up demonstrated an overall diagnostic yield of 79.3% (95% CI: 60.3–92.0%), with a diagnostic yield for malignancy (sensitivity) trending towards 88.2% (95% CI: 63.6–98.5%) and specificity trending towards 63.6% (95% CI: 30.8–89.1%). However, it should be noted that this was not designed as a performance study.

Discussion/Conclusion

The results of the first-in-human evaluation of a novel robotic bronchoscope system in a cohort of very small peripheral nodules are very encouraging. The system demonstrated a strong safety profile, with no instances of pneumothorax or bleeding observed. The majority of the procedure-related complications reported are commonly associated with the use of an endotracheal tube or general anesthesia.

Regarding safety, the non-slippage of the catheter, the combination with fluoroscopy, and a continuous virtual display of the actual catheter position confirmed that no inadvertent movement of the catheter occurred. No bronchial injury occurred because forward movement of the catheter was only possible when the visualizing optic was in situ. Of note, while no bleeding was observed, bleeding management training in a preclinical setting is worth mentioning. This experience confirmed the catheter can stop bleeding by tamponading the airway where it sits, similar to the guide sheath used in rEBUS procedures, which have a low incidence of bleeding [14]. Airway bleeding can be detected when the vision probe is reinserted during repositioning throughout the procedure. The absence of bleeding was confirmed by visual inspection at the end of the procedure. If bleeding had occurred, it could have been managed through the deployment of an endoluminal tamponade balloon through the catheter or through quick system disengagement allowing access for intervention. Additionally, while the observed pneumothorax rate in this first human use experience is 0%,

Table 2. Target nodule characteristics (n = 29)

Target nodule size (mean ± SD) [range], mm	
Axial diameter	12.2±4.2 [6.7–22.0]
Coronal diameter	12.3±3.3 [5.9–21.1]
Sagittal diameter	11.7±4.1 [4.5–26.4]
Largest diameter in any dimension	14.8±4.5 [10.0–26.4]
Nodule/lesion location, n (%)	
Left upper lobe	9 (31.0)
Left lower lobe	2 (6.9)
Right upper lobe	11 (37.9)
Right middle lobe	2 (6.9)
Right lower lobe	5 (17.2)
Lesion position by number of airway generations	
Mean ± SD [range]	6.7±1.4 [3.0–9.0]
Nodule edge characteristics, n (%)	
Smooth	4 (13.8)
Lobulated	8 (27.6)
Spiculated	
Slightly irregular	10 (34.5)
Grossly irregular	5 (17.2)
Other	2 (6.9)
Irregular, feature of subsegmental atelectasis	1
Smooth and lobulated	1
Nodule type, n (%)	
Solid	23 (79.3)
Semisolid/partly solid	5 (17.2)
Ground glass/nonsolid	1 (3.4)
CT bronchus sign, n (%)	
Present	17 (58.6)
Absent	12 (41.4)
EBUS characteristic, n (%)	
Concentric	14 (48.3)
Eccentric	13 (44.8)
Not visible	1 (3.3)
Not reported	1 (3.3)

which is consistent with the expected rate for biopsies performed bronchoscopically, it is important to note that lesions for enrolled subjects were at least 15 mm from the visceral pleura, which may have influenced the observed pneumothorax incidence.

The methodology is similar to the principles of virtual bronchoscopy [15], enabling good decision making at peripheral branch points. Navigating the thin catheter into the periphery under real-time visualization displayed several smaller airways not visible on CT. Also, we could visualize subtle endobronchial disease in very peripheral parts of the lung and directly take endobronchial brushes and biopsies. As shown in the rEBUS images, half of the lesions were extrinsic to the bronchus, so it was important that peripheral airway visualization enabled better decision making for the TBNA needle deployment site, specifically the most perpendicular location to facilitate the exit of the needle from the bronchus towards the lesion. The controlled articulation provided by the system facilitated optimal rEBUS operation, refining the technique described by Kurimoto et al. [16] to find the best bronchoscope angulation for the best EBUS image, after which samples are taken through a guide sheath. Other dedicated navigational methods [17, 18] rely on virtual redirection of the catheter, theoretically making subtle adjustments of the catheter position in small airways more difficult. The facilitation of these fine adjustments enabled the biopsy of different areas of the same target with subtle distal tip adjustments or movements, or a cloud biopsy approach, which was utilized to obtain tissue samples from locations around the target nodule location.

Through CT planning, we could segment a path to the nodule in all cases, even for very peripheral lesions. The eligibility criteria required pulmonary nodules to be bronchoscopically accessible within 3 cm on CT reconstruction through the planning software, which was visually assessed by the physician planning and performing the procedure, and may have provided the physician with an initial idea as to the virtual proximity of the nodule. The ability to perform manual segmentation was helpful for bronchus sign-negative lesions as landmarks including pulmonary vasculature were used to complete segmentation of the path. Therefore, despite CT bronchus sign absence in more than 40% of subjects, over 93% of the nodules were visible using rEBUS.

