5 Technique and Equipment in Transbronchial Cryobiopsy

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5.1 Introduction

There is a large amount of evidence that underlines the importance of technical aspects in transbronchial lung cryobiopsy (TBLC) since, as in many other medical procedures, optimizing the technique means consequently optimizing its safety and its utility (diagnostic yield).

In the published studies, a variability in the technique and in the equipment used is found; therefore a call for standardization was proposed in a recent document by Hetzel et al. [1], in which technical recommendations to enhance safety and optimize the diagnostic yield were proposed.

In the following chapter, the potential variability of the technical aspects of TBLC will be analysed, pointing out advantages and disadvantages in the various techniques and equipment proposed.

5.2 A Summary of What TBLC Needs to Be Carried Out

As general rule, TBLC needs to be carried out in a centre with experience in interstitial lung diseases (ILDs); in an endoscopic room with standard monitoring that includes oxygen saturation, electrocardiography and non-invasive blood pressure; by trained interventional pulmonologists; and where a prompt management of potential complications is possible.

The list below illustrates the technical points one has to consider in performing TBLC:

- Sedation/anaesthesia
- Airway management
- Patient ventilation
- Bronchial blockers
- Fluoroscopic guidance
- Cryogenic gas
- Cryoprobes and freezing times
- Where to take a TBLC and how many samples should be taken
- How to manage the TBLC samples

For each point, a variability in the technique and in the equipment used could be found, but it has to be underlined that for many of these points, a head-to-head comparison has not been done, so there is no or little evidence regarding clear benefits of an operating method over another one.

5.3 Sedation/Anaesthesia

Deep sedation or general anaesthesia is mandatory in order to improve the tolerance of the procedure, to better manage the patient oxygenation, to reduce potential harmful complications and to improve the working conditions [2].

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Table 5.1 A summary of the type of sedation/anaesthesia commonly used

Author, year	Type of study	Number of patients	GA/DS/CS (name used in the article)	Agent
Bango-Alvarez, 2017 [11]	Prosp	106	DS	Midazolam + fentanyl
Kronborg-White, 2017 [12]	Retro	38	DS	Propofol + remifentanil
Ravaglia, 2017 [13]	Prosp	46	DS	Propofol + remifentanil
Ravaglia, 2016 [6]	Retro	297	GS	Propofol + remifentanil
Tomassetti, 2016 [14]	Prosp	58	DS	Propofol + remifentanil
Ramasway, 2016 [15]	Retro	56	CS	Midazolam + fentanyl
Hernandez-Gonzalez, 2015 [7]	Retro	33	GA	Propofol + remifentanil
Gershman, 2015 [16]	Retro	300	CS	Midazolam + afentanyl ± Diprivan
Casoni, 2014 [10]	Prosp	69	GA	Propofol + remifentanil
Griff, 2014 [17]	Retro	52	DS	Disoprivan + midazolam
Frutcher, 2014 [18]	Retro	75	DS	Midazolam + alfentanyl
Yarmus, 2013 [9]	Prosp	21	GA/DS	Propofol ± paralytics

Different drugs are used, commonly propofol, midazolam and remifentanil [3]: the use of some of these agents is regulated in different ways since some of them could be used only by anaesthesiologists in some countries whilst in others could be used also by other physicians or even nurses in some protocols [4, 5]. A different terminology is also used across the studies: agents considered for deep sedation by some authors [6, 7] are considered for general anaesthesia by others [8–10]; therefore it is a matter of what agent is used rather than of the name used to indicate the anaesthesiologist support. In Table 5.1 an overview of the agents used in some studies is shown.

Muscle relaxation could be added, but in this case, the patient has to be ventilated, with either mechanical, manual or jet ventilation [9].

The addition of local anaesthesia is important as well, and it is used with the same modalities as in other bronchoscopic procedures [19].

Conscious sedation with the use of midazolam and fentanyl without the need to intubate the patient is described by some authors [11, 15] without reporting a higher complication rate compared to other studies, but apparently there are no clear benefits to prefer conscious sedation over deep sedation or general anaesthesia.

