Feasibility of Cryobiopsy Specimen Retrieval Through Standard Guide Sheath for Peripheral Pulmonary Lesions Without Bronchoscope Removal

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Background: Transbronchial cryobiopsy is a promising technique for biopsy of peripheral pulmonary lesions (PPL). However, cryobiopsy specimen retrieval can pose problems due to the risk of bleeding during the blind period when the bronchoscope and cryoprobe are removed *en bloc*. Artificial airways and prophylactic balloon placement are risk-reducing measures, but the latter is challenging in upper lobe PPL. Specimen retrieval through standard guide sheath (GS) system without the need for bronchoscope removal may now be feasible with the ultrathin cryoprobe.

Methods: Retrospective review of radial endobronchial ultrasound (rEBUS)-guided transbronchial cryobiopsy for PPL cases in which cryobiopsy specimen was retrieved through the GS over a 6-month period.

Results: Twenty patients were included with an overall median age of 66.50 (IQR: 53.0 to 76.7). The median procedural time was 30 (IQR: 25.0 to 33.7) minutes. Median target size was 3.20 (IQR: 2.17 to 4.84) cm with 85% of lesions demonstrated "within" rEBUS orientation. Overall technical feasibility was 85% with median cryoactivation of 4.0 (IQR: 3.0 to 4.0) seconds. No specimen was retrieved in 3 patients. The diagnostic yield for forceps and cryobiopsy was 70% and 60%, respectively, and the combined diagnostic yield was 85% ($P < 0.01$ vs. forceps biopsy). Median aggregate size for forceps and cryobiopsy was 8.0 (IQR: 5.3 to 10.0) and 4.5 (IQR: 2.3 to 7.0) mm respectively ($P < 0.01$). No pneumothorax was reported and mild self-limiting bleeding was encountered in 30% of cases.

Conclusion: Retrieval of cryoprobe through standard GS appears to be a safe and feasible method that can simplify the transbronchial cryobiopsy procedure and complement forceps biopsy in specific cases.

Key Words: radial endobronchial ultrasound, bronchoscopy, interventional pulmonology, cryobiopsy, guide sheath

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Peripheral pulmonary lesions (PPL) are defined as lesions not visible beyond the visual segmental bronchi.[1] In the current era of immunotherapy and targeted therapy for lung cancer, transbronchial cryobiopsy (TBCB) has enhanced the diagnosis of PPL by providing high-quality specimens for molecular testing.[2,3]

However, specimen retrieval during TBCB may risk unchecked airway bleeding, owing to the blind period during which the bronchoscope and cryoprobe are simultaneously removed *en bloc*.[4] Recommended measures to mitigate this risk include performing transbronchial cryobiopsy through endotracheal intubation for placement of a prophylactic balloon blocker or rigid bronchoscopy.[5] While prophylactic balloon placement may address the blind period, placement of the balloon into the upper lobe or other angulated regions may be particularly challenging.[6]

The development of the 1.1 mm ultrathin cryoprobe presents a viable solution to the clinical dilemma of unchecked bleeding, as it allows specimen retrieval through the standard GS system, thus eliminating the blind period altogether. Wedging the GS and bronchoscope in the airway after cryobiopsy provides a tamponade effect which may address the issue of bleeding and allow the bronchoscopist to maintain bronchoscopic vision at all times during the procedure. In this retrospective case series, the feasibility and safety of this method is discussed.

METHODS

Study Design and Study Site

This was a retrospective case series of all adult patients undergoing radial endobronchial ultrasound (rEBUS) guided TBCB for PPL in the respiratory care unit of Sarawak General Hospital, Malaysia over 6 months' duration (July to December 2022) in which cryobiopsy specimen was retrieved through the GS. The cases were extracted from a study approved by the medical research and ethics committee, Ministry of Health Malaysia [NMRR-ID-23-00520-LMM (IIR)]. This study was conducted in compliance with ethical principles outlined in the Declaration of Helsinki and Malaysian Good Clinical Practice Guideline.

