CT-Fluoroscopic Guidance for Performance of Targeted Transbronchial Cryobiopsy: A Preliminary Report

Daniel P. Steinfort^{a, b} Robert D. D'Agostino^c Ivan Vrljic^c Paul Einsiedel^c
Jyotika D. Prasad^a Barton R. Jennings^d Stefan Heinze^c Louis B. Irving^a

^aDepartment of Respiratory Medicine, Royal Melbourne Hospital, Parkville, VIC, Australia; ^bDepartment of Medicine (RMH), University of Melbourne, Parkville, VIC, Australia; ^cDepartment of Radiology, Royal Melbourne Hospital, Parkville, VIC, Australia; ^dDepartment of Respiratory and Sleep Medicine, Monash Medical Centre, Clayton, VIC, Australia

Keywords

Bronchoscopy · Complications · Interstitial lung disease · Interventional pulmonology · Transbronchial lung biopsy cryobiopsy

Abstract

Background: Bronchoscopic transbronchial cryobiopsy is increasingly used for the histological assessment of diffuse parenchymal lung disease. Diagnostic performance may be improved by more accurate targeting of biopsy to radiologic abnormalities, and complication rates may be reduced by avoiding biopsy of pleura or larger vessels. **Objectives:** To report the preliminary experience of using CT-fluoroscopic guidance for accurate targeting of bronchoscopic transbronchial cryobiopsy. **Methods:** Bronchoscopic cryobiopsy was performed in a hybrid CT theatre. 3D CT images were acquired following positioning of the cryoprobe in a distal airway segment. Where cryoprobe position was observed to be too close to the chest wall/diaphragm pleura, or not within the region of interest within the lung parenchyma, re-positioning of probe was undertaken and repeat 3D images were acquired to confirm positioning prior to cryobiopsy. **Results:** CT-fluoroscopic transbronchial cryobiopsy was successfully performed in 4 patients: 3 patients with interstitial

lung infiltrates, and one with an enlarging left upper lobe mass. Images were reviewed following each acquisition to accurately assess the probe position within the lung parenchyma, and relative to other thoracic structures. Intra-procedural imaging was of sufficient quality to allow the accurate positioning of the cryoprobe tip with respect to both the parenchymal region of interest and pleural surfaces. No complications were experienced, and all procedures yielded diagnostic specimens. **Conclusions:** Our preliminary experience confirms the feasibility of performing transbronchial cryobiopsy under CT-fluoroscopic guidance. Accurate targeting of transbronchial cryobiopsy may be achieved using CT-fluoroscopic guidance. Positioning of the probe tip, both with respect to parenchymal region of interest and to pleural surfaces, can be established with high accuracy.

© 2018 S. Karger AG, Basel

Introduction

Transbronchial cryobiopsy is increasingly used in the assessment of diffuse parenchymal lung disease (DPLD). Evidence to date suggests that the diagnostic yield in the assessment of DPLD may be comparable to surgical lung biopsy, with significantly lower morbidity and mortality

[1]. Transbronchial cryobiopsy has also been reported to improve the diagnostic yield of radial endobronchial ultrasound (EBUS) in the assessment of peripheral pulmonary lesions [2].

The use of fluoroscopic guidance has been shown to reduce intercostal drain rates following conventional forceps transbronchial biopsy [3], and accurate positioning of the probe tip is even more paramount for the safe performance of cryobiopsy, where a larger volume of cryobiopsy specimens [4] implies a much larger disruption to lung parenchyma and pleura.

No standardized protocol for cryoprobe positioning has been established [5]. Sampling within 1 cm of pleural surface has been advocated by some authors to ensure that a representative tissue is obtained [1, 6], but this may occur at the expense of a higher pneumothorax rate [7, 8]. Relationship of the probe tip to the pleura can generally be established with the lateral positioning of the cryoprobe tip [7], though the probe-to-pleura distance is not so clear when the probe path is not perpendicular to the P-A plane of C-arm imaging.

We hypothesized that CT-fluoroscopic guidance may improve the targeting of cryobiopsy sampling toward radiologically affected areas within the lung, and may improve the safety profile by accurately establishing the probe-to-pleura relationship. We report our preliminary experience in CT-fluoroscopic guidance for the accurate targeting of transbronchial cryobiopsy to establish feasibility of the technique.