5.4 Airway Management

The majority of the reports in the literature describe the TBLC technique with intubated patient, with either a rigid tracheo-bronchoscope or an endotracheal tube [3]. The choice of a rigid bronchoscope or an endotracheal tube is mainly related to the operator skills.

Supraglottic devices (such as laryngeal mask) were also described and were proven to have also an acceptable safety [8, 20] but may raise some concerns in the management of severe bleeding.

TBLC can be performed also without the need to intubate the patient, with a trans-oral approach: in this case two bronchoscopes are used, one for taking the biopsy and the second one immediately after to manage the bleeding with suction or wedge the bronchoscope in the selected segmental bronchus [8, 16]. Among the studies that used the trans-oral approach, no bleeding complications were reported by some authors [11, 21, 22], whilst a percentage that ranges between 2% [15] and 5.2% was reported by others [16].

Ravaglia et al. [6] analysed the impact of airway management and sedation on the diagnostic yield and on the pneumothorax rate: in comparison with patients non-intubated in conscious sedation, the diagnostic yield was slightly lower in intubated patients in deep sedation (83% versus 81%, respectively), and in this group, the proportion of pneumothorax was higher (1% versus 7%, respectively).

Thus, intubation, with either a rigid bronchoscope or an endotracheal tube, is recommended in TBLC [1], since there are advantages over the trans-oral approach in terms of patient's safety and operator's comfort. Moreover, a better

stability of the bronchial blocker is ensured with the intubated patient, since the bronchial blocker can be fixed at the proximal part of the airway device. However, the trans-oral approach could be also possible, apparently without an increased rate of complications.

5.5 Patient Ventilation

A consequent aspect of the choice of sedation rather than anaesthesia is the ventilation of the patient. Whereas in case of conscious sedation a spontaneous breathing is maintained, in case of general anaesthesia or deep sedation, a support in ventilation could be needed.

Three modalities have been described, spontaneous, manual, mechanical and jet ventilation. During spontaneous ventilation, only oxygen supply via nasal or endotracheal cannula is given, and this is the most common ventilation modality reported. Manual and mechanical ventilation is also used, in which the patient is connected, respectively, to a balloon or to a ventilator. Jet ventilation consists in sending small air volumes, manually or mechanically, enriched with O_2 at high speed, and to do so, the induction of a respiratory muscle paralysis is needed: the main advantage is to reduce the possibility of lung barotrauma, but the efficacy decreases when several instruments are introduced into the rigid bronchoscope like forceps or suction catheters [23].

Data from surgical lung biopsy indicates that a higher risk of barotrauma could be observed in case of single lung ventilation [1], but similar data regarding TBLC has never been reported. A summary of ventilation support across the studies is provided in Table 5.2.

Table 5.2 An overview of the sedation/anaesthesia used and the ventilation support across the studies

Author, year	Type of study	Number of patients	GA/DS/CS (name used in the article)	Agent	ETT/RB/ SGD/NI	Ventilation
Almeida, 2017 [24]	Retro	100	GA	–	RB	Manual jet 2 bar
Schmutz, 2017 [25]	Retro	132	GA	–	SGD	–
Bango-Alvarez, 2017 [11]	Prosp	106	DS	Midazolam + fentanyl	NI	Spontaneous
Kronborg-White, 2017 [12]	Retro	38	DS	Propofol + remifentanil	ETT	Spontaneous
Siprasart, 2017 [8]	Retro	74	GA	–	ETT	Spontaneous
Ravaglia, 2017 [13]	Prosp	46	DS	Propofol + remifentanil	RB	Spontaneous
Ussavarungsi, 2017 [26]	Retro	74	DS	–	ETT	Spontaneous
DiBardino, 2017 [20]	Retro	25	CS	–	SGD/ETT	–
Berim, 2017 [27]	Retro	10	GA	–	ETT	–
Marcoa, 2017 [28]	Prosp	90	GA	–	ETT	Jet
Sousa-Neves, 2017 [29]	Retro	3	GA	–	RT	–
Echevarria-Uraga, 2016 [30]	Retro	100	GA	–	ETT	Mechanical
Ravaglia,2016 [6]	Retro	297	GS	Propofol + remifentanil	ETT	Spontaneous
Hagmeyer, 2016 [31]	Retro	23	DS/GA	–	ETT/RB	–/jet
Tomassetti, 2016 [14]	Prosp	58	DS	Propofol + remifentanil	ETT	Spontaneous
Hagmeyer, 2016 [31]	Prosp	32	DS	–	ETT	–
Ramasway, 2016 [15]	Retro	56	CS	Midazolam + fentanyl	NI	Spontaneous
Pourabdollah, 2016 [32]	Prosp	41	DS	–	–	–
Hernandez-Gonzalez, 2015 [7]	Retro	33	GA	Propofol + remifentanil	ETT	–

