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Robotic Bronchoscopy for Diagnosis of Suspected Lung Cancer

A Feasibility Study

José R. Rojas-Solano, MD, Luis Ugalde-Gamboa, MD,* and Michael Machuzak, MD†*

Background: **Robotic bronchoscopy may offer alternative approaches to address limitations of current bronchoscopic techniques for biopsy of suspected peripheral lung lesions. This study sought to evaluate complications and feasibility of robotic bronchoscopy performed with the Robotic Endoscopy System (RES).**

Methods: **Adult patients from a single institution underwent bronchoscopy of suspected lesions with a bronchus sign with the RES. The primary outcome was complication rate, as assessed by the incidence of related serious adverse events (SAE). The secondary outcome was technical feasibility. Data are presented as median (range), counts, and percentage. *P*-value was calculated using the Mann-Whitney *U* test.**

Results: **Of 17 screened patients, 15 were eligible. The median age was 67 (38 to 79) years. The lesions (12 peripheral and 3 central) were located in the right lower lobe (33%), right upper lobe (27%), left upper lobe (27%), and left lower lobe (13%). No SAE, including pneumothorax and significant bleeding, occurred. Biopsy samples were obtained from 93% of patients. One sampling (right upper lobe) required conventional bronchoscopy and another required surgery to confirm malignancy. Cancer was confirmed in 60% (9/15) of patients. Benign features were found in 5 of 6 patients. Time to biopsy location reduced from 45 (21 to 84) minutes (first 5 cases) to 20 (7 to 47) minutes (last 9 cases), $P = 0.039$.**

Conclusions: **The study results and absence of SAE support feasibility of the RES in accessing the periphery of the lung. The RES has potential to address challenges associated with biopsy of peripheral lung lesions.**

Key Words: lung cancer, bronchoscopy, robotic bronchoscopy, robotic surgery, diagnosis of lung cancer

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Lung cancer is the leading cause of cancer-related death in the United States.[1] The 5-year survival rate (~18%) remains poor compared with other prevalent cancers, such as colon (65%), breast (90%), and prostate (99%). The low survival rate may be partially attributed to delays in diagnosis.[2] The implementation of low-dose computed tomography (CT) screening in patients with a specific risk profile may improve early detection and long-term survival.[3] In addition, lung cancer screening may lead to an increase in number of diagnostic procedures performed to characterize lung lesions.

Since the introduction of the flexible bronchoscope in 1968,[4] bronchoscopy has become a cornerstone in the evaluation of patients suspected of lung cancer.[5] Despite its wide acceptance, flexible bronchoscopy has limitations. Many peripheral lung lesions (PLL) cannot be easily accessed by currently available bronchoscopic technologies.[6] Thus, most of the PLL identified by CT imaging cannot be directly visualized by the bronchoscope.[5] In many instances, the extension of biopsy instruments into the periphery is required to access nodules. However, these instruments lack direct visualization and the steerability often necessary to access a nodule. These limitations are more obvious when PLL are small. As a result, the diagnostic accuracy of current

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From the *Clínica Bíblica Hospital, San José, Costa Rica; and †Cleveland Clinic, Cleveland, OH.

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Reprints: José R. Rojas-Solano, MD, Clínica Bíblica Hospital, San José, Av. 14, San José 10104, Costa Rica (e-mail: jrrojass@gmail.com).

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bronchoscopic approaches remains suboptimal. This leads to frequent utilization of more invasive diagnostic procedures.[7] In addition, the diagnostic accuracy may be operator dependent.[8]

Diagnostic accuracy of CT-guided transthoracic needle aspiration (CT-TTNA) for PLL is high but is associated with higher complication rates as compared with bronchoscopy[7] and requires a subsequent procedure for staging. Development of novel bronchoscopic tools and technologies such as radial probe endobronchial ultrasound (R-EBUS) and navigation systems have increased the diagnostic yield for PLL, compared with traditional transbronchial biopsy under fluoroscopy, with much lower complication rates than CT-TTNA.[9,10] Despite these advances, the diagnostic yield of transbronchial biopsy remains inferior to that of CT-TTNA. Innovative devices and techniques to improve bronchoscopic diagnostic yield while maintaining a high safety profile are desirable.