Materials and Methods

Institutional Human Research Ethics Committee approval was granted for performing this study. We prospectively recorded procedural and diagnostic outcomes for 4 patients undergoing transbronchial cryobiopsy under CT-fluoroscopic vision for investigation of parenchymal lung abnormalities.

Bronchoscopic Procedure

Bronchoscopy was performed under general anesthesia (endotracheal tube) in a hybrid CT theatre. The video bronchoscope (BF-1TH-190, Olympus Japan) was used to place an Arndt bronchial blocker (Cook Medical, Bloomington, IN, USA) at the origin of the lobe targeted for biopsy prior to cryobiopsy in all cases, as previously described [9].

Where cryobiopsy was performed for sampling of a lung mass, radial EBUS (UM-S20-17S; Olympus, Tokyo, Japan) was performed earlier, to confirm the tumor location within a sub-segment of the target bronchus and select an optimal segment for cryobiopsy.

The 1.9 mm cryoprobe (ERBE, Solingen, Germany) was advanced under fluoroscopic vision into the target bronchial seg-

ment under routine 2-D fluoroscopic vision. When the probe was positioned within the proposed target segment, CT-fluoroscopic imaging was performed.

CT-Fluoroscopic Imaging and Performance of Cryobiopsy

Imaging was performed following the positioning of the cryoprobe in a distal airway segment. 3D CT images (Artis Zeego Q, Siemens AG, Munich, Germany) were acquired using 90 kV 6 s Digital Chest Tomosynthesis 200 degree rotational acquisition at a frame rate of 0.5 degrees per frame (397 frames).

Images were reviewed following each acquisition, and they were examined in axial, coronal and sagittal planes to most accurately assess the probe position within the lung parenchyma, and relative to other thoracic structures. Where required, multi-planar reconstruction (MPR) was used to optimize views along the probe pathway, as is frequently performed for the guidance of percutaneous needle biopsy using oblique pathways.

Where the cryoprobe position was observed to be within 10 mm of the chest wall/diaphragm pleura, or not within the region of interest within the lung parenchyma, re-positioning of probe was undertaken and repeat 3D images were acquired to confirm positioning prior to biopsy. The 10 mm probe-pleura distance was based on previous studies identifying distances of less than 1 cm being associated with a significantly increased risk of pneumothorax [10]. The number of imaging acquisitions was recorded for each patient.

Cryobiopsy was performed (5 s freeze time [11]) following accurate probe positioning using nitrous oxide as the cryogen. CT-fluoroscopic imaging was repeated following positioning of cryoprobe for subsequent biopsies. We sought to perform 2 biopsies per patient, as is our standard institutional practice. This number was chosen based on available evidence indicating a good balance between diagnostic yield [12], and complication rates [13]. Patients routinely underwent post-procedure chest X-ray to screen for pneumothorax. Bleeding severity was graded, as described by Pajares et al. [14].

Results

Four patients underwent CT-fluoroscopic transbronchial cryobiopsy between July 19, 2017 and August 16, 2017. Three patients were investigated for interstitial lung infiltrates (2 female, 1 male) and 1 male underwent EBUS-guided transbronchial cryobiopsy of an enlarging left upper lobe mass, where prior EBUS-GS forceps biopsy was non-diagnostic. Clinical details and procedural outcomes of the 4 patients are presented in Table 1. More detailed case descriptions are presented below.

Multiple cryobiopsy specimens were successfully collected from each patient. All procedures yielded diagnostic specimens. No major complications occurred. Grade 0 bleeding (none) was observed in 2 patients, and Grade 1 bleeding (managed with bronchoscopic suction only) was observed in 2 patients. All patients were discharged home the same day.

Fig. 1. Diagnostic and fluoroscopic CT images from *patient 1*. Diagnostic axial CT (**a**) demonstrating radiographic abnormality targeted by cryobiopsy. CT-fluoroscopy was used to identify the position of the probe within the area of radiographic abnormality. Probe tip position is demonstrated in axial (**b**) and coronal (**c**)

CT-fluoroscopic imaging. P-A 2D fluoroscopic imaging would be unlikely to identify the proximity of the probe tip to visceral pleural surface. Biopsy was successfully performed following the withdrawal of probe by 1 cm from the position pictured.

