Complications of Transbronchial Cryobiopsy

6

Claudia Ravaglia

Safety profile of transbronchial lung cryobiopsy has been recently compared to that of the conventional forceps or surgical lung biopsy; however, literature shows a variable incidence of complications, mostly bleeding and pneumothorax (Table 6.1). The significant variability of complications is related to the rapid spread of the technique around the world with variable competency and safety standards in different centers and the consequent variability of the procedure itself, in terms of airway access, ventilation, sedation, use of balloon/endobronchial blockers, probe size and freezing time, distance from the pleura, or sampling strategy.

Unlike conventional transbronchial biopsy, which is more rarely complicated by pneumothorax [39], pneumothorax seems to be the most common complication occurring after transbronchial lung cryobiopsy (TLCB), with a rate that varies considerably between different studies: from less than 1% to almost 30% [2, 3, 5, 6, 9, 11, 12, 15, 40–43]. In a meta-analysis that included 15 studies comprising 994 patients, the average rate was 10% [15], and similar results were confirmed by a more recent meta-analysis of 13 studies with an incidence of post-procedural pneumothorax of 9.5% (5.9–14.9%) [41]. There are very few data regarding chest drain-

age; however Ravaglia et al. showed that out of the pneumothoraces reported, 70% required chest tube drainage, with an overall probability of developing a pneumothorax requiring chest tube drainage of 0.03 (95% CI 0.01–0.08); furthermore, when chest drainage is necessary, time of drainage is usually similar to that of drainage after video-assisted thoracoscopy (VATS) [15]. The risk of pneumothorax can be influenced by patient-related factors (radiological fibrotic score and UIP pattern) or procedure-related factors (type of sedation/airway control, distance from the pleura, size of the probe and freezing time, sampling strategy, skill level of operator) (Table 6.2). Ravaglia et al. showed a higher proportion of events among intubated patients undergoing the procedure under deep sedation compared to those under conscious sedation [15]; this difference could be mainly due to the type of ventilation used, as patients undergoing the procedure under general anesthesia with invasive jet ventilation may develop pneumothorax much more frequently than under conditions of sedation and spontaneous breathing over a bronchoscopy tube [11]. In a large cohort of 699 patients who underwent transbronchial lung cryobiopsy for suspected diffuse parenchymal lung diseases at the Pulmonology Unit of Morgagni Hospital in Forlì (Italy), the risk of pneumothorax appears to be significantly reduced when a 1.9 mm probe is used compared to the 2.4 mm probe (2.7% vs 21.1%,

C. Ravaglia (✉)
Department of Diseases of the Thorax, Pulmonology Unit, GB Morgagni – L Pierantoni Hospital, Forlì, Italy

Table 6.1 Comparison between transbronchial forceps biopsy, transbronchial cryobiopsy, and surgical lung biopsy (Modified by Hetzel J et al. [1])