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Procedural Considerations

All patients provided written informed consent before bronchoscopic procedure. All the procedures were performed by either consultant pulmonologists or pulmonology fellows under direct consultant supervision. Decisions on advanced artificial airway usage such as rigid bronchoscope, endotracheal intubation, or laryngeal mask airway were made at the discretion of the bronchoscopist. The procedures were performed under either conscious sedation or total intravenous anesthesia as per unit protocol. A stop-marker was affixed to the proximal end of the cryoprobe at a distance which corresponded with the cryoprobe tip extending 1 cm beyond the distal end of the GS; this ensured accurate insertion depth in lieu of fluoroscopy (Fig. 1B–E).

Target planning and navigation was performed using the bronchial branch tracing method. This method involves identifying the airway bifurcations leading into the target lesion and translating them into a schematic map which correlates to the actual bronchoscopic view.[7,8] After initial bronchoscopic examination with a flexible therapeutic bronchoscope (BF-1TH190; Olympus Medical, Tokyo, Japan), a 20 Hz 2.0 mm rEBUS probe (UM-S20-20R; Olympus Medical) within a standard 2.55 mm diameter, 1050 mm GS (SG-201C; Olympus Medical) was inserted into the preplanned target segment through the bronchoscope's working channel. Following target lesion identification, the GS was locked and the bronchoscope was wedged firmly in place, before the rEBUS probe was removed from the GS. Forceps biopsy was performed with a standard fenestrated cup flexible forceps (FB231-D; Olympus Medical) through the standard GS. A total of 8 to 10 passes were taken.