Table 1. Clinico-radiologic details and procedural outcomes

Patient (age, years)	Clinical scenario	Target lobe	Number biopsies*	Probe-to pleura distance, mm	Number of CT-imaging acquisitions	Number of CT acquisitions prior to first biopsy	CT-fluoroscopic screening duration, s	Procedure duration, min	Histological diagnosis	Effective radiation dose, mSv
#1 (70)	Steroid-responsive relapsing lung infiltrates; Bland BAL	RLL	2	25 and 32	7	4	42		Eosinophilic bronchitis	60.8
#2 (73)	ILD, atypical for UIP	Lingula	1	18	8	5	48		Fibrosing NSIP	36.5
		LLL	1	15						
#3 (78)	Hypoplastic myelodysplasia, progressive LUL mass; EBUS-GS non-diagnostic	LUL	2	44	3	2	15		EBV+ lymphocytic vasculitis	9.2
#4 (67)	Steroid-resistant bilateral lower zone interstitial infiltrates	LLL	2	14	4	2	20		Cryptogenic organizing pneumonia	19.2

* Where multiple biopsies were performed from the same lobe, individual biopsies were taken from adjacent bronchial segments [21].

BAL, bronchoalveolar lavage; ILD, interstitial lung disease; UIP, usual interstitial pneumonia; NSIP, non-specific interstitial pneumonia; LUL, left upper lobe; RLL, right lower lobe; mSv, milliSievert; EBV, Epstein-Barr virus.

Contribution of CT-Fluoroscopic Guidance

Patient 1: CT-fluoroscopic transbronchial cryobiopsy was successfully used to target migratory infiltrates in a 70-year-old female with transient peripheral blood eosinophilia and migratory pulmonary infiltrates (Fig. 1). Prior bronchoalveolar lavage had not demonstrated eosinophilia, thus diagnostic uncertainty remained. CT-fluoroscopy was used to confirm the position of the probe within radiographically abnormal region, and to ascertain the exact distance of the probe from visceral pleura prior to performance of cryobiopsy.

Patient 2: A 72-year-old male was referred for cryobiopsy to investigate progressive interstitial lung infiltrates, with radiology felt atypical for usual interstitial pneumonia (Fig. 2). Infiltrates were patchy and CT-fluoroscopy was used to direct cryobiopsy to areas with significant radiographic abnormality.

Real-time image manipulation using multi-planar reconstruction was successfully undertaken to view images in oblique planes to optimally assess the probe position (Fig. 3).

Patient 3: CT-fluoroscopic transbronchial cryobiopsy was successfully used to perform “real-time” cryobiopsy

Fig. 2. Diagnostic and fluoroscopic CT images from *patient 2*. Diagnostic CT axial imaging of left upper lobe (**a**) and left lower lobe (**b**) demonstrating patchy peripheral sub-pleural reticular opacities without apicobasal gradient, not typical for usual interstitial pneumonia. Cryobiopsy could be accurately targeted to regions of interest in both LUL (**c**) and LLL (**d**) with imaging demonstrating the bronchoscope tip in central lobar airways and probe tip in the sub-pleural lung parenchyma.

in a 77-year-old male with a progressive left upper lobe mass (Fig. 4a). Following confirmation of positioning within the target lesion (Fig. 4b), cryobiopsy was successfully performed.

Patient 4: A 67-year-old female was referred for cryobiopsy to investigate steroid-resistant bilateral basal infiltrates (Fig. 5). High quality images allowed the repositioning of probe when CT-fluoroscopy demonstrated that the probe position was not optimal relative to target area/lesion or relative to pleura/diaphragm.

Discussion

Our preliminary experience confirms the feasibility of performing transbronchial cryobiopsy under CT-fluoroscopic guidance. Intra-procedural imaging was of sufficient quality to allow accurate positioning of the cryoprobe tip with respect to both the parenchymal region of interest and pleural surfaces. Cryobiopsy in all 4 patients was diagnostic, with no complications observed.

Images could be reviewed following each acquisition in axial, coronal and sagittal planes to most accurately assess the probe position within the lung parenchyma, and relative to other thoracic structures. Where necessary, real-time image manipulation allowed viewing in oblique

Fig. 3. Real-time image manipulation of CT-fluoroscopic images via Multi-planar reconstruction (MPR) allows oblique plane imaging to optimally assess the probe position. Images demonstrate 45-degree oblique coronal imaging within a plane identified by purple MPR line in Figure 2c (**a**) and Figure 2d (**b**; patient 2). Images demonstrate path of cryoprobe and clearly establish the position of the probe tip relative to chest wall.

