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Early View

Research letter

Safety and Feasibility of Ultrathin Probe Transbronchial Lung Cryobiopsy (UP-TBLC) without balloon blocker *via* Robotic Bronchoscopy in the evaluation of Peripheral Lung Lesions (PPLs): a retrospective pilot study

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" Safety and Feasibility of Ultrathin Probe Transbronchial Lung Cryobiopsy (UP-TBLC) without balloon blocker via Robotic Bronchoscopy in the evaluation of Peripheral Lung Lesions (PPLs): a retrospective pilot study."

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Ismael Matus: Contributed to conceptualization, designed procedural protocol and performed procedures. Data collection, analysis and interpretation of data. Drafting and approval of the final manuscript.

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Introduction:

The incidence of radiographically detected asymptomatic peripheral pulmonary lesions (PPLs) is growing with adoption of lung cancer screening by low-dose chest 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 optimize 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 localization 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 uni-directional tools tend to fail.

To our knowledge we herein report a first experience of UP-TBLC via the Monarch robotic-assisted bronchoscopy (RAB) system for the diagnosis of PPLs with primary endpoints of safety and feasibility.

Methods:

IRB-approved (CCC#42079) retrospective review of 58 lesions in 53 patients that underwent RAB with RP-EBUS guided UP-TBLC, complimenting traditional sampling methods of PPLs during single user's first adoption of RAB between June 2022 and November 2022.

Data collected included patient demographics, PPLs' computed tomography (CT) characteristics including size based on the longest diameter on any computed tomographic plane, morphology, lobar location, centrality determined by PPLs' closest edge to pleural distance measured, bronchus sign's status, 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 visualized 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 categorized based on a Delphi Consensus Statement from the Nashville Working Group's standardization of definitions for bleeding after transbronchial lung biopsy.

Patient Selection:

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.

Procedural Protocol and Technique:

Under general anesthesia via an endotracheal tube, Monarch™ (Johnson and Johnson, Indiana, United States) 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, Minnesota United States) and 15G Gencut™ (Medtronic, Minnesota, United States) aspirations, 1.1 mm UP-TBLC (Erbecryo™ 2,Tuebingen, Germany), forceps biopsy (Radial Jaw, Boston Scientific, Massachusetts, United States) and bronchoalveolar lavage (BAL). Three to five cryobiopsies and forcep 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 seconds applied followed by simultaneous continuous tissue freezing with cryoprobe activation during rapid tissue retrieval through the working channel. Prophylactic endobronchial balloon blockade was not performed. Three- 4 Fr Fogarty balloons were available for blockade if deemed necessary.

Results:

The median age was 69 (range 40-86) with a majority female subjects (57.4% n=31). The PPLs' median longest diameter of 15 mm (range 7 - 39 mm; IQR 11 mm) was obtained from measuring nodules on ax-

ial, coronal and sagittal computed tomographic planes. PPLs' closest edge to pleural distance was a median of 13.5 mm (range 0-31 mm) with IQR of 8 mm. A majority were solid (n=46, 79%) localized to the upper lobes (n=34, 58.6%) and with a-bronchus sign (n=34, 58.6%).

Diagnostic yield (DY) of 74% (43/58) was calculated based on rate of specific pathological findings. Malignancy was confirmed in 34 nodules (58.6%), specific benign etiology confirmed in 9 nodules (15.5%) and 15 nodules (25.9%) were considered inconclusive on the basis of obtaining either normal bronchial/alveolar tissue or non-specific inflammation (Table 1). Golden standard follow-up of inconclusive results with surveillance CT scan for 6-12 months and/or additional CT guided tissue sampling is ongoing as part of the strict methodology for calculating diagnostic yield, and therefore not available at time of manuscript production.

RP-EBUS views were observed confirming localization of 94.8% (55/58) of the PPL's . DY of 84% for concentric lesions (21/25) and 73% for eccentric or adjacent lesion (22/30) (Table 1).

UP-TBLC offered incremental yields of 15.5 % (9/58), with a 12% (3/25) and 20% (6/30) DY for the concentric and eccentric/adjacent lesions, respectively. FB alone and Gencut™ offered incremental 1.7% (1/58) and 1.7% (1/58) yields, respectively (Table 1).

Complications:

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

Four Grade 2 bleeds (6.9%) occurred based on the Nashville Bleeding Scale, meaning a requirement of one or more tools were used to control or prevent further bleeding- i.e. suctioning more than 1 minute required or repeat wedging of the bronchoscope for persistent bleeding or instillation of cold saline, diluted vasoactive substances or thrombin.

Zero mortality (Table 1).

Discussion:

Discrepancies between successful real-time lesion localization by RP-EBUS confirmation and obtaining definitive diagnostic specimens emphasize 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 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 exist suggesting that TBLC is an acceptable alternative to surgical lung biopsy for undetermined ILD in medical centers with experience performing and interpreting TBLC [3].

Complications of TBLCB in ILD include bleeding, pneumothorax and death. The incidence of PTX (1.4%-20.2%) appears related to the number of samples, number of segment and lobes sampled, probe size, functional impairment, fibrotic HRCT scores and the presence of usual interstitial pneumonitis pattern [4,5]. Clinically significant or severe bleeding when using prophylactic bronchial blocker is 0% - 6.3% and mortality is 0% - 4.1% [5].

Safety data has 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 secs 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 of 2-4 secs.

Recent studies evaluating TBLC with differing probe sizes using an alternative RAB system and a variety of non-robotic 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) in which cryobiopsy was the sole diagnostic modality [11], and a 20% incremental yield with eccentric/adjacent PPL localizations on RP-EBUS. TBLC's impact on diagnostic accuracy will need to be studied, ideally with reporting of the definition of 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 endeavor given acceptable complication rates of pneumothorax (4.3%), 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 DY which does not allow for the inclusion of clinical follow-up data of the inconclusive results, thereby potentially underestimating DY [13]. The observational nature of our study did not support an independent evaluation of each tissue acquisition tool's performance.

Conclusion:

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 (ie. cone beam computed tomography) and the role for standardization of procedural technique focusing on safety.

Table 1. Results, complications and diagnoses.

Number of Lesions	n=58; frequency (%)
Overall Diagnostic Yield (n,%)	43/58 (74%)
Malignant	34/58 (58.6%)
Non-Malignant	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 visualized	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	**n= 58, Frequency (%)**
Malignancy	**34 (58.6%)**
Poorly differentiated non small 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-necrotizing granuloma	**5 (8.6%)**
Organizing pneumonia	**2 (3.4%)**
Hamartoma	**1 (1.7%)**
Aspergillus infection	**1 (1.7%)**
Inconclusive	**15 (25.9%)**
Non-specific inflammation	**9 (15.5%)**
Atypical cells	**3 (5.2%)**
Normal alveolar parenchyma	**2 (3.4%)**
Atypical metaplasia	**1 (1.7%)**

* All bleeds were classified as Grade 2 based on the Delphi Consensus Statement from teh Nashville Working Group

PPL- Peripheral pulmonary lesion; *BAL*- Bronchoalveolar lavage

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