The Robotic Endoscopy System (RES, Auris Surgical Robotics, San Carlos, CA) is a robotic system developed to address the limitations of current peripheral diagnostic approaches. The RES was designed to improve peripheral reach, provide direct continuous visualization of the periphery, and offer precise control of instruments. This paper describes the initial experience with the RES in patients with suspicious lesions. The purpose of this pilot study was to assess complication rate and technical feasibility of robotic bronchoscopy performed with the RES.

METHODS

Ethics and Permissions

The local regulatory authorities (Instituto Costarricense de Investigaciones Clinicas) and the Western Institutional Review Board (Puyallup, WA) approved the study protocol. The study was prospectively registered (anzctr.org.au; trial ID ACTRN12614000984695) and conducted in accordance with the Declaration of Helsinki and Good Clinical Practices. All patients were enrolled after giving a written informed consent. All authors had access to study data, reviewed, and approved the final manuscript.

Study Design and Patients

This prospective study was carried out at the Hospital Clínica Bíblica, San Jose, Costa Rica. Patients with suspicious central or bronchus-sign PLL were enrolled (Table 1). The bronchus sign was defined as the presence of a bronchus leading to or contained within the target nodule as seen in a high-resolution chest CT scan.[11] Bronchus-sign lesions were included in this study because the CT bronchus-sign is seen in all cell types of malignant pulmonary lesions,[12] and these lesions have been shown to be associated with a higher diagnostic yield.[11] This approach was chosen because the objective of the current study were to assess technical feasibility and complications of robotic bronchoscopy performed with the RES.

TABLE 1. Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Men and women age ≥18 y	Uncontrolled or irreversible coagulopathy
Bronchus-sign lesions	A positive pregnancy test in a woman with child-bearing potential
CT scan performed within 30 d before the bronchoscopy procedure	Female subjects who are pregnant or nursing or those of child-bearing potential refusing a pregnancy test
Able and willing to give written informed consent	Participation in any other clinical trial 30 d before and throughout the duration of the study
	Any medical contraindication for bronchoscopy

CT indicates computed tomography.

RES

The RES consisted of 4 major components: the robotic endoscope, the patient-side system, controller rack, and operator console (Fig. 1).

The robotic endoscope (Fig. 2A) is comprised of a video bronchoscope and an outer sheath, which both allow 4-way steering control. This enables the telescoping capability, which may enhance the endoscope reach, stability and distal control. The bronchoscope and sheath are manipulated by 2 robotic arms under continuous, direct, visual control by a physician using an endoscopy controller. The length and the outer diameter of the bronchoscope were 1450 and 3.2 mm, respectively. The bronchoscope's design facilitates distal navigation within the airways, while providing a 1.2 mm working channel for biopsy tools. A distal view of the bronchoscope is shown in Figure 2B. The bronchoscope's distal section is capable of achieving 180 degrees of deflection in any direction. The proximal section (Fig. 2C) allows for control of irrigation and aspiration.

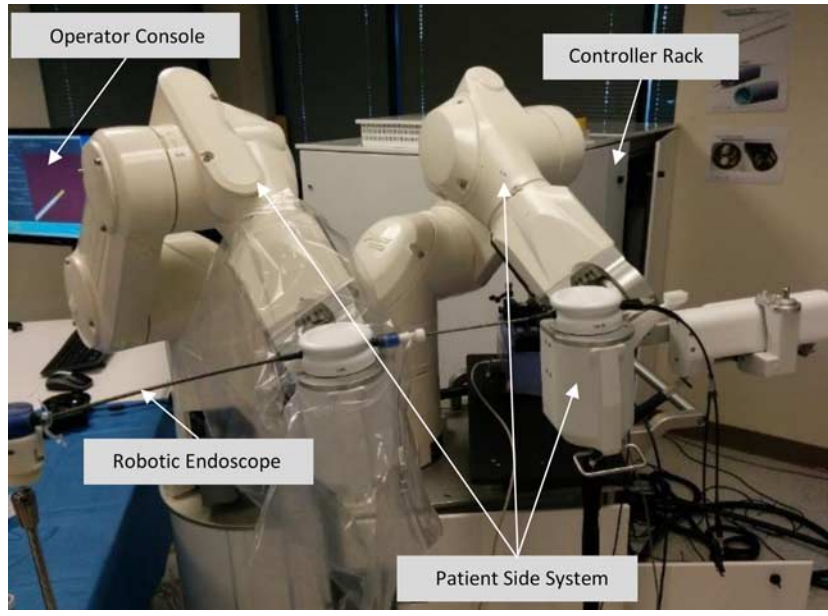

FIGURE 1. The Robotic Endoscopy System used in the study.