Wang-Memoli et al. [7] reported a meta-analysis of studies utilizing complementary technologies in the diagnosis of peripheral nodules , establishing the weighted yield as significantly better than that of conventional bronchoscopy, but the yield still remains lower than that of transthoracic needle aspiration [9]. The diagnostic yields of lesions ≤20 mm were reported as 60.9% (95% CI, 54.0–67.7%) and 82.5% (95% CI, 78.6–86.4%) respectively, although it should be noted that the meta-analysis included both benign and malignant yields. Although this current series was a first-in-human use of novel technology with a mean lesion size <2 cm, early performance trends in a population of mostly small peripheral lesions demonstrated a diagnostic yield for malignancy >85%. Of note, the population enrolled in this study had a moderate likelihood of malignancy or suspicion of metastatic disease, as the highest likelihood for malignancy was 67.4%. More so than with nonactuated

Table 3. Procedure and safety characteristics (n = 29[1])

Means ± SD (ranges)	
Bronchoscopy suite time, min	103.6±33.5 (60.0–209.0)
Procedure time[2], min	63.9±24.4 (26.0–141.0)
Anesthesia time, min	93.8±30.1 (46.0–193.0)
Fluoroscopy time, min	11.0±4.8 (2.0–22.0)
Biopsy attempts, *n*	2.6±1.8 (1.0–7.0)
Sampling method – overall, n[3]	
System-specific biopsy needle	28 (96.6%)
OTS brush	22 (75.9%)
OTS forceps	20 (69.0%)
OTS BAL/wash	25 (86.2%)
Periprocedural pneumothorax, all grades, *n*	0 (0%)
95% exact Clopper-Pearson binomial CI	0.0–11.9%
Periprocedural bleeding, all grades, *n*	0 (0%)
95% exact Clopper-Pearson binomial CI	0.0–11.9%
Device-related complications, *n*	0 (0%)
CTCAE >2 complications reported, *n*	2
Adverse reaction to anesthesia	1
Contralateral pneumonia	1
CTCAE ≤2 complications reported, *n*[4]	8

OTS, off the shelf; BAL, bronchoalveolar lavage; CI, confidence interval.
[1] The excluded subject was included in the safety analysis due to the design of this study.
[2] Defined as time from catheter in to catheter out.
[3] One subject may have more than 1 response, so overall counts and percentages may not add up.
[4] Complications included sore throat/throat pain, unrelated chest infection, headache, or nausea. Unrelated chest infections include pseudomonas in a bronchus unrelated to the nodule in 1 subject with a previous tracheostomy and 1 subject reporting a self-limiting respiratory infection approximately 5.5 months after the procedure.

Table 4. Clinical feasibility outcome and early performance trends (n = 29)

Target nodule reached and sample obtained, *n* (%)	28 (96.6)
95% CI	82.2–99.9%
Diagnostic yield trend – sample obtained by system, *n* (%)	23 (79.3)
Malignant	15 (51.7)
Benign	08 (27.6)
Inconclusive	06 (20.7)
Physician-assessed disease status through 6 months, *n* (%)	
Malignant	17 (58.6)
Benign	11 (37.9)
Indeterminate	1 (3.4)
Reported tumor characteristics	
Tumor size (mean ± SD), mm[1]	15.4±6.3
Primary lung cancer, *n* (%)	15 (83.3)

[1] When the pathologic size was not available, the largest diameter of the target nodule was used as approximation of the tumor size. Tumor size was provided for all nodules with malignant assessment through the follow-up.

endoluminal devices, distal tip articulation facilitated orientation of instruments by gently deforming the airway towards the target which may contribute to these performance trends.

Furthermore, studies by Minezawa et al. [19] and Nakai et al. [20] have described the impact of a bronchus sign as an influential factor for the diagnostic yield in nonnavigational bronchoscopic cases. Electromagnetic navigation has been described elsewhere. One study [21] showed that the diagnostic yield of rEBUS combined with ENB (88%) was greater than that of rEBUS (69%) or ENB alone (59%; p = 0.02). The yield of the combined procedure was independent of lesion size or lobar distribution. In another study [22] utilizing electromagnetic navigation with EBUS at completion of navigation, the diagnostic yield was 93% when EBUS verified the lesion location but only 48% when the location was not confirmed in lesions with a mean diameter of 23.3 mm. Notably, many studies evaluating ENB required subjects to have a bronchus sign or to be of much larger nodule size, which have been shown

to be factors influencing the diagnostic yield [11], and these results have not been able to be reproduced consistently outside of a controlled research setting [23].