Fig. 4. Diagnostic and fluoroscopic CT images from patient 3. Diagnostic CT demonstrates left upper lobe mass (a) with CT-fluoroscopic image (b) demonstrating accurate positioning of cryoprobe tip within LUL mass. Cryobiopsy was successfully performed at this site.

Fig. 5. Diagnostic imaging from patient 4 (a, b) demonstrating basal distribution of infiltrates. First acquisition CT-fluoroscopic coronal imaging (c) demonstrates the initial probe position. While positioning of the probe tip relative to chest wall may have been appropriate, imaging demonstrated that the probe was positioned too close to diaphragmatic pleura (<5 mm) to allow safe performance of cryobiopsy even with partial withdrawal of probe to more proximal position. No biopsy was performed from this airway segment, and probe was repositioned in a more superior segment prior to repeat CT-fluoroscopic imaging (d). Safe distance from diaphragm was identified and the probe was advanced more distally prior to the successful performance of cryobiopsy.

planes to optimally assess probe position. Beyond feasibility of CT-fluoroscopic guidance of cryobiopsy, our preliminary experience indicate the further potential of the technique to achieve more accurate targeting of sampling to regions of radiologic abnormality (e.g., patchy interstitial infiltrates – patients #1 and 2, or parenchymal mass lesions – patient #3), and in identifying areas where a higher risk of complications may be anticipated (e.g., patient #4) to allow redirection of sampling.

Transbronchial cryobiopsy continues to gain acceptance as an important technique for the evaluation of patients with DPLD. Studies suggest that diagnostic performance may be comparable to surgical lung biopsy [1, 15,

16], with significantly favorable morbidity/mortality [17, 18]. Isolated reports have expressed concerns regarding the safety of transbronchial cryobiopsy [19], and diagnostic performance remains variable [1, 17]. Notwithstanding significant methodological limitations in the study by DiBardino et al. [5, 20, 21], certainly, refinement of technique may achieve further improvements in diagnostic performance and complication rates.

The original report describing the performance of transbronchial cryobiopsy utilized fluoroscopic guidance [22], and subsequent reports included fluoroscopic guidance as part of the cryobiopsy procedure. High rates of complications have been observed in procedures per-

formed without fluoroscopic vision [13, 19], and subsequent comment has noted the importance of fluoroscopic guidance during transbronchial cryobiopsy [20]. It is possible that high complication rates observed in some studies utilizing fluoroscopy are a result of sub-optimal imaging achieved by 2-D C-arm fluoroscopy.

Our findings indicate a potential for CT-fluoroscopic guidance of transbronchial cryobiopsy to improve both diagnostic performance, through more targeted sampling of lung parenchyma, and complication rates, through more accurate positioning of the cryoprobe tip within radiologically affected areas. Systematic reviews indicate non-diagnostic sampling in approximately 20% of patients [1, 23], though isolated reports describe non-diagnostic outcomes in up to 49%. This is particularly relevant to patient #1, where more peripheral sampling may not have demonstrated pathologic abnormalities. More central airway sampling is suggested to allow examination of small caliber airways [7], though interestingly, presence of bronchiolar airways in cryobiopsy specimens has been reported by multiple authors even following sampling approximately 2 cm from the pleura [18, 24]. The ability of CT-fluoroscopy to confirm the position of cryoprobe may have been instrumental in achieving a diagnosis in this patient – adjacent lung parenchyma demonstrated only normal findings, and biopsy performed more peripherally may not have retrieved diagnostic tissue.

A recent study by Ravaglia et al. [12] reported increased diagnostic yield when cryobiopsy was performed from 2 separate bronchial segments, though this came at the cost of increased pneumothorax rate (4.5 vs. 26%). Accurate positioning of the cryoprobe relative to pleura using C-arm fluoroscopy is possible in only a limited number of bronchial segments, mostly in a lateral plane (perpendicular to the C-arm imaging plane). Rotational fluoroscopy, as sometimes used in coronary angiography, may more accurately establish probe-pleura distance in patients where the probe pathway is oblique to the lateral plane. However, the relationship of the probe to the radiologic abnormality, as well as to diaphragm and other intrathoracic structures, would remain unelucidated. The use of CT-fluoroscopy may allow increased yield associated with sampling of more than one bronchial segment, while minimizing complications.