The irrigation and aspiration control consists of a peristaltic pump and valves. An integrated pump (Fig., Supplemental Digital Content 1, http://links.lww.com/LBR/A148) provides pressure needed to deliver saline through the endoscope. A pinch valve actuates aspiration of fluids to an external hospital vacuum. The irrigation and aspiration is under direct continuous control by the user with an endoscopy controller. The amount of saline used to irrigate is constantly displayed on the graphic user interface.

A description of the patient-side system, controller rack, and operator console is included in the Supplemental Digital Content 2 (http://links.lww.com/LBR/A149).

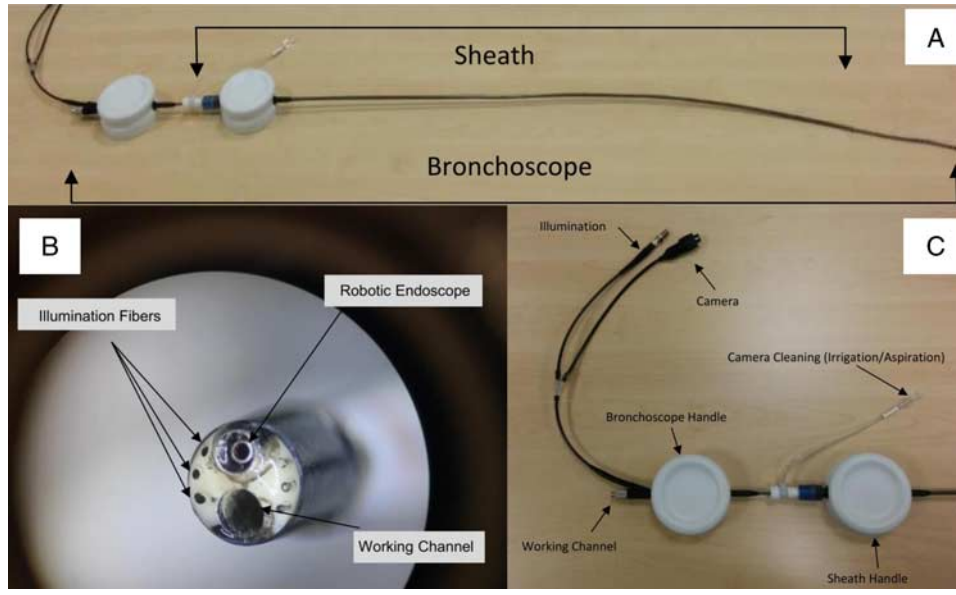

FIGURE 2. The robotic endoscope used in the study (A). A distal view of the bronchoscope (B). The bronchoscope includes a camera that provides endoscopic visualization to the operator during the procedure and integrated illumination fibers that transmit light from the proximal light source to the surgical field Robotic endoscope proximal handle (C).

Preprocedure Evaluation

Eligible patients underwent preprocedure evaluation including physical examination and baseline assessments consisting of medical history focusing on pulmonary status. Coagulation tests, complete blood cell count, and kidney function tests were performed before the procedure. Antiplatelets and anticoagulants were discontinued before the procedure consistent with the institutional protocol and were restarted 24 hours after the procedure if no bleeding persisted. Size of targeted lesions and distance to pleura were manually characterized using a digital ruler (Fig. 3). Flowcharts for immediate identification and management of pneumothorax and airway bleeding were designed before study initiation (Supplemental Digital Content 3, http://links.lww.com/LBR/A150), and a thoracic surgeon was readily available.

Robotic Bronchoscopy Procedure

Preplanning was completed for all procedures using CT scans to localize the targeted lesions. Prespecified CT scan parameters (scan field of view of 500 mm, rotation time of 0.5 s, detector configuration of 64×0.5 mm, slice thickness of 1 mm, interval of 0.5 mm) were used in all cases.