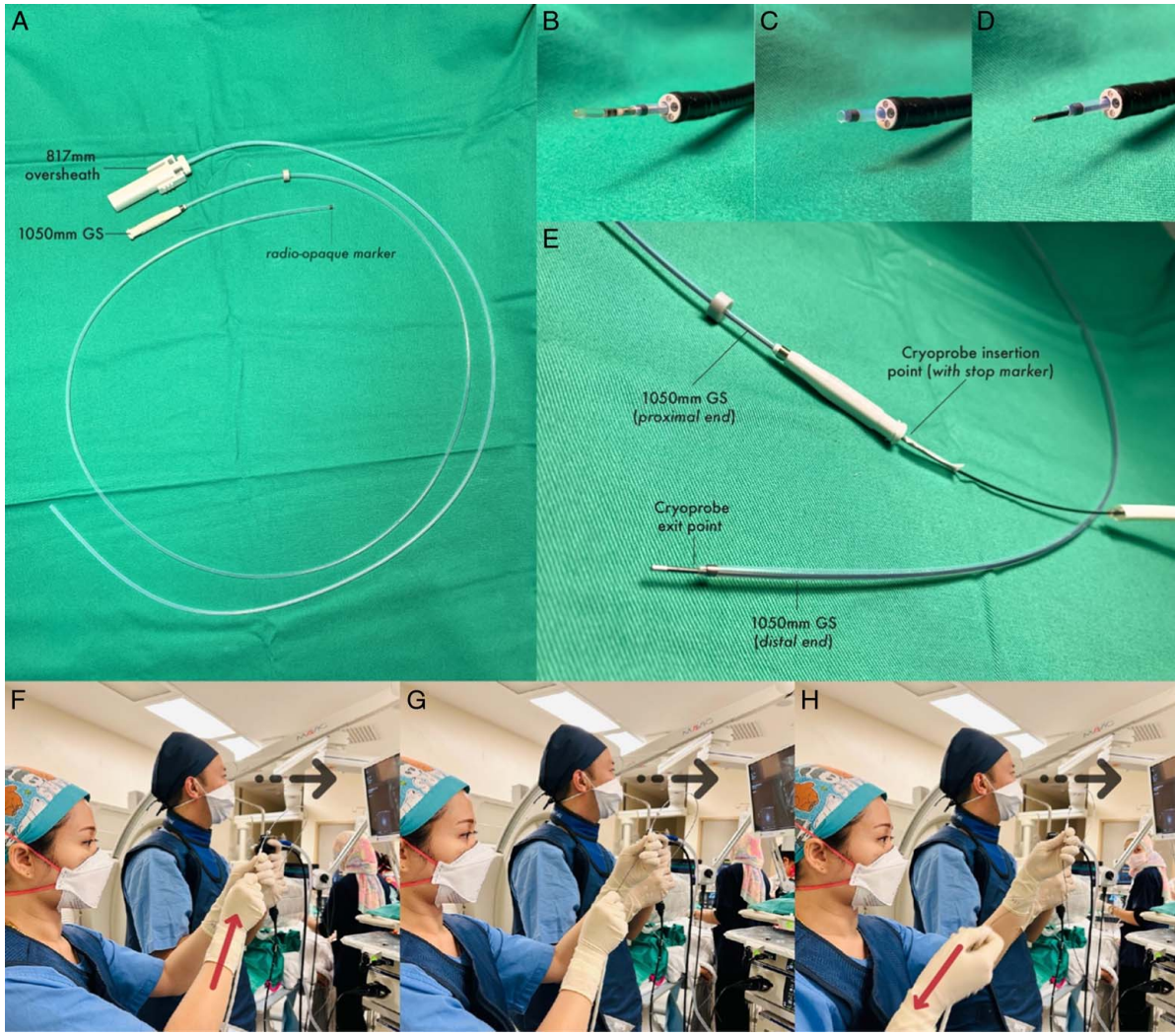

FIGURE 1. Procedure setup: a longer 1050 mm GS with a radio-opaque marker at the distal end was used in this series instead of the shorter 817 mm oversheath (A). After initial rEBUS/GS localization (B), the GS was locked and the rEBUS probe was removed (C), followed by insertion of the 1.1 mm cryoprobe into the lesion through the GS (D). A stop-marker was affixed to the proximal end of the cryoprobe at a distance which corresponded with the cryoprobe tip extending 1 cm beyond the distal end of the GS; this ensured accurate insertion depth in lieu of fluoroscopy (E). Procedure simulation: the first assistant inserts the cryoprobe into the GS until the stop-marker point (F) and activates the cryoprobe (G). The bronchoscopist maintains the bronchoscope and GS in place as the first assistant promptly removes the cryoprobe from the GS; cryoactivation continues until the cryoprobe is fully out from the GS (H). The specimen is then thawed by the first assistant while the bronchoscopist carefully readjusts the GS and addresses any complications that arise.

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Following repeat rEBUS target site verification, the 1150 1.1 mm single-use flexible cryoprobe (20402-401, ERBE; Medizintechnik, Tübingen, Germany) was then inserted into the locked GS up to the stop-marker point. After 3-second cryoactivation, the cryoprobe was retracted from the GS while the bronchoscope and GS remained firmly wedged, thus allowing the bronchoscopist to maintain bronchoscopic vision at all times. A 5 Fr prophylactic balloon blocker was available on-hand for all cases.

The procedure was repeated with increments of 1 second until the cryoprobe was unable to be retracted, following which the freezing time would be reduced by 1 second to facilitate retrieval. The biopsy was repeated until the biopsy specimen was deemed adequate by the bronchoscopist. In the event that the cryoprobe failed to be retracted, it was allowed to thaw and was subsequently removed through the GS. Instances of increased blood flow through the GS lumen signaled potential bleeding complications.

Tissue from cryobiopsy was thawed, retrieved in normal saline from the cryoprobe, fixed in formalin solution and sent to pathology lab immediately for processing and analysis. Post-cryobiopsy, the GS was removed from the target segment slowly while maintaining bronchoscopic vision. In the event of bleeding, the GS was wedged back into the target segment to provide a tamponade effect, followed by instillation of hemostatic agent such as cold saline, tranexamic acid, or adrenaline saline. Post-procedure, a chest radiograph was performed to look for pneumothorax 2 hours after the procedure.

Statistical Analysis

SPSS (version 20; Chicago, IL) was used for data analysis. Normality was assessed with the Shapiro-Wilk test. Results were presented as mean ± SD for normally distributed variables, and as median (IQR) for non-normally distributed variables. Categorical data were expressed as absolute numbers and percentages. Independent sample *t* tests and Mann-Whitney or Wilcoxon signed rank tests were used to compare normally and non-normally distributed variables between groups, respectively, when appropriate. A *P*-value of < 0.05 is considered to be significant.

