Safety and feasibility of ultrathin probe transbronchial lung cryobiopsy without balloon blocker *via* robotic bronchoscopy in the evaluation of peripheral lung lesions: a retrospective pilot study

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To the Editor:

The incidence of radiographically detected asymptomatic peripheral pulmonary lesions (PPLs) is growing with the adoption of lung cancer screening by low-dose chest computed tomography (CT) [1]. Diagnostic yields depend on synergy between guided bronchoscopic technologies, real-time procedural imaging feedback and tissue acquisition tools.

Industry investments and research have advanced technologies to optimise bronchoscopic platforms and real-time intraprocedural imaging feedback. Unfortunately, the evolution of tissue acquisition tools lags behind. Considerations for the use of old tools for new applications is often adopted for areas lacking novel technology to improve upon diagnostic challenges.

Despite advances in bronchoscopic and imaging technologies, a gap is observed between virtual and real-time localisation of PPLs and diagnostic tissue acquisition, given the challenges surrounding the use of sampling tools with directional limitations. Obtaining spherical and thus laterally adjacent specimens in relation to a cryoprobe may improve tissue acquisition and diagnostic yield in lesions that are eccentric or not identified on radial probe endobronchial ultrasound (RP-EBUS), where such unidirectional tools tend to fail.

Herein, to our knowledge, we report a first experience of ultrathin probe transbronchial lung cryobiopsy (UP-TBLC) *via* the Monarch robotic-assisted bronchoscopy (RAB) system for the diagnosis of PPLs, with primary end-points of safety and feasibility.

We present an institutional review board-approved (CCC#42079) retrospective review of 58 lesions in 53 patients who underwent RAB with RP-EBUS-guided UP-TBLC, complementing traditional sampling methods of PPLs during single users' first adoption of RAB between June 2022 and November 2022.

Data collected included patient demographics, CT characteristics of PPLs, including size based on the longest diameter on any CT plane, morphology, lobar location, centrality determined by the PPL's closest edge to pleural distance measured, bronchus sign status and RP-EBUS orientation described as concentric, eccentric or adjacent. Lesions of adjacent orientations were defined as the echogenic identification of nodule with the radial probe visualised outside the perimeter of the nodule. All formal reports of pathology and cytology specimens were collected.

Complications including pneumothorax, bleeding and mortality were recorded. Management of the pneumothorax cases are described. Bleeding complications were categorised based on a Delphi consensus statement from the Nashville working group's standardisation of definitions for bleeding after transbronchial lung biopsy.

Shareable abstract (@ERSpublications)
Ultrathin probe transbronchial lung cryobiopsy (UP-TBLC) *via* robotic bronchoscopy can be safely performed without prophylactic balloon blockade. UP-TBLC offers incremental diagnostic yields of ultrasonographic eccentric lesions. https://bit.ly/3YUEWx4

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Patients with incidental or lung cancer screening-detected PPLs were directly referred to the thoracic interventional pulmonology service and deemed as candidates for RAB based upon physician discretion and patient clinical safety profile for undergoing bronchoscopy.

Under general anesthaesia *via* an endotracheal tube (Monarch; Johnson & Johnson, IN, USA) RAB with RP-EBUS (Olympus Medical, Japan) lesion confirmation was performed. Tissue acquisition was obtained for all lesions in the following sequence: 21-gauge ARC Point (Medtronic, MN, USA) and 15G Gencut (Medtronic) aspirations, 1.1-mm UP-TBLC (Erbecryo 2; Erbe, Tuebingen, Germany), forceps biopsy (Radial Jaw; Boston Scientific, MA, USA) and bronchoalveolar lavage. Three to five cryobiopsies and forceps biopsies each were obtained under fluoroscopy guidance.

UP-TBLCB was performed using a 1.1-mm flexible cryoprobe (Erbecryo 2) which was advanced *via* the 2.0-mm working channel with freeze times of 2–4 s followed by simultaneous continuous tissue freezing with cryoprobe activation during rapid tissue retrieval through the working channel. Prophylactic endobronchial balloon blockade was not performed. 3–4-Fr Fogarty balloons were available for blockade if deemed necessary.