Of note, Rojas-Solano et al. [24] published a first human use case series evaluating the feasibility of a different robotic bronchoscopy system with an outer diameter of 3.2 mm and a 1.2-mm working channel. A total of 15 subjects underwent bronchoscopy with the robotic system, and no instances of pneumothorax or bleeding requiring intervention were reported for tissue acquired in 93% of the subjects. While the initial safety and feasibility results are similar in the current series, it should be noted that median lesion size was 26 mm with a range up to 63 mm, and subjects were selected based on the presence of a bronchus sign ,whereas in the current series subjects had both bronchus sign present and absent, and a mean nodule size of approximately 14.8 mm and a range up to 26.6 mm.

Some potential limitations are worth mentioning. rEBUS was used for lesion location confirmation at the end of navigation; most studies of dedicated navigational bronchoscopy utilize rEBUS, and the catheter design facilitated quick deployment of the rEBUS probe to allow the choice of needle aspiration in cases where there was an eccentric image. Secondly, the procedures required general anesthesia and endotracheal intubation to allow stabilization of the robotic catheter insertion. Many bronchoscopy units perform general anesthetic procedures; however, the requirement for a deeper level of anesthesia may limit applicability to patients with higher ASA status or for units that perform peripheral bronchoscopy under conscious sedation. With regard to the study, this was a single center study with 2 experienced operators and a controlled population. However, selection was in accordance with bronchoscopy guidelines and not based on lesion location or bronchus sign. Lastly, the 6-month follow-up period of this study was to ensure safety and feasibility; studies which focus on diagnostic performance may require a longer follow-up.

In conclusion, this new robotic bronchoscopy system shows great promise for safe and effective sampling of small peripheral pulmonary nodules. Multicenter studies are planned to assess its performance in a larger cohort and confirm the results of this study.

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Statement of Ethics

This study was conducted in accordance with the amended Declaration of Helsinki. The Royal Brisbane and Women's Human Research Ethics Committee (HREC) approved the protocol, and written informed consent was obtained from all participating subjects.

This study was registered at the Australian New Zealand Clinical Trial Registry (ACTRN12616001185459).

Disclosure Statement

The authors report no conflict of interest for any author related to this effort with the exception of sponsorship for study planning and execution by Intuitive Surgical.

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Author Contributions

All authors made substantial contributions to the study conduct and manuscript review, including study design (D.I.K.F., F.B.), data acquisition (D.I.K.F., F.B., J.H.S., M.T., A.C., L.T., K.S., M.N.W.), data interpretation (D.I.K.F., F.B.), safety review (A.W.S.), radiographic image review and data acquisition (K.S.), manuscript writing (D.I.K.F.), critical revisions (D.I.K.F., F.B., K.S., A.C., A.W.S., M.N.W.), and study oversight, review of and approval of the manuscript (all authors). The corresponding author (D.I.K.F.) is accountable for accuracy and integrity of the work.

References

1 Cheng TY, Cramb SM, Baade PD, Youlden DR, Nwogu C, Reid ME. The International Epidemiology of Lung Cancer: Latest Trends, Disparities, and Tumor Characteristics. J Thorac Oncol. 2016;11(10):1653-71.

2 Aberle DR, Adams AM, Berg CD, Black WC, Clapp JD, Fagerstrom RM, et al.; National Lung Screening Trial Research Team. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med. 2011 Aug;365(5):395–409.