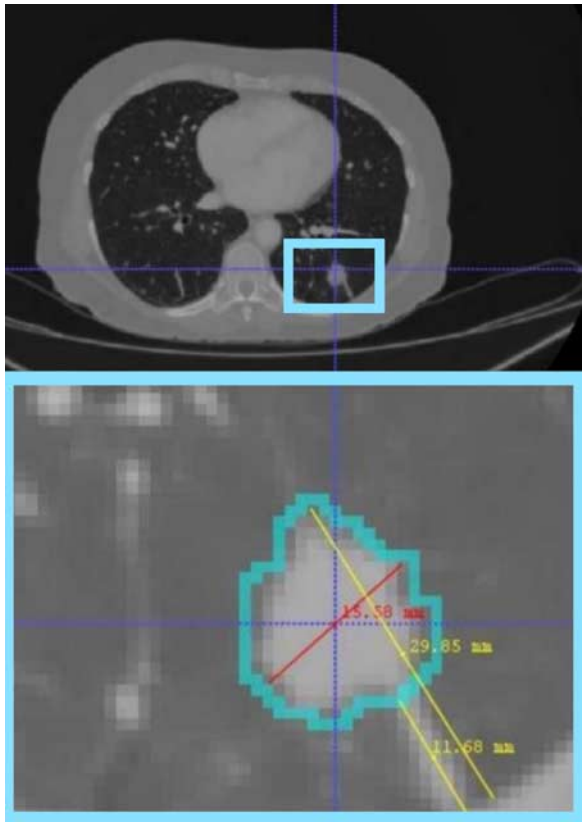

FIGURE 3. Manual characterization of targeted lesions.

All procedures were performed in an operating room under general intravenous anesthesia, given by an accredited anesthesiologist. The procedures were performed by 2 bronchoscopists with over 22 years of combined experience (J.R. R.-S. and L.U.-G.). Patients were intubated with an endotracheal tube (8 mm internal diameter) under direct laryngoscopy. Then, the RES was placed in an operative position and covered by a sterile drape. A study investigator connected the sterile robotic bronchoscope to the light source and camera box, manually inserted the bronchoscope into the endotracheal tube and attached it to the robot. The investigator advanced the bronchoscope into the bronchial tree using the endoscopy controller and navigated the bronchoscope to the targeted segment with the aid of the CT scan and mono-planar fluoroscopy. Direct continuous visualization was also used during all procedures. R-EBUS and electromagnetic navigation (EMN) were not used in the study. Once the bronchoscope was positioned close to the targeted lesion, biopsy instruments were inserted into the working channel and advanced through the bronchoscope to the lesion. Biopsies were performed using sterile 24.5-G needle aspiration devices and biopsy forceps (Spybite, Boston Scientific, biopsy cup 4.1 mm opening at 55 degrees). In all cases, the tissue was first obtained by the biopsy needle aspiration device and then by the forceps. A brushing technique was not used in this study. Rapid on-site evaluation of cytologic specimen was performed by a cytopathologist in all cases. We did as many needle passes and forceps biopsies as the on-site cytopathologist considered necessary for a sample to be adequate.

All study patients were managed postprocedure as per standard practices. Patients underwent a chest x-ray within 2 hours from the conclusion of the procedure to rule out complications.

Postinterventional Follow-up Evaluation

All patients completed 2 prespecified follow-up visits (2 and 7 days postprocedure). Adverse events, medication usage and postprocedure symptoms were recorded at the follow-up visits. Final pathologic results were recorded at the 7-day follow-up.

Study Endpoints

The primary endpoint was the complication rate, as determined by the incidence of device or

procedure-related serious adverse events (SAE). The relationship between complications and procedure was assessed by the study principal investigator. A SAE was defined as an event which leads to death or life-threatening condition, results in persistent or significant disability/incapacity, requires in-patient hospitalization or prolonged hospitalization or necessitates an intervention to prevent a permanent impairment of a body function or permanent damage to a body structure. The following significant clinical events were of interest: (i) if occurred in > 5% of patients (shortness of breath, coughing, wheezing); (ii) if occurred in > 1% of patients (bleeding, hemoptysis, lung leak or collapse, infection, pneumonia, transitory fever); (iii) if occurred in > 0.1% of patients (bronchoscopic airway puncture, cardiovascular event including irregular heartbeat, bronchial asthma, respiratory failure, death). The thresholds were chosen to conduct preliminary assessments of the procedure and device-related complications.[13]

The secondary endpoint was the technical success. The technical success was defined as the ability of the RES to complete the intended procedure. The ability to directly visualize deployment of the biopsy instruments and to observe the bronchial tree during bronchoscopy was also assessed. The total procedure time was defined by the time the bronchoscope is inserted into the oropharynx until the time the bronchoscope was removed. It has been shown in a preclinical research that 5 cases should be performed to achieve an acceptable learning curve. Therefore, we used 5 cases cut-off to assess the time to biopsy location in this study.