	Reference, year	Pneumothorax	Serious bleeding	Mortality due to AE (in 30 days)
Cryobiopsy	Babiak [2], 2009	2 (4.8%)	0	–
	Kropski [3], 2013	0	0	–
	Fruchter [4], 2013	0	0	–
	Yarmus [5], 2013	1 (4.8%)	0	0
	Pajares [6], 2014	3 (8%)	0	–
	Fruchter [7], 2014	2 (2.6%)	3 (4%)	0
	Pourabdollah [8], 2016	–	–	–
	Griff [9], 2014	0	0	0
	Hernández-Gonzáles [10], 2015	4 (12%)	0	0
	Hagmeyer [11], 2016	6 (19%)	2 (6%)	–
	Gershman [12], 2015	15 (5%)	16 (5%)	–
	Ramaswamy [13], 2016	11 (20%)	1 (2%)	0
	Echevarria-Uraga [14], 2016	3 (3%)	10 (10%)	–
	Ravaglia [15], 2016	60 (20%)	0	1 (0.3%)
	Ussavarungsi [16], 2017	1 (1.4%)	9 (12%)	–
	DiBardino [17], 2017	2 (8%)	3 (12%)	–
	Bango-Alvarez [18], 2017	5 (4.7%)	0	0
	Kronborg-White [19], 2017	10 (26%)	3 (8%)	0
	Sriprasart [20], 2017	5 (7%)	1 (1%)	–
	Ravaglia [21], 2017	7 (16%)	0	–
Forceps biopsy	Wall [22], 1981	2/52 (3.8%)	0	0
	O'Brien [23], 1997	10/83 (14.3%)	5/83 (6.0%)	0
	Berbescu [24], 2006	–	–	–
	Casoni [25], 2008	0	0	0
	Facciolongo [26], 2009	22/1660 (1.3%)	21/1660 (1.3%)	0
	Tomassetti [27], 2012	5/64 (8%)	–	0
	Yarmus [5], 2013	1/21 (4.76%)	0	0
	Pajares [6], 2014	2/38 (5.3%)	0	0
	Pourabdollah [8], 2016	–	–	–
	Gershman [12], 2015	9/286 (3.15%)	13/288 (4.4%)	0
	Ramaswamy [13], 2016	–	–	–
	Sheth [28], 2017	–	–	–
Surgical biopsy	Rena [29], 1999	NA	0	0
	Kreider [30], 2007	NA	0	3/68 (4.4%)
	Zhang [31], 2010	NA	0	3/418 (0.7%)
	Fibla [32], 2012	NA	0	–
	Blackhall [33], 2013	NA	0	4/103 (3.9%)
	Morris [34], 2014	NA	0	1/66 (1.5%)
	Rotolo [35], 2015	NA	0	4/161 (2.5%)
	Fibla [32], 2015	NA	0	28 (9%)
	Hutchinson [36], 2016	NA	–	2051/32,022 (6.4%)
	Hutchinson [37], 2016	NA	–	68/2820 (2.4%)
	Ravaglia [15], 2016	NA	0	4/150 (2.7%)
	Sheth [28], 2017	NA	0	–
	Lieberman [38], 2017	NA	0	1 (2.1%)

respectively, p 0.00010). Furthermore, the risk of pneumothorax increases when samples are taken from different sites instead of a unique site (p 0.0005) [21] and if they are taken close to the pleura [15, 25]. Finally, the risk of pneumo-thorax seems to correlate significantly with the presence of histological UIP pattern on biopsy, high-resolution computed tomography (HRCT) fibrosis score of the lower lung zones, and the bronchoscopist's learning curve [15, 25]. Chest

Table 6.2 Factors that can influence the risk of pneumothorax

Procedure-related factors
1. Type of sedation/airway control
2. Distance from the pleura
3. Size of the probe and freezing time
4. Sampling strategy
5. Skill level of operator
Patient-related factors
(a) HRCT fibrotic score
(b) UIP pattern

HRCT high-resolution computed tomography, *UIP* usual interstitial pneumonia

computed tomography (CT) represents currently the gold standard for the diagnosis of pneumothorax; however it is not routinely used, to avoid excess of radiation [37], and it is applicable only to uncertain cases; chest X-ray is used routinely for pneumothorax diagnosis, but with a sensitivity of 46% [44]. In recent years, the use of chest ultrasonography (US) has spread for the diagnosis of pneumothorax as it can reach a pooled sensitivity of 87% (95% CI 81–92%) and a specificity of 99% (95% CI 98–99%) [45] according to a standardized method searching for specific pathognomonic signs [46]. Accuracy of US for the detection of pneumothorax is higher than that of chest X-ray with reference to CT scan as a gold standard, and its use would have some advantages, avoiding exposure to radiation and reducing costs of health care and hospital stay. Chest US in pneumothorax diagnosis after transbronchial lung cryobiopsy has been evaluated for the first time by Viglietta et al. [47]: the analysis showed a sensitivity and a specificity of 90% and 94%, respectively. This approach exploits the ready availability of US that allows the pulmonologist who perform cryobiopsy to detect post-procedural pneumothorax within a short time and optimizes the use of ionizing radiation. A post-procedural chest X-ray or ultrasound examination should be performed to assess for the occurrence of pneumothorax either immediately (if desaturation, persistent cough, and/or thoracic pain are present) or 2–3 h after the end of the procedure if the patient is asymptomatic [47]; this is particularly relevant in the outpatient setting. Patients should be observed in the recovery area as per local institutional guidelines.