RESULTS

A total of 20 patients were included in this study with their details summarized in Table 1. A representative case is illustrated in Figure 2.

Baseline Demographic and Target Lesion Characteristics

Our cohort consisted of an equal proportion of male and female patients with an overall median age of 66.50 (IQR: 53.0 to 76.7) years. The median target size was 3.20 (IQR: 2.17 to 4.84) cm with 60% (12/20) of lesions situated in the upper lobe. Eighty-five percent (17/20) of target lesions demonstrated a "within" rEBUS orientation (75% concentric and 10% eccentric) while the remaining 15% (3/20) had an adjacent orientation.

Baseline Procedural Characteristics

Median procedural time was 30.0 (IQR: 25.0 to 33.7) minutes. The majority (85%) of procedures were performed under conscious sedation without artificial airway. Fluoroscopy was only used in 8 patients (40%). Forceps biopsy was performed in all patients with a median of 8 (IQR: 6 to 10) passes.

Technical Feasibility

Although the cryoprobe was successfully retracted through the GS in all cases—there was no biopsy tissue on the cryoprobe in 3 of the cases, translating to an overall technical feasibility of 85% (17/20). TBCB was performed with a median of 3 (IQR: 3 to 4) passes and 4 (IQR: 3.0 to 4.0) seconds of activation. The maximum median duration associated with failure to retrieve cryoprobe was 5.0 (IQR: 4.25 to 5.75) seconds. Median aggregate size for forceps and cryobiopsy was 8.0 (IQR: 5.3 to 10.0) and 4.5 (IQR: 2.3 to 7.0) mm, respectively ($P < 0.01$).

Diagnostic Yield

The diagnostic yield for forceps and cryobiopsy was 70% and 60%, respectively. Overall diagnostic yield in our cohort was 85% (17/20) which was significantly higher than forceps biopsy alone ($P < 0.01$). On a closer look, both forceps and cryobiopsy provided a diagnosis in 45% (9/20) of cases. When forceps biopsy was inconclusive (6/20, 30%), cryobiopsy provide a diagnosis in 50% (3/6) of cases in which 2 were adjacently orientated rEBUS lesion while 1 was concentric in orientation (Table 2).

The overall conclusive cases were comprised of malignancy (n = 13), benign lung lesion (n = 1, case 12), infection or inflammatory (n = 2, case 14, 15), and tuberculosis (n = 1, case 16). In 3 inconclusive cases (case 6, 7, and 9), both forceps and cryobiopsy failed to establish a diagnosis, thus requiring CT-guided transthoracic needle biopsy which confirm to be malignancy eventually.

Complication Rate

No pneumothorax was encountered in the current cohort. Mild bleeding was reported in 30% (6/20) of cases, all of which were self-limiting. Only 1 patient required adrenaline saline flush through GS uneventfully.

DISCUSSION

The traditional setup for TBCB is complex, requiring both the expertize to manage life-threatening bleeding complications and auxiliary equipment such as artificial airways and prophylactic balloon blockers.[9] The elegance of the GS retrieval technique described in our cohort lies in its sound technical success rate and relative simplicity; being reminiscent of a standard radial EBUS procedure in terms of setup and equipment.

Recent reports such as the FROSTBITE trial demonstrated technical feasibility and safety of this technique, although only 3 of the trial's 50 patients were PPLs.[9] Moreover, the procedures were performed using the shorter oversheath (2.60 mm diameter, 817 mm length) which came equipped with the 1.1 mm cryoprobe.[9] Scattered case reports utilizing a longer GS (2.55 mm diameter, 1050 mm length) have also shown good results recently.[6,10] Moreover, a similar technique was utilized in robotic assisted bronchoscopy, demonstrating technical feasibility, and satisfactory safety outcomes.[11] Notably, our current cohort is the largest-to-date to demonstrate the feasibility of this cryobiopsy GS retrieval technique for the biopsy of PPL through the standard longer GS.