The median age was 69 years (range 40–86 years), with a majority of female subjects (57.4%, n=31). The PPLs' median longest diameter of 15 mm (range 7–39 mm; interquartile range (IQR) 11 mm) was obtained from measuring nodules on axial, coronal and sagittal CT planes. The PPLs' closest edge to pleural distance was a median 13.5 mm (range 0–31 mm, IQR 8 mm). A majority were solid (n=46, 79%), localised to the upper lobes (n=34, 58.6%) and with a bronchus sign (n=34, 58.6%).

Diagnostic yield of 74% (43 out of 58) was calculated based on rate of specific pathological findings. Malignancy was confirmed in 34 (58.6%) nodules; specific benign aetiology confirmed in nine (15.5%) nodules; and 15 (25.9%) nodules were considered inconclusive on the basis of obtaining either normal bronchial/alveolar tissue or nonspecific inflammation (table 1). Our implementation of a strict methodology for calculating diagnostic yield by definition excludes the gold-standard follow-up of inconclusive results with surveillance CT scans for 6-12 months and/or additional CT-guided tissue sampling. As such, these follow-up results are not available at the time of writing.

RP-EBUS views were observed confirming localisation of 94.8% (55 out of 58) of the PPLs. Diagnostic yield of 84% for concentric lesions (21 out of 25) and 73% for eccentric or adjacent lesions (22 out of 30) (table 1).

UP-TBLC offered incremental yields of 15.5% (nine out of 58), with diagnostic yields of 12% (three out of 25) and 20% (six out of 30) for the concentric and eccentric/adjacent lesions, respectively. Forceps biopsy alone and GenCut offered incremental 1.7% (one out of 58) and 1.7% (one out of 58) yields, respectively (table 1).

Three (5%) incidents of pneumothorax occurred. All required interventions. One was discharged on the same day without small-bore chest tube (SBCT) after successful manual aspiration; one was discharged with SBCT for ambulatory management; and one was hospitalised with SBCT after failing manual aspiration. Both chest tubes were removed within 72 h.

Four (6.9%) grade 2 bleeds occurred based on the Nashville bleeding scale, meaning that one or more tools were required to control or prevent further bleeding, *i.e.* suctioning >1 min required or repeat wedging of the bronchoscope for persistent bleeding or instillation of cold saline, diluted vasoactive substances or thrombin.

Mortality was zero (table 1).

Discrepancies between successful real-time lesion localisation by RP-EBUS confirmation and obtaining definitive diagnostic specimens emphasise the need for smarter sampling tools.

Knowledge supporting the use of TBLC for PLLs draws from experience in the diagnostic evaluation of interstitial lung disease (ILD). European Respiratory Society guidelines suggest its safety in this ILD population, as evidence supporting adverse events from TBLC as a high-risk procedure is limited [2]. Clinical practice guidelines now suggest that TBLC is an acceptable alternative to surgical lung biopsy for undetermined ILD in medical centres with experience performing and interpreting TBLC [3].

Complications of TBLCB in ILD include bleeding, pneumothorax and death. The incidence of pneumothorax (1.4–20.2%) appears to be related to the number of samples, number of segments and lobes sampled, probe size, functional impairment, fibrotic high-resolution CT scores and the presence of a usual