Another common complication of cryobiopsy is bleeding [2, 3, 5, 6, 9, 11, 14, 43, 48–51], although is generally readily controlled endoscopically, e.g., by the use of bronchial blockers (Fogarty balloon or other tools) and/or use of rigid bronchoscopy [5, 14, 15, 25, 51, 52]. There is no generally accepted bleeding severity scale, and therefore comparability of different papers is difficult. However, most papers grade on a scale of four steps: no bleeding, mild bleeding (e.g., requiring suction to clear but no other endoscopic procedures), moderate bleeding (e.g., requiring endoscopic procedures like bronchial occlusion-collapse and/or instillation of ice-cold saline), and severe bleeding (e.g., causing hemodynamic or respiratory instability, requiring tamponade or other surgical interventions, transfusions, or admission to the intensive care unit) [53]. In a previous meta-analysis, moderate bleeding after cryobiopsy was observed in 65 cases among 383 patients from 12 studies (16.9%), with an overall pooled probability of developing a moderate bleeding of about 0.12 (CI 0.02–0.25) [15]. No episodes of severe bleeding, as defined above, are reported in literature (in some papers bleeding has been reported as severe, but it was controlled by placement of bronchial blocker or catheter) [49], and no bleeding-related deaths have been reported after cryobiopsy. A recently published report highlights the risk of potentially life-threatening complications when these precautions are not taken [17]. Abnormal coagulation parameters and the use of clopidogrel or other new antiplatelet drugs are considered contraindications; treatment with aspirin is regarded as a relative contraindication. In the absence of more definitive data and given the increased bleeding risk compared to conventional forceps biopsies, a conservative approach would be to hold all medications potentially associated with increased bleeding risk. Thrombocytopenia ($<50 \times 10/L$) is suggested to be a contraindication for biopsies during flexible bronchoscopy [51]. These values may be accepted also for TLCB until data on this topic will become available. Patients with clinical or radiological signs of pulmonary hypertension should have a pre-procedural evaluation of pulmonary artery pressure by echocardiography or right heart catheterization. An estimated systolic

pulmonary artery pressure >50 mmHg on echo-cardiography indicates an increased likelihood of pulmonary hypertension and, in the absence of more definitive data, is considered a relative contraindication to TLCB [51].

Other complications are anecdotal and can comprise transient respiratory failure, neurological manifestations (e.g., seizures), pneumomediastinum, prolonged air leak, and pulmonary abscess [52].

Regarding mortality, current data are showing that TLCB appears to be safer than surgical lung biopsy; a recent meta-analysis has revealed an overall mortality rate with this procedure of about 0.1% among approximately 1000 patients [15]. A more recent analysis of data published in the literature on cryobiopsy documents seven deaths within a month after the procedure: one patient died from respiratory failure due to carcinomatous lymphangitis, one from acute myocardial infarction manifesting weeks later, one from pulmonary edema from newly diagnosed severe aortic stenosis, one with organizing pneumonia and who was on palliative care, one from pulmonary embolism, and two patients from acute exacerbation of idiopathic pulmonary fibrosis (IPF) [14, 20, 25, 49] (in both cases of death from acute exacerbation of IPF, diffuse alveolar damage was the histological background on autopsy and the death developed after significant procedural complications: tension pneumothorax with subsequent ventilation with high positive airway pressures and severe bleeding). A more recent case of acute exacerbation of interstitial lung disease (ILD) as a complication of TLCB has been reported in a patient with nonspecific interstitial pneumonitis (although this case report does not describe the TLCB technique specifically analysis of histology, description of HRCT features, and clinical information documenting the presence of a stable disease or rapid progressive deterioration before the TLCB) [53]. The risk of acute exacerbation needs to be assessed before the procedure, particularly in case of recent worsening [37, 54, 55]: recent onset of patchy ground-glass areas on HRCT scan, functional deterioration and/or increased dyspnea on exertion in the last month, and/or high levels of inflammatory or more specific markers (KL-6) could be predictors of high acute exacerbation risk [56, 57]. Acute deterioration in respiratory status should be considered a relative contraindication, although the decision needs to be individualized based on assessment of benefits and risks [1].