Additional techniques to minimize risks of complications have been reported. Berim et al. [25] described use of radial EBUS prior to cryobiopsy to identify peri-bronchial vessels prior to cryobiopsy. Bleeding was not observed among 6 patients, where cryobiopsy was directed by radial EBUS. Given that the radial EBUS guidance is

not “real-time,” there is some risk that sampling may still occur adjacent to vessels. Images acquired during CT-fluoroscopy are non-contrast and hence visualization of vessels is not achieved. However, identification of central positioning of the probe, where risk of biopsy of larger caliber vessels (and therefore risk of major hemorrhage) is possible with CT-fluoroscopy, and confirmation that probe positioning correlates with safe areas for sampling as suggested by Radial EBUS may allow these 2 techniques to be complementary in minimizing the risk of complications.

CT-fluoroscopic guidance of bronchoscopic techniques may in future also be used to target therapeutic applications, and with use of onsite cytology [26] may even allow diagnosis and therapy to be undertaken in the one procedure, as has been described for fiducial marker implantation [27]. Increasing use of cryobiopsy for the assessment of non-interstitial diseases [28] and parenchymal masses has been reported [2, 29]. Advent of a new 1.1 mm mini-cryoprobe [30] may further expand the potential of cryobiopsy, particularly when combined with highly accurate guidance from CT-fluoroscopy.

Across these 4 cases, we refined imaging protocols to reduce radiation exposure whilst observing maintenance of imaging quality. Reduction in infero-superior imaging field dimension saw a 50% reduction in dose per acquisition, and reduction in interval of imaging (6–5 s) and exposure factors further reduced radiation dose by approximately 30% per acquisition. Notably, effective doses for the final 2 patients are well within that reported for other diagnostic interventions [31, 32]. Further studies should examine acquisition protocols that achieve adequate imaging with minimal effective radiation.

We present a limited experience confirming feasibility of this technique; however, the effect on diagnostic performance and complication rates remains to be established. The expert statement published subsequent to the completion of this study recommends 3–5 biopsies per patient, though the authors acknowledge that “the optimal number of biopsies cannot be uniformly established” [10]. While increased diagnostic yield has been reported in studies where sampling was performed from more than one bronchial segment [12], complication rates were also higher [12, 13]. Future studies are required to determine if CT-fluoroscopy allows increased biopsy number without a concomitant increased complication rate.

Refinement of the technique should include minimization of effective radiation dose, which clearly exceeds that associated with conventional C-arm fluoroscopic guidance for bronchoscopic procedures [33].

Conclusion

We confirm that accurate targeting of transbronchial cryobiopsy may be achieved using CT-fluoroscopic guidance. Positioning of the probe tip, both with respect to the parenchymal region of interest and pleural sur-

faces, can be established with high accuracy. The potential for CT-fluoroscopic guidance of transbronchial cryobiopsy in the assessment of parenchymal lung abnormalities to improve both the diagnostic performance and complication rates should be established in prospective studies.