In terms of the safety profile of this technique, no pneumothorax was reported and only a third of the cases incurred mild, self-limiting bleeding. This is remarkable as

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TABLE 1. Patient, Target and Procedural Characteristics (n = 20)

Case	Age (y)	Sex	Target segment	Target size (cm)	rEBUS orientation	Number of cryopass	Median cryoactivation time (s)	Total aggregate cryospecimen size (mm)	Result from forceps biopsy		Result from cryobiopsy	
									Conclusive	Y/N	Conclusive	Y/N
1	80	F	RB^3	2.13	Eccentric	3	3.00	9	Adenocarcinoma lung	Y	Adenocarcinoma lung	Y
2	53	F	RB^2	3.20	Concentric	3	4.00	2	Bronchial epithelium	N	Adenocarcinoma lung	Y
3	47	M	RB^4	6.60	Concentric	4	5.00	7	Squamous cell carcinoma	Y	Squamous cell carcinoma	Y
4	80	M	RB^3	5.92	Concentric	4	4.00	7	Adenocarcinoma lung	Y	Adenocarcinoma lung	Y
5	70	M	RB^2	3.20	Concentric	4	4.00	5	Squamous cell carcinoma	Y	Squamous cell carcinoma	Y
6	77	F	LB^9	4.90	Concentric	3	4.00	4	Bronchial epithelium	N	Atypical malignant cells	N
7	46	F	RB^2	3.00	Concentric	4	4.00	5	Bronchial epithelium	N	Fibrotic alveolar septa	N
8	65	M	LB^3	2.13	Adjacent	3	5.00	8	Bronchial epithelium	N	Small cell carcinoma	Y
9	76	F	LB^4	2.12	Concentric	2	4.00	3	Bronchial epithelium	N	Bronchial epithelium	N
10	71	F	RB^9	1.83	Adjacent	2	5.00	4	Adenocarcinoma lung	Y	Collapsed alveolar tissue	N
11	65	M	RB^2	4.47	Concentric	4	2.75	8	Adenocarcinoma lung	Y	Adenocarcinoma lung	Y
12	65	F	RB^8	1.25	Adjacent	5	3.80	3	Collapsed alveolar tissue	N	Sclerosing pneumocytoma	Y
13	49	M	LB^3	4.68	Concentric	2	3.00	4	Adenocarcinoma lung	Y	Adenocarcinoma lung	Y
14	53	M	LB^3	3.85	Eccentric	2	3.00	*No specimen*	Fibrotic alveolar septa	Y*	*No specimen retrieved*	N
15	57	F	RB^1	2.98	Concentric	3	4.00	*No specimen*	Fibrotic alveolar septa	Y*	*No specimen retrieved*	N
16	68	F	LB^8	4.96	Concentric	3	3.00	*No specimen*	Caseating granuloma	Y	*No specimen retrieved*	N
17	36	F	RB^{10}	6.20	Concentric	4	4.00	2	Adenoid cystic carcinoma	Y	Adenoid cystic carcinoma	Y
18	74	M	LB^{1+2}	3.20	Concentric	3	2.00	7	Adenocarcinoma lung	Y	Adenocarcinoma lung	Y
19	80	M	RB^1	3.50	Concentric	3	2.00	5	Squamous cell carcinoma	Y	Fibrotic alveolar septa	N
20	80	M	LB^4	2.31	Concentric	4	3.00	10	Adenocarcinoma lung	Y	Adenocarcinoma lung	Y

*Target lesion resolved on repeated CT scan.
F indicates female; M, male; N, no; Y, yes.