Anecdotal data suggest that complications are more frequent when pulmonary function is severely impaired. Forced expiratory volume in the first second (FEV_1) <0.8 L or <50% predicted, forced vital capacity (FVC) <50% predicted, and diffusing capacity of the lungs for carbon monoxide (DLCO) <35% or <50% predicted have been used to exclude biopsy candidates in some series, though not in all [2, 15, 25]; however, these limitations are drawn from data reported in studies dealing with SLB; additionally, in the subset of patients with severe fibrosing ILD, the risk-benefit analysis is less advantageous, because in these patients it seems that the prognostic significance of an exact histological diagnosis is reduced [58] and data on the efficacy of a specific "anti-fibrotic" drug on patients with severe IPF are still scanty [58–63]. Our large cohort of 699 patients who underwent transbronchial lung cryobiopsy for suspected diffuse parenchymal lung diseases, pneumothorax incidence, was significantly higher when FVC was <50% (p 0.008), but it was not influenced by DLCO (p 0.7842), while bleeding appeared independent by the lung function tests (both FVC and DLCO). We suggest that FVC < 50% should be considered as a relative contraindication to transbronchial lung biopsy on safety grounds while baseline DLCO should be evaluated together with other clinical, radiological, and laboratory features [1]. Significant hypoxemia, defined as $PaO_2 < 55–60$ mmHg on room air or while receiving 2 L/min of nasal oxygen, has also been considered a contraindication by some but not others [3, 6, 25]. A high body mass index (BMI > 35) can result in failure of the procedure [1, 25], mainly because of desaturation in intubated and spontaneously breathing patients. Additionally, a study evaluated TBCB in mechanically ventilated patients in the intensive care unit, though the experience remains anecdotal at this time [1, 64]. No age limit has been suggested at this time, as TBCB has been

performed safely in a wide age range of patients, which need to be carefully evaluated in terms of comorbidities and fitness for anesthesia [1].

References

1. Hetzel J, Maldonado F, Ravaglia C, et al. 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.

2. Babiak A, Hetzel J, Krishna G, et al. Tranbronchial cryobiopsy: a new tool for lung biopsies. Respiration. 2009;78:203–8.

3. Kropski JA, Pritchett JM, Mason WR, et al. Bronchoscopic cryobiopsy for the diagnosis of diffuse parenchymal lung disease. PLoS One. 2013;12:e78674.

4. Fruchter O, Fridel L, Rosengarten D, et al. Transbronchial cryobiopsy in immunocompromised patients with pulmonary infiltrates: a pilot study. Lung. 2013;91:619–24.

5. Yarmus L, Akulian J, Gilbert C, et al. Cryoprobe transbronchial lung biopsy in patients after lung transplantation: a pilot safety study. Chest. 2013;143:621–6.

6. Pajares V, Puzo C, Castillo D, et al. Diagnostic yield of transbronchial cryobiopsy in interstitial lung disease: a randomized trial. Respirology. 2014;19:900–6.

7. Fruchter O, Fridel L, El Raouf BA, et al. Histological diagnosis of interstitial lung diseases by cryo-transbronchial biopsy. Respirology. 2014;19:683–38.

8. Pourabdollah M, Shamaei M, Karimi S, et al. Transbronchial lung biopsy: the pathologist's point of view. Clin Respir J. 2016;10:211–6.