Data Collection and Statistical Analysis

Data from a 12-page case report form were transferred into a password protected Excel spreadsheet (Microsoft, Redmond, WA). The Shapiro-Wilk test was used for normality testing. The median (range), counts, and percentage were reported. *P*-value was calculated using the Mann-Whitney *U* test. All statistical analyses were performed using the JMP 13.0 software (Cary, NC).

RESULTS

Baseline Characteristics of the Patients

Of the 17 screened patients, 15 eligible patients (88%) underwent bronchoscopy with the RES (Supplemental Digital Content 4, http://links.lww.com/LBR/A151). Of the 2 excluded patients, one had no lesion identifiable on the preprocedure CT scan and another showed a lung nodule with no bronchus sign. The demographics and baseline characteristics of all included patients are summarized in Table 2. The medial platelet count was 253,000 (181,000 to 745,000) platelets/ml of blood. Only 1 (7%) patient was on an antiplatelet drug (clopidogrel) before the procedure. Observed comorbidities were hypertension, diabetes, and hypercholesterolemia in 4 patients, past colon cancer in 2 patients, past breast and past lung cancer in 1 patient each.

TABLE 2. Baseline and Clinical Characteristics of Study Patients

Female	6 (40%)
Age (y)	67 (38-79)
< 50	2 (13%)
50-65	5 (33%)
> 65	8 (53%)
Body mass index (kg/m^2)	24.0 (14.5-31.6)
Blood urea nitrogen (mg/dL)	12.9 (0.7-19.7)
Prothrombin time (s)	14.1 (12.3-15.6)
Internationalized normalized ratio	1.1 (1.0-1.2)
Partial thromboplastin time (s)	27.1 (24.2-31.9)
Lesion localization	
Right lower lobe	5 (33%)
Right upper lobe	4 (27%)
Left lower lobe	2 (13%)
Left upper lobe	4 (27%)
Lesions size (largest diameter in cm)	2.6 (1.0-6.3)
Lesions distance from pleura (cm)	
Closest edge to pleura	0.6 (0-3.4)
Furthest edge to pleura	3.2 (2.6-4.7)

Values are medians (range) and counts (%).

Procedure and Complications

During the study period, there were no reports of SAE, such as pneumothorax or significant bleeding requiring intervention, related to the use of the RES. Three minor unrelated complications were reported. Four days after the procedure, 1 patient reported symptoms of a "fever sensation." The symptoms resolved spontaneously and were absent at the 7-day follow-up. Another patient experienced anesthesia-related nausea and vomiting. These events resolved within 6 hours. The third patient reported back pain. A physical examination showed no abnormality except for contracture of the paravertebral muscles.

Tissue acquisition under direct visualization was performed using the RES in 14 of 15 (93%) patients. During tissue acquisition, the biopsy instruments were directly visualized in all patients (Fig. 4). One biopsy (right upper lobe), which was confirmed to be malignant, required use of a