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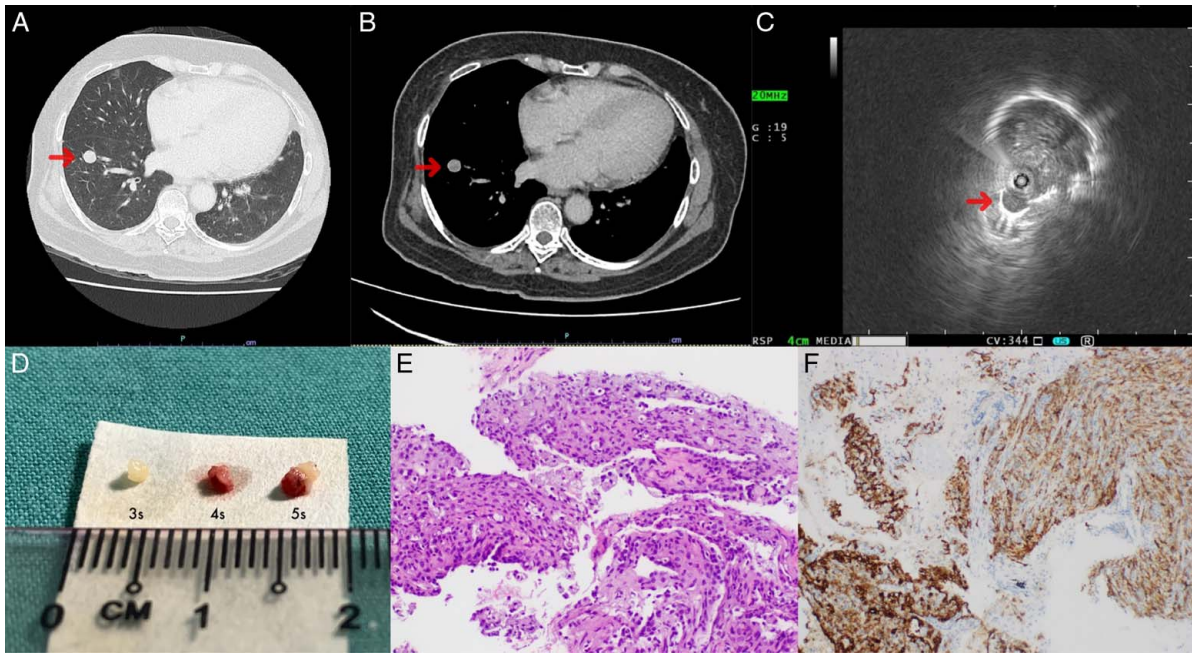

FIGURE 2. Representative case (case 12). A 65-year-old woman presented with incidental finding of a 1.25 cm solid nodule in the anterior segment of the right lower lobe (A and B). Radial EBUS examination at target segment RB^{8ai} (under conscious sedation and in lieu of fluoroscopy) revealed an adjacently orientated lesion with a significant vessel at the opposite end (arrow, C). Following forceps biopsy, cryobiopsy was performed with specimen retrieval through GS for a total of 5 passes with incremental activation times of 3 to 5 seconds (D). Mild bleeding was successfully controlled by the wedged GS. Forceps biopsy was nondiagnostic, demonstrating a nonspecific alveolated parenchymal structure, while cryobiopsy yielded high-quality specimens demonstrating papillary surface cells and round stromal cells within papillary cores and solid sheets (E, H&E x10). Both surface and round stromal cells displayed moderate to strong, diffuse positivity for EMA, TTF-1, panCK, and CK7 (F, x10). The overall features were consistent with sclerosing pneumocytoma.

bleeding from PPL-TBCB cohorts generally report an overall bleeding rate (any grade) of 16.2% to 79.4%.[12,13] Various methods of bleeding control have been previously reported for TBCB, including the usage of prophylactic balloon blocker, tube-wedging, and the two-bronchoscope technique.[14–16] However, these methods still require the bronchoscope and cryoprobe to be removed *en bloc*, leaving a blind period when the bronchoscopist has no direct control or access. While the lower bleeding rate in our cohort may be explained by the tamponade effect from the GS, the 1.1 mm cryoprobe itself may potentially carry a better bleeding profile compared with the conventional 1.9 mm cryoprobe due to the ease of peripheral placement and activation, thus avoiding vessel injury in the middle third of the lung.[17]