9. Griff S, Schönfeld N, Ammenwerth W, et al. Diagnostic yield of transbronchial cryobiopsy in non-neoplastic lung disease: a retrospective case series. BMC Pulm Med. 2014;14:171.

10. Hernández-González F, Lucena CM, Ramírez J, et al. Cryobiopsy in the diagnosis of diffuse interstitial lung disease: yield and cost- effectiveness analysis (in English, Spanish). Arch Bronconeumol. 2015;6:261–7.

11. Hagmeyer L, Theegarten D, Wohlschläger J, et al. The role of transbronchial cryobiopsy and surgical lung biopsy in the diagnostic algorithm of interstitial lung disease. Clin Respir J. 2016;10:589–95.

12. Gershman E, Fruchter O, Benjamin F, et al. Safety of cryo-transbronchial biopsy in diffuse lung diseases: analysis of three hundred cases. Respiration. 2015;90:40–6.

13. Ramaswamy A, Homer R, Killam J, et al. Comparison of transbronchial and cryobiopsies in evaluation of diffuse parenchymal lung disease. J Bronchology Interv Pulmonol. 2016;23:14–21.

14. Echevarria-Uraga JJ, Pèerez-Izquierdo J, Garcìa-Garai N, et al. Usefulness of an angioplasty balloon as selective bronchial blockade device after transbronchial cryobiopsy. Respirology. 2016;21:1094–9.

15. Ravaglia C, Bonifazi M, Wells AU, et al. 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;91:215–27.

16. Ussavarungsi K, Kern RM, Roden AC, et al. Transbronchial cryobiopsy in diffuse parenchymal lung disease: retrospective analysis of 74 cases. Chest. 2017;151:400–8.

17. DiBardino DM, Haas AR, Lanfranco AR, et al. High complication rate after introduction of transbronchial cryobiopsy into clinical practice at an Academic Medical Center. Ann Am Thorac Soc. 2017;14:851–7.

18. Bango-Alvarez A, Ariza-Prota M, Torres-Rivas H, et al. Transbronchial cryobiopsy in interstitial lung disease: experience in 106 cases—how to do it. ERJ Open Res. 2017;3:00148-2016.

19. Kronborg-White S, Folkersen B, Rasmussen TR, et al. Introduction of cryobiopsies in the diagnostics of interstitial lung diseases—experiences in a referral center. Eur Clin Respir J. 2017;4:1274099.

20. Sriprasart T, Aragaki A, Baughman R, et al. A single US center experience of transbronchial lung cryobiopsy for diagnosing interstitial lung disease with a 2-scope technique. J Bronchology Interv Pulmonol. 2017;24:131–5.

21. Ravaglia C, Wells AU, Tomassetti S, et al. 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;93:285–92.

22. Wall CP, Gaensler EA, Carrington CB, et al. Comparison of transbronchial and open biopsies in chronic infiltrative lung diseases. Am Rev Respir Dis. 1981;123:280–5.

23. O'Brien JD, Ettinger NA, Shevlin D, et al. Safety and yield of transbronchial biopsy in mechanically ventilated patients. Crit Care Med. 1997;25:440–6.

24. Berbescu EA, Katzenstein AL, Snow JL, et al. Transbronchial biopsy in usual interstitial pneumonia. Chest. 2006;129:1126–31.

25. Casoni GL, Tomassetti S, Cavazza A, et al. Transbronchial lung cryobiopsy in the diagnosis of fibrotic interstitial lung diseases. PLoS One. 2014;9:e86716.

26. Facciolongo N, Patelli M, Gasparini S, et al. Incidence of complications in bronchoscopy. Multicentre prospective study of 20,986 bronchoscopies. Monaldi Arch Chest Dis. 2009;71:8–14.

27. Tomassetti S, Piciucchi S, Tantalocco P, et al. The multidisciplinary approach in the diagnosis of idiopathic pulmonary fibrosis: a patient case-based review. Eur Respir Rev. 2015;24:69–773.