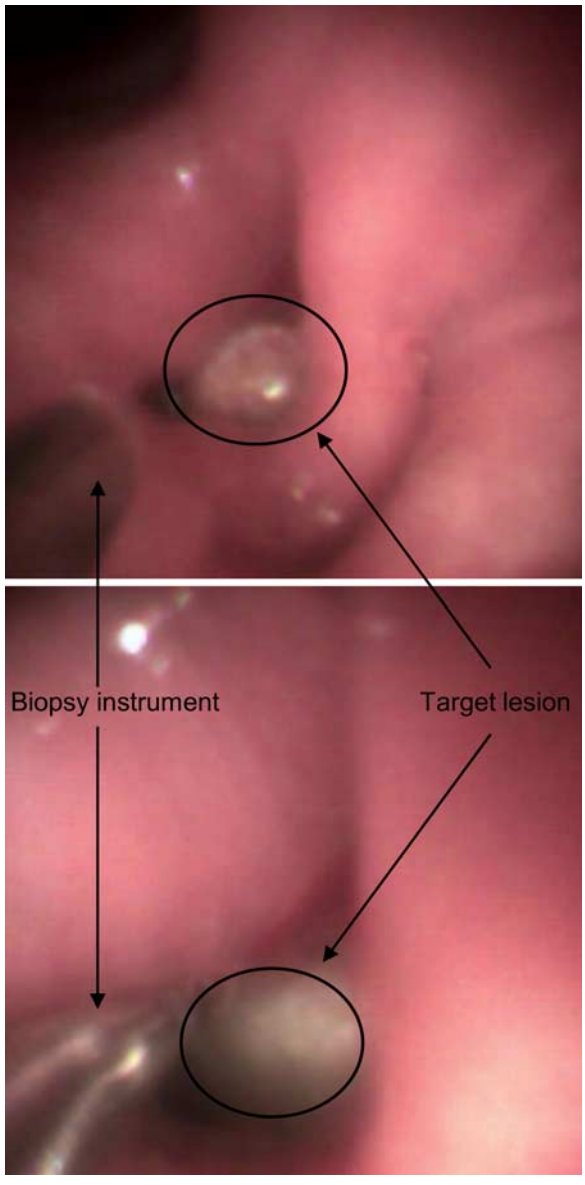

FIGURE 4. Direct visualization of a distal endobronchial lesion and a biopsy instrument during tissue acquisition.

conventional flexible bronchoscope. Our analysis of system data revealed that the robotic tension parameters were not set appropriately in this case and thus the conversion from robotic to conventional bronchoscopy. Another patient required a surgical biopsy to confirm a malignant diagnosis as the pathology from a bronchoscopy sample was nondiagnostic. Adenocarcinoma was confirmed in nine patients, 2 of which metastasized from colorectal cancer. Benign features were found in 5 of 6 patients and included necrotizing pneumonia, Loeffler syndrome, actinomycosis, surgical scar, and atypical mycobacteria.

The median number of aspiration with the biopsy needle aspiration device was 3 (0 to 5) per target; the median number of forceps biopsies taken was 7 (0 to 12) per target. The total median time to biopsy location was 21 (7 to 84) minutes. The median time to biopsy location reduced from 45 (21 to 84) minutes (first 5 cases) to 20 (7 to 47) minutes (last 9 cases), $P = 0.039$. All patients were discharged within 6 hours following the procedure.

Device Performance

The RES performed without malfunctions in 14 of 15 (93%) cases. In one case, the system required to be restarted during the procedure and the bronchoscope had to be removed for cleaning. After cleaning, the procedure continued and the biopsy found no malignancy.

DISCUSSION

Despite several advances in technology including EMN and R-EBUS, the diagnosis and management of PLL remains challenging.[14] Current diagnostic approaches for patients with suspected lesions are often determined based on estimation of preprocedure probability of malignancy. In cases where the probability of cancer is low ($< 5\%$), careful CT scan surveillance is recommended.[7] In a medically operable patient with a solid, indeterminate lesion that measures > 8 mm in diameter where the probability of cancer is high ($> 65\%$), surgical resection is usually recommended. Surgical resection may be contraindicated in some patients due to comorbidities. After functional imaging is performed to characterize the lesion, nonsurgical biopsy (CT-TTNA or flexible bronchoscopy) may be recommended for patients where the probability of cancer is low to moderate.[7] Despite the addition of R-EBUS and EMN, some PPL in the outer third of a lung remain nondiagnostic after bronchoscopy. Therefore, CT-TTNA may be the preferred technique to biopsy these lesions. Unfortunately, CT-TTNA is associated with higher rate of pneumothorax (15% with 7% requiring management with a chest tube).[15] In the same study, hemorrhage complicated only 1% of cases, although 18% of patients with hemorrhage from biopsy required transfusion.[15] In our study, no SAE occurred; 3 minor adverse events that resolved within 6 hours were not procedure or device related. The observed success of the procedure and absence of SAE suggests

that robotic bronchoscopy performed with the RES is technically feasible.