This TBCB method may also complement forceps biopsy—in our small cohort, we demonstrated an additional 15% increase in overall diagnostic yield to forceps biopsy. This complementary effect to forceps biopsy is likely due to better biopsy capability of cryobiopsy in eccentric and adjacently orientated rEBUS lesions, for which studies have consistently demonstrated better diagnostics yields with PPL-TBCB.[3,13,18] It is well established that multimodality biopsy method can enhance the overall diagnostic yield of PPL biopsy.[19] Other tools such as transbronchial needle aspiration has been shown to be effective and may be considered in such situations as well.[20]

Our described technique also poses some challenges. Notably, the median size of our cohort's target lesions were large due to case selection to determine technical feasibility. Despite this, the diagnostic yield of cryobiopsy or forceps alone remained low, with 8 cryobiopsy-inconclusive cases. Of these 8, forceps biopsy failed to secure the diagnosis in 3 cases (case 6, 7, and 9), demonstrating only bronchial epithelium, while cryobiopsy yielded atypical cells. These findings not only suggest incomplete mucosal invasion by the malignant lesion, but also raise questions about the ability of ultrathin cryoprobe to achieve deep biopsies when activated at shorter times.[21] In the remaining 5 cases, no tissue was retrieved from cryobiopsy in 3 cases (case 14, 15, and 16). All 3 cases of irretrievable specimens in our cohort were due to non-malignant, infective causes. It is known that the inflammatory nature of these diseases may cause non stenotic airways, leading to poor probe-airway contact which we postulate may have resulted in failure of cryoadhesion with no specimen retrieved.[22] This may also be applicable in lung lesions with "penetrating" type bronchus sign which may hinder proper cryoprobe contact.[23] For the remaining 2 cases (case 10 and 19), forceps biopsies were conclusive. We postulate that the GS might have dislodged after forceps biopsy as the act of

TABLE 2. Detailed Analysis of Forceps and Cryobiopsy Diagnostic Yield (n = 20)

	Cryobiopsy, n		
Conclusive	**Inconclusive**		**Total**
Forceps, n			
Conclusive	9	5	14
Inconclusive	3	3	6
Total	12	8	20

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pulling cryoprobe swiftly and rapidly from the GS may have dislodged the GS, thus translating to inconclusive cryobiopsy in these 2 cases.

Moreover, the optimal activation time required for optimal biopsy yield remains unknown.[6] Previous studies report varying sheath sizes and length with different activation times—ranging from 3 seconds when utilizing a smaller GS (2.0 mm), to 5 seconds through a similar sized GS (2.55 mm) used in our study.[10] The FROSTBITE trial, which used a shorter oversheath, reported a mean activation time of 4.2 seconds.[9] Nevertheless, these reports are in line with our median activation time of 3 seconds and a maximum median activation time of <5 seconds. However, performing forceps biopsy before cryobiopsy, as we did in our cohort, may lead to kinking of the GS or a serrated luminal surface from repeated forceps movement—this may have affected the optimal cryoactivation time in our cohort by hindering the smooth passage of cryoprobe during retrieval process.

While the 1.1 mm cryoprobe yielded significantly smaller sized specimens compared with forceps biopsy in our cohort, this disparity may not be truly representative as we performed more forceps passes than cryopasses. Future studies should adopt a standard number of passes to allow fair comparison between the 2 biopsy methods. Nevertheless, if the argument that smaller specimen size negates the intended benefit of cryobiopsy to obtain larger specimens, we posit that accurate navigation and the acquisition of high-quality tissue are more important in PPL-TBCB compared with TBCB in interstitial lung disease.[16,17]

Another potential drawback in our method is the use of a therapeutic bronchoscope to accommodate the 2.55 mm GS. Its relatively larger caliber may limit access to more peripheral regions of the lung. A potential solution to this problem lies in the use of thin bronchoscopes; a similar technique describing cryobiopsy specimen retrieval through the working channel of a 4 mm thin bronchoscope without a GS was recently described with no reported bronchoscope breakage.[24]

CONCLUSION

Cryoprobe retrieval through GS is potentially safe and feasible. While it can be a helpful complement to forceps biopsy in situations that require lateral biopsy or greater tissue depth, it is important to recognize that relying solely on this method may potentially lead to an unsatisfactory diagnostic yield. Thus, larger prospective trials are required to address the technical issues and its broader applicability in the respiratory community.

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