3 Fintelmann FJ, Gottumukkala RV, McDermott S, Gilman MD, Lennes IT, Shepard JO. Lung Cancer Screening: Why, When, and How? Radiol Clin North Am. 2017 Nov;55(6):1163–81.
4 Rivera MP, Mehta AC, Wahidi MM. Establishing the diagnosis of lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143(5 Suppl):e142S–e165S.
5 Ishida T, Asano F, Yamazaki K, Shinagawa N, Oizumi S, Moriya H, et al.; Virtual Navigation in Japan Trial Group. Virtual bronchoscopic navigation combined with endobronchial ultrasound to diagnose small peripheral pulmonary lesions: a randomised trial. Thorax. 2011 Dec;66(12):1072–7.
6 Asano F. Advanced bronchoscopy for the diagnosis of peripheral pulmonary lesions. Respir Investig. 2016 Jul;54(4):224–9.
7 Wang Memoli JS, Nietert PJ, Silvestri GA. Meta-analysis of guided bronchoscopy for the evaluation of the pulmonary nodule. Chest. 2012 Aug;142(2):385–93.
8 Oki M, Saka H, Ando M, Asano F, Kurimoto N, Morita K, et al. Ultrathin Bronchoscopy with Multimodal Devices for Peripheral Pulmonary Lesions. A Randomized Trial. Am J Respir Crit Care Med. 2015 Aug;192(4):468–76.
9 Wong KY, Tse HN, Pak KK, Wong CC, Lok PS, Chan KC, et al. Integrated use of virtual bronchoscopy and endobronchial ultrasonography on the diagnosis of peripheral lung lesions. J Bronchology Interv Pulmonol. 2014 Jan;21(1):14–20.
10 Asano F, Aoe M, Ohsaki Y, Okada Y, Sasada S, Sato S, et al. Complications associated with endobronchial ultrasound-guided transbronchial needle aspiration: a nationwide survey by the Japan Society for Respiratory Endoscopy. Respir Res. 2013 May;14(1):50.
11 Gex G, Pralong JA, Combescure C, Seijo L, Rochat T, Soccal PM. Diagnostic yield and safety of electromagnetic navigation bronchoscopy for lung nodules: a systematic review and meta-analysis. Respiration. 2014;87(2):165-76.
12 MedCalc Statistical Software version 18.5. Ostend: MedCalc Software bvba; 2018. http://www.medcalc.org.
13 Izumo T, Matsumoto Y, Sasada S, Chavez C, Nakai T, Tsuchida T. Utility of rapid on-site cytologic evaluation during endobronchial ultrasound with a guide sheath for peripheral pulmonary lesions. Jpn J Clin Oncol. 2017 Mar;47(3):221–5.
14 Hayama M, Izumo T, Matsumoto Y, Chavez C, Tsuchida T, Sasada S. Complications with Endobronchial Ultrasound with a Guide Sheath for the Diagnosis of Peripheral Pulmonary Lesions. Respiration. 2015;90(2):129–35.
15 Oshige M, Shirakawa T, Nakamura M, Mineshita M, Kurimoto N, Miyazawa T, et al. Clinical application of virtual bronchoscopic navigation system for peripheral lung lesions. J Bronchology Interv Pulmonol. 2011 Apr;18(2):196–202.
16 Kurimoto N, Miyazawa T, Okimasa S, Maeda A, Oiwa H, Miyazu Y, et al. Endobronchial ultrasonography using a guide sheath increases the ability to diagnose peripheral pulmonary lesions endoscopically. Chest. 2004 Sep;126(3):959–65.
17 Eberhardt R, Anantham D, Ernst A, Feller-Kopman D, Herth F. Multimodality bronchoscopic diagnosis of peripheral lung lesions: a randomized controlled trial. Am J Respir Crit Care Med. 2007 Jul;176(1):36–41.
18 Krochmal R, Arias S, Yarmus L, Feller-Kopman D, Lee H. Diagnosis and management of pulmonary nodules. Expert Rev Respir Med. 2014 Dec;8(6):677–91.
19 Minezawa T, Okamura T, Yatsuya H, Yamamoto N, Morikawa S, Yamaguchi T, et al. Bronchus sign on thin-section computed tomography is a powerful predictive factor for successful transbronchial biopsy using endobronchial ultrasound with a guide sheath for small peripheral lung lesions: a retrospective observational study. BMC Med Imaging. 2015 Jun;15(1):21.
20 Nakai T, Matsumoto Y, Suzuk F, Tsuchida T, Izumo T. Predictive factors for a successful diagnostic bronchoscopy of ground-glass nodules. Ann Thorac Med. 2017 Jul-Sep;12(3):171–6.
21 Herth FJ, Eberhardt R. Endobronchial ultrasound and electromagnetic navigation bronchoscopy in the diagnosis of peripheral lung lesions. Expert Opin Med Diagn. 2008 May;2(5):461–6.
22 Eberhardt R, Morgan RK, Ernst A, Beyer T, Herth FJ. Comparison of suction catheter versus forceps biopsy for sampling of solitary pulmonary nodules guided by electromagnetic navigational bronchoscopy. Respiration. 2010;79(1):54–60.
23 Ost DE, Ernst A, Lei X, Kovitz KL, Benzaquen S, Diaz-Mendoza J, et al.; AQuIRE Bronchoscopy Registry. Diagnostic Yield and Complications of Bronchoscopy for Peripheral Lung Lesions. Results of the AQuIRE Registry. Am J Respir Crit Care Med. 2016 Jan;193(1):68–77.
24 Rojas-Solano JR, Ugalde-Gamboa L, Machuzak M. Robotic Bronchoscopy for Diagnosis of Suspected Lung Cancer: A Feasibility Study. J Bronchology Interv Pulmonol. 2018 Jul;25(3):168–75.
25 Oken M, Creech R, Tormey D, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982 Dec(6);5:649–55.