The absence of SAE in this study may be attributed to several factors including the atraumatic tip of the bronchoscope, precise control of the bronchoscope's discrete movements, the locking capability of the bronchoscope into a desired position, and thorough investigator training before study initiation. The primary purpose of the training was for the physician and technical staff to develop confidence and proficiency in the use of the RES, and to provide a thorough understanding of the bronchoscopy procedure performed with the RES. The training course included an in-depth didactic session (introduction to the RES), and a hand-on training lab to learn how to control the system (6 h of bench driving in a plastic model and 6 h of training in a live animal). The authors believe that a standardized training for any user of the system will be required in the future. While the low complication rate of the robotic bronchoscopy performed with the RES observed in this study is encouraging, we recognize that the sample size in the current study was not large enough to demonstrate that procedure-related complications did not occur due to the performance of the system. A study with a larger and more diverse patient population is needed to establish the safety profile of the robotic bronchoscopy performed with the RES.

Technological advancements, including R-EBUS, EMN bronchoscopy, and virtual bronchoscopy, have been introduced to assist bronchoscopists attempting to biopsy PLL not accessible to conventional bronchoscope under direct vision. While these adjunctive technologies have improved diagnostic accuracy of traditional bronchoscopy,[10] diagnostic yield of these guided transbronchial approaches remains inferior to that of CT-TTNA. Wang Memoli et al[10] reported a 70% pooled diagnostic yield which is much higher than those previously reported using traditional bronchoscopic techniques. In this study, we did not use R-EBUS and EMN as the equipment was not available. Moreover, our current study was not designed to assess the diagnostic yield of the robotic bronchoscopy. Furthermore, in some of nonmalignant cases, the follow-up period was limited to rule out malignancy (ie, the patients with surgical scar). We feel these obvious limitations of our study are understandable as this was a brief initial clinical investigation of a device early in development[16] with a goal to assess a complication rate and technical feasibility of the RES in a small number of patients.

During the study, we were able to directly visualize deployment of biopsy instruments in all cases (Video, http://links.lww.com/LBR/A153, Supplemental Digital Content 5, http://links.lww.com/LBR/A152). Endobronchial abnormalities were noted while targeting a lesion (Fig. 4). In the few cases in which vision was lost due to collapse of peripheral airways, the integrated irrigation feature was used to distend the peripheral airways. This technique resulted in quick recover of direct visualization while advancing and articulating the bronchoscope.

During 1 case, bronchial secretions caused a temporary visual impairment that required bronchoscope removal and cleaning. A successful biopsy was performed after the cleaning; the final pathology found no malignancy. This issue was considered minor and did not compromise the well-being of the patient. The bronchoscope removal for cleaning to visualize the field may be avoided in the future by gently rubbing the bronchoscope vertically against the mucosa of the airway or positioning the bronchoscope against the airway and irrigating the operating port.[17] The integrated fluidics control may be helpful in cases where visual impairment is observed. We believe that optimized direct continuous visualization in the periphery is one of the most promising capabilities of the RES.

Furthermore, we are encouraged by the control and stability of the robotic bronchoscope and instruments in the periphery as well as by the reach achieved. While a peripheral reach comparison between a conventional bronchoscope and the robotic bronchoscope was not performed in this study, our subjective assessment, based on our clinical experience with conventional bronchoscopes, led us to believe that the robotic bronchoscope is capable of reaching further in the periphery than a conventional bronchoscope. We believe that this is due to the column strength and telescoping design of the robotic bronchoscope. This observation needs to be quantified in a prospective study. Moreover, the robotic bronchoscope has a distal section capable of achieving 180 degrees of deflection in any direction. Both irrigation and aspiration are robotically operated by the user with an endoscopy controller. These technological enhancements may lead to potential advantages over traditional peripheral bronchoscopy. In addition, the ability to lock the bronchoscope in a specific position and minimize changes in position associated with human error or torque on peripheral instruments may have future benefits, yet to be described.

CONCLUSIONS

The robotic bronchoscopy performed with the RES appears to be technically feasible. The absence of SAEs and procedure or device-related complications is encouraging. The system holds promises of addressing current limitations of the transbronchial diagnostic approached by providing a continuous direct visualization, further peripheral reach and improved instrument control to target suspected lesions located in the outer third of the lung. Future prospective studies are needed to establish a diagnostic accuracy of the system.

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