28. Sheth JS, Belperio JA, Fishbein MC, et al. Utility of transbronchial versus surgical lung biopsy in the diagnosis of suspected fibrotic interstitial lung disease. Chest. 2017;151:389–99.

29. Rena O, Casadio C, Leo F, et al. Videothoracoscopic lung biopsy in the diagnosis of interstitial lung disease. Eur J Cardiothorac Surg. 1999;16:624–7.

30. Kreider ME, Hansen-Flaschen J, Ahmad NN, et al. Complications of video-assisted thoracoscopic lung biopsy in patients with interstitial lung disease. Ann Thorac Surg. 2007;83:1140–4.

31. Zhang D, Liu Y. Surgical lung biopsies in 418 patients with suspected interstitial lung disease in China. Intern Med. 2010;49:1097–102.

32. Fibla JJ, Molins L, Blanco A, et al. Video-assisted thoracoscopic lung biopsy in the diagnosis of interstitial lung disease: a prospective, multi-center study in 224 patients. Arch Bronconeumol. 2012;48:81–5.

33. Blackhall V, Asif M, Renieri A, et al. The role of surgical lung biopsy in the management of interstitial lung disease: experience from a single institution in the UK. Interact Cardiovasc Thorac Surg. 2013;17:253–7.

34. Morris D, Zamvar V. The efficacy of video-assisted thoracoscopic surgery lung biopsies in patients with interstitial lung disease: a retrospective study of 66 patients. J Cardiothorac Surg. 2014;9:45.

35. Rotolo N, Imperatori A, Dominioni L, et al. Efficacy and safety of surgical lung biopsy for interstitial disease. Experience of 161 consecutive patients from a single institution in Italy. Sarcoidosis Vasc Diffuse Lung Dis. 2015;32:251–8.

36. Hutchinson JP, McKeever TM, Fogarty AW, et al. Surgical lung biopsy for the diagnosis of interstitial lung disease in England: 1997–2008. Eur Respir J. 2016;48:1453–61.

37. Hutchinson JP, Fogarty AW, McKeever TM, et al. In-hospital mortality after surgical lung biopsy for interstitial lung disease in the United States. 2000 to 2011. Am J Respir Crit Care Med. 2016;193:1161–7.

38. Lieberman S, Gleason JB, Ilyas MIM, et al. Assessing the safety and clinical impact of thoracoscopic lung biopsy in patients with interstitial lung disease. J Clin Diagn Res. 2017;11:OC57–9.

39. Patel RR, Utz JP. Bronchoscopic lung biopsy. In: Wang K-P, Metha AC, Turner Jr JF, editors. Flexible bronchoscopy. Chichester: Wiley-Blackwell; 2011. p. 117–31.

40. Griff S, Ammenwerth W, Schönfeld N, et al. Morphometrical analysis of transbronchial cryobiopsies. Diagn Pathol. 2011;6:53.

41. Iftikhar IH, Alghothani L, Sardi A, et al. Transbronchial lung cryobiopsy and video-assisted thoracoscopic lung biopsy in the diagnosis of diffuse parenchymal lung disease: a meta-analysis of diagnostic test accuracy. Ann Am Thorac Soc. 2017;14:1197–211.

42. O'Donovan JP, Khan KA, Burke L, et al. Bronchoscopic cryobiopsy: initial experience in an interstitial lung disease centre. Irish J Med Sci. 2014;183(11 Suppl 1):S515–6.

43. Sharp C, McCabe M, Adamali H, et al. Use of transbronchial cryobiopsy in the diagnosis of interstitial lung disease-a systematic review and cost analysis. QJM. 2017;110:207–14.

44. Ball CG, Kirkpatrick AW, Laupland KB, et al. Factors related to the failure of radiographic recognition of occult post traumatic pneumothoraces. Am J Surg. 2005;189:541.

45. Ebrahimi A, Yousefifard M, Mohammad Kazemi H, et al. Diagnostic accuracy of chest ultrasonography versus chest radiography for identification of pneumothorax: a systematic review and meta-analysis. Tanaffos. 2014;13:29–40.