References

- Ravaglia C, Bonifazi M, Wells AU, Tomassetti S, Gurioli C, Piciucchi S, Dubini A, Tantalocco P, Sanna S, Negri E, Tramacere I, Ventura VA, Cavazza A, Rossi A, Chilosi M, La Vecchia C, Gasparini S, Poletti V: Safety and diagnostic yield of transbronchial lung cryobiopsy in diffuse parenchymal lung diseases: a comparative study versus video-assisted thoracoscopic lung biopsy and a systematic review of the literature. *Respiration* 2016;91:215–227.
- Schuhmann M, Bostanci K, Bugalho A, Warth A, Schnabel PA, Herth FJ, Eberhardt R: Endobronchial ultrasound-guided cryobiopsies in peripheral pulmonary lesions: a feasibility study. *Eur Respir J* 2014;43:233–239.
- Smyth CM, Stead RJ: Survey of flexible fiberoptic bronchoscopy in the United Kingdom. *Eur Respir J* 2002;19:458–463.
- Kropski JA, Pritchett JM, Mason WR, Sivara-jan L, Gleaves LA, Johnson JE, Lancaster LH, Lawson WE, Blackwell TS, Steele MP, Loyd JE, Rickman OB: Bronchoscopic cryobiopsy for the diagnosis of diffuse parenchymal lung disease. *PLoS One* 2013;8:e78674.
- Poletti V, Hetzel J: Transbronchial cryobiopsy in diffuse parenchymal lung disease: need for procedural standardization. *Respiration* 2015;90:275–278.
- Casoni GL, Tomassetti S, Cavazza A, Colby TV, Dubini A, Ryu JH, Carretta E, Tantalocco P, Piciucchi S, Ravaglia C, Gurioli C, Romagnoli M, Gurioli C, Chilosi M, Poletti V: Transbronchial lung cryobiopsy in the diagnosis of fibrotic interstitial lung diseases. *PLoS One* 2014;9:e86716.
- Lentz RJ, Argento AC, Colby TV, Rickman OB, Maldonado F: Transbronchial cryobiopsy for diffuse parenchymal lung disease: a state-of-the-art review of procedural techniques, current evidence, and future challenges. *J Thorac Dis* 2017;9:2186–2203.
- Linhas R, Marcoa R, Oliveira A, Almeida J, Neves S, Campainha S: Transbronchial lung cryobiopsy: associated complications. *Rev Port Pneumol* (2006) 2017;23:331–337.
- Hohberger LA, DePew ZS, Utz JP, Edell ES, Maldonado F: Utilizing an endobronchial blocker and a flexible bronchoscope for transbronchial cryobiopsies in diffuse parenchymal lung disease. *Respiration* 2014;88:521–522.
- Hetzel J, Maldonado F, Ravaglia C, Wells AU, Colby TV, Tomassetti S, Ryu JH, Fruchter O, Piciucchi S, Dubini A, Cavazza A, Chilosi M, Sverzellati N, Valeyre D, Leduc D, Walsh SLF, Gasparini S, Hetzel M, Hagmeyer L, Haentschel M, Eberhardt R, Darwiche K, Yarmus LB, Torrego A, Krishna G, Shah PL, Annema JT, Herth FJF, Poletti V: Transbronchial cryobiopsies for the diagnosis of diffuse parenchymal lung diseases: expert statement from the cryobiopsy working group on safety and utility and a call for standardization of the procedure. *Respiration* 2018;95:188–200.
- Ing M, Oliver RA, Oliver BG, Walsh WR, Williamson JP: Evaluation of transbronchial lung cryobiopsy size and freezing time: a prognostic animal study. *Respiration* 2016;92:34–39.
- Ravaglia C, Wells AU, Tomassetti S, Dubini A, Cavazza A, Piciucchi S, Sverzellati N, Gurioli C, Gurioli C, Costabel U, Tantalocco P, Ryu JH, Chilosi M, Poletti V: Transbronchial lung cryobiopsy in diffuse parenchymal lung disease: comparison between biopsy from 1 segment and biopsy from 2 segments – diagnostic yield and complications. *Respiration* 2017;93:285–292.
- Dhooria S, Mehta RM, Srinivasan A, Madan K, Sehgal IS, Pattabhiraman V, Yadav P, Sivaramakrishnan M, Mohan A, Bal A, Garg M, Agarwal R: The safety and efficacy of different methods for obtaining transbronchial lung cryobiopsy in diffuse lung diseases. *Clin Respir J* 2018;12:1711–1720.
- Pajares V, Puzo C, Castillo D, Lerma E, Montero MA, Ramos-Barbon D, Amor-Carro O, Gil de Bernabe A, Franquet T, Plaza V, Hetzel J, Sanchis J, Torrego A: Diagnostic yield of transbronchial cryobiopsy in interstitial lung disease: a randomized trial. *Respirology* 2014;19:900–906.
- Tomassetti S, Wells AU, Costabel U, Cavazza A, Colby TV, Rossi G, Sverzellati N, Carloni A, Carretta E, Bucciolini M, Tantalocco P, Ravaglia C, Gurioli C, Dubini A, Piciucchi S, Ryu JH, Poletti V: Bronchoscopic lung cryobiopsy increases diagnostic confidence in the multidisciplinary diagnosis of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2016;193:745–752.
- Sharp C, McCabe M, Adamali H, Medford AR: Use of transbronchial cryobiopsy in the diagnosis of interstitial lung disease—a systematic review and cost analysis. *QJM* 2017;110:207–214.
- Tomassetti S, Ravaglia C, Poletti V: Diffuse parenchymal lung disease. *Eur Respir Rev* 2017;26:pii:170004.
- Lentz RJ, Taylor TM, Kropski JA, Sandler KL, Johnson JE, Blackwell TS, Maldonado F, Rickman OB: Utility of flexible bronchoscopic cryobiopsy for diagnosis of diffuse parenchymal lung diseases. *J Bronchology Interv Pulmonol* 2018;25:88–96.
- DiBardino DM, Haas AR, Lanfranco AR, Litzky LA, Serman D, Bessich JL: High complication rate after introduction of transbronchial cryobiopsy into clinical practice at an academic medical center. *Ann Am Thorac Soc* 2017;14:851–857.
- Lentz RJ, Argento AC, Rickman OB, Ryu JH, Poletti V, Hetzel J, Maldonado F: Transbronchial cryobiopsy: a cautionary tale and opportunities for improvement. *Ann Am Thorac Soc* 2017;14:1230–1231.
- Bendstrup E, Kronborg-White S, Poletti V, Folkersen B, Voldby N, Rasmussen TR: Careful planning reduces cryobiopsy complications. *Ann Am Thorac Soc* 2017;14:1229.
- Babiak A, Hetzel J, Krishna G, Fritz P, Moeller P, Balli T, Hetzel M: Transbronchial cryobiopsy: a new tool for lung biopsies. *Respiration* 2009;78:203–208.
- Johannson KA, Marcoux VS, Ronksley PE, Ryerson CJ: Diagnostic yield and complications of transbronchial lung cryobiopsy for interstitial lung disease. A systematic review and metaanalysis. *Ann Am Thorac Soc* 2016;13:1828–1838.
- Lentz RJ, Fessel JP, Johnson JE, Maldonado F, Miller RF, Rickman OB: Transbronchial cryobiopsy can diagnose constrictive bronchiolitis in veterans of recent conflicts in the middle east. *Am J Respir Crit Care Med* 2016;193:806–808.
- Berim IG, Saeed AI, Awab A, Highley A, Colanta A, Chaudry F: Radial probe ultrasound-guided cryobiopsy. *J Bronchology Interv Pulmonol* 2017;24:170–173.
- Steinfert DP, Leong TL, Laska IF, Beaty A, Tsui A, Irving LB: Diagnostic utility and accuracy of rapid on-site evaluation of bronchoscopic brushings. *Eur Respir J* 2015;45:1653–1660.
- Steinfert DP, Siva S, Kron T, Chee RR, Ruben JD, Ball DL, Irving LB: Multimodality guidance for accurate bronchoscopic insertion of fiducial markers. *J Thorac Oncol* 2015;10:324–330.