(continued)

Table 5.2 (continued)

Author, year	Type of study	Number of patients	GA/DS/CS (name used in the article)	Agent	ETT/RB/ SGD/NI	Ventilation
Gershman, 2015 [16]	Retro	300	CS	Midazolam + afentanyl ± Diprivan	NI	Spontaneous
Pajares, 2014 [33]	RCT	77	DS	–	ETT	Spontaneous
Casoni, 2014 [10]	Prosp	69	GA	Propofol + remifentanil	ETT	Spontaneous
Griff, 2014 [17]	Retro	52	DS	Disoprivan + midazolam	–	–
Frutcher, 2014 [18]	Retro	75	DS	Midazolam + alfentanyl	NI	Spontaneous
Kropski, 2013 [5]	Retro	25	CS	–	ETT	Spontaneous
Fruchter, 2013 [18]	Retro	11	CS	–	ETT	Spontaneous
Fruchter, 2013 [18]	Retro	40	CS	–	NI	Spontaneous
Yarmus, 2013 [9]	Prosp	21	GA/DS	Propofol ± paralytics	RB/LMA	Jet/ spontaneous
Griff, 2011 [34]	Prosp	15	Sedation (?)	–	–	–
Babiak, 2009 [35]	Prosp	41	DS	–	ETT	Spontaneous

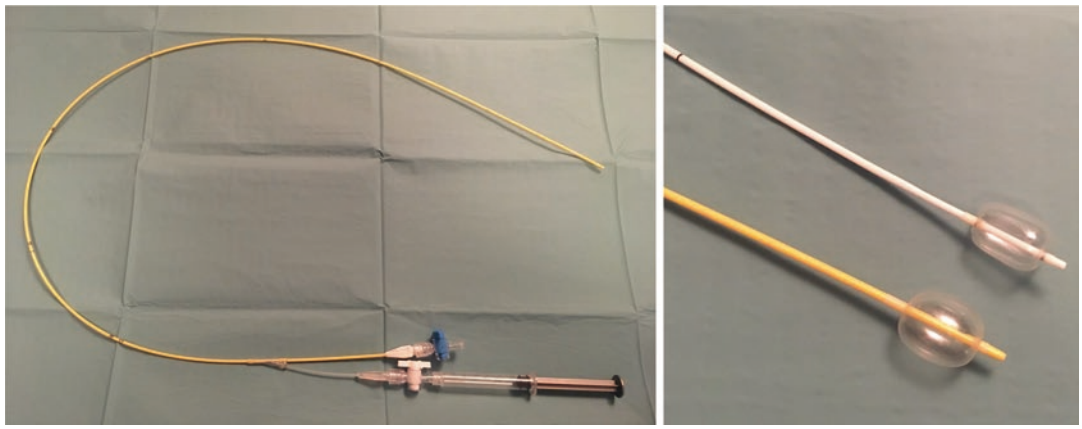

Fig. 5.1 Fogarty catheters

5.