46. Husain LF, Hagopian L, Wayman D, et al. Sonographic diagnosis of pneumothorax. J Emerg Trauma Shock. 2012;5:76–81.

47. Viglietta L, Inchingolo R, Pavano C, et al. Ultrasonography for the diagnosis of pneumothorax after transbronchial lung cryobiopsy in diffuse cryobiopsy in diffuse parenchymal lung diseases. Respiration. 2017;94:232–6.

48. Poletti V, Hetzel J. Transbronchial cryobiopsy in diffuse parenchymal lung disease: need for procedural standardization. Respiration. 2015;90:275–8.

49. Hagmeyer L, Theegarten D, Treml M, et al. Validation of transbronchial cryobiopsy in interstitial lung disease—interim analysis of a prospective trial and critical review of the literature. Sarcoidosis Vasc Diffuse Lung Dis. 2016;33:2–9.

50. Linhas R, Marçôa R, Oliveira A, et al. Transbronchial lung cryobiopsy: associated complications. Rev Port Pneumol (2006). 2017;23:331–7.

51. Chan JWM, Yeung YC, Sin KM, et al. Guidelines of procedural and sedation safety in flexible bronchoscopy and pleuroscopy. Hong Kong Thoracic Society, American College of Chest Physicians (Hong Kong and Macau Chapter), Hong Kong Lung Foundation. 2016.

52. Skalski JH, Kern RM, Midthun DE, et al. Pulmonary abscess as a complication of transbronchial lung cryobiopsy. J Bronchology Interv Pulmonol. 2016;23:63–6.

53. Tomic R, Cortes-Puentes GA, Murugan P, et al. Acute exacerbation of interstitial lung disease after cryobiopsy. J Bronchology Interv Pulmonol. 2017;24:319–22.

54. Ernst A, Eberhardt R, Wahidi M. Effect of routine clopidogrel use on bleeding complications after transbronchial biopsy in humans. Chest. 2006;129:734–7.

55. Utz JP, Ryu JH, Douglas WW, et al. High short-term mortality following lung biopsy for usual interstitial pneumonia. Eur Respir J. 2001;17:175–9.

56. Qiu M, Chen Y, Ye Q. Risk factors for acute exacerbation of idiopathic pulmonary fibrosis: a systematic review and meta-analysis. Clin Respir J. 2018;12:1084–92.

57. Fujimoto K, Taniguchi H, Johkoh T, et al. Acute exacerbation of idiopathic pulmonary fibrosis: high resolution CT scores predict mortality. Eur Radiol. 2012;22:83–92.
58. Latsi PI, du Bois RM, Nicholson AG, et al. Fibrotic idiopathic interstitial pneumonia: the prognostic value of longitudinal functional trends. Am J Respir Crit Care Med. 2003;168:531–7.
59. King TE Jr, Bradford WZ, Castro-Bernardini S, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med. 2014;370:2083–92.
60. Richeldi L, du Bois RM, Raghu G, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med. 2014;370:2071–82.
61. Harari S, Caminati A, Albera C, et al. Efficacy of pirfenidone for idiopathic pulmonary fibrosis: an Italian real life study. Respir Med. 2015;109:904–13.
62. Martinez FJ, Flaherty KR. Comprehensive and individualized patient care in idiopathic pulmonary fibrosis: refining approaches to diagnosis, prognosis, and treatment. Chest. 2017;151:1173–4.
63. Lee SH, Shim HS, Cho SH, et al. Prognostic factors for idiopathic pulmonary fibrosis: clinical, physiologic, pathologic, and molecular aspects. Sarcoidosis Vasc Diffuse Lung Dis. 2011;28:102–12.
64. Munoz Fernandez AM, Pajares V, Lucena C, et al. Safety of transbronchial lung criobiopsy in mechanically ventilated patients in critical care. Multicenter study. European Respiratory Congress. 2016.