TABLE 1 Results, complications and diagnoses

Lesions	58
Overall diagnostic yield	43/58 (74)
Malignant	34/58 (58.6)
Nonmalignant	9/58 (15.5)
Inconclusive	15/58 (25.8)
Diagnostic yield per RP-EBUS view	
Concentric	25/58 (43)
Diagnostic yield	21/25 (84)
Eccentric and adjacent	30/58 (51.8)
Diagnostic yield	20/27 (74)
Lesions not visualised	3/58 (5.2)
Diagnostic yield	0/3 (0)
Diagnostic yield per PPL size, mm	
PPL ⩽20	38/58 (65.5)
Diagnostic yield	25/38 (65.7)
PPL 21–40	20/58 (34.5)
Diagnostic yield	18/20 (90)
Diagnostic yield per sample method	
21-gauge needle	15/58 (25.8)
15-gauge needle	13/58 (22.4)
Cryobiopsy	41/58 (70.6)
Forceps biopsy	31/58 (53.4)
BAL	6/58 (10.3)
Complications	
Bleeds[#]	4/58 (6.9)
Pneumothorax	3/58 (5)
Mortality	0
Diagnoses	58
Malignancy	34 (58.6)
Poorly differentiated nonsmall cell lung cancer	3 (5.2)
Adenocarcinoma, lung	14 (24)
Squamous cell carcinoma, lung	7 (12)
Small cell carcinoma, lung	2 (3.4)
Carcinoid, lung	2 (3.4)
MALT, non-Hodgkin lymphoma	1 (1.7)
Squamous cell carcinoma, larynx	1 (1.7)
Papillary thyroid carcinoma	1 (1.7)
Renal cell carcinoma	1 (1.7)
Adenocarcinoma, colon	1 (1.7)
Prostate carcinoma	1 (1.7)
Benign	9 (15.5)
Non-necrotising granuloma	5 (8.6)
Organising pneumonia	2 (3.4)
Hamartoma	1 (1.7)
Aspergillus infection	1 (1.7)
Inconclusive	15 (25.9)
Nonspecific inflammation	9 (15.5)
Atypical cells	3 (5.2)
Normal alveolar parenchyma	2 (3.4)
Atypical metaplasia	1 (1.7)

Data are presented as n, n/N (%) or n (%). RP-EBUS: radial probe endobronchial ultrasound; PPL: peripheral pulmonary lesion; BAL: bronchoalveolar lavage; MALT: mucosa-associated lymphoid tissue. [#]: all bleeds were classified as grade 2 based on the Delphi consensus statement from the Nashville working group.

interstitial pneumonitis pattern [4, 5]. Clinically significant or severe bleeding when using a prophylactic bronchial blocker is 0–6.3% and mortality is 0–4.1% [5].

Safety data have been derived from the use of 1.9–2.4-mm cryoprobes [4–6]. However, there is growing evidence for safety with ultrathin 1.1-mm cryoprobes for PPLs [7–11].

Of note, freezing times of 12–13 s are recommended when using 1.1-mm cryoprobes in ILD. As *en bloc* cryospecimen retrieval with the bronchoscope was not our method, our experience suggests specimen

retrieval *via* the Monarch system's 2.0-mm working channel restricts obtaining larger specimens, thereby limiting freeze times to 2–4 s.

Recent studies evaluating TBLC with differing probe sizes using an alternative RAB system and a variety of nonrobotic bronchoscopic platforms and techniques have also shown encouraging diagnostic results and safety profile with and without prophylactic balloon blockade [7–11]. In our cohort, UP-TBLC offered a 15.5% incremental diagnostic yield, similar to a recently published 17.6% *via* the Ion robotic system (Intuitive Surgical, Sunnyvale, CA, USA) in which cryobiopsy was the sole diagnostic modality [11], and a 20% incremental yield with eccentric/adjacent PPL localisations on RP-EBUS. The impact of TBLC on diagnostic accuracy will need to be studied, ideally with reporting of the definition of the method used and clinical follow-up of inconclusive results, as should be the case with the evaluation of any novel bronchoscopic technology and techniques for PPLs [12, 13].

Our safety profile in performing TBLC for ILD encouraged this endeavour given acceptable complication rates of pneumothorax (4.3%) and clinically insignificant bleeds (16.6%) and no mortality [6]. We report similar complications rates with UP-TBLC of PPLs for both grade 2 bleeds and pneumothoraces, the latter successfully treated per our algorithmic management [14, 15].

Our study limitation lies in applying a strict methodology for determining the diagnostic yield which does not allow for the inclusion of clinical follow-up data of the inconclusive results, thereby potentially underestimating diagnostic yield [13]. The observational nature of our study did not support an independent evaluation of each tissue acquisition tool's performance.

UP-TBLC without prophylactic balloon blockade *via* robotic bronchoscopy is feasible, with suggested safety, and may increase diagnostic yields when combined with traditional sampling modalities, specifically in eccentrically oriented lesions. Future studies are necessary to evaluate its role in improving diagnostic accuracy with other imaging technologies (*i.e.* cone beam CT) and the role of standardisation of procedural technique focusing on safety.

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