- 28 Sanchez-Cabral O, Martinez-Mendoza D, Fernandez-Bussy S, Lopez-Gonzalez B, Perea-Talamantes C, Rivera-Rosales RM, Luna-Rivero C, Martinez-Orozco JA, Flores-Suarez LF, Santillan-Doherty P, Reyes-Teran G: Utility of transbronchial lung cryobiopsy in non-interstitial diseases. *Respiration* 2017;94: 285–292.
- 29 Herath S, Yap E: Novel hybrid cryo-radial method: an emerging alternative to CT-guided biopsy in suspected lung cancer. A prospective case series and description of technique. *Respirol Case Rep* 2018;6:e00287.
- 30 Franke KJ, Linzenbold W, Nuessle D, Enderle M, Boesmueller H, Nilius G, Hetzel J: A new tool for transbronchial cryobiopsies in the lung: an experimental feasibility ex vivo study. *Respiration* 2016;91:228–234.
- 31 Garcia-Garcia HM, van Mieghem CA, Gonzalo N, Meijboom WB, Weustink AC, Onuma Y, Mollet NR, Schultz CJ, Meliga E, van der Ent M, Sianos G, Goedhart D, den Boer A, de Feyter P, Serruys PW: Computed tomography in total coronary occlusions (CTTO registry): radiation exposure and predictors of successful percutaneous intervention. *EuroIntervention* 2009;4:607–616.
- 32 Lumbreras B, Vilar J, Gonzalez-Alvarez I, Gomez-Saez N, Domingo ML, Lorente MF, Pastor-Valero M, Hernandez-Aguado I: The fate of patients with solitary pulmonary nodules: clinical management and radiation exposure associated. *PLoS One* 2016;11:e0158458.
- 33 Steinfert DP, Einsiedel P, Irving LB: Radiation dose to patients and clinicians during fluoroscopically-guided biopsy of peripheral pulmonary lesions. *Respir Care* 2010;55: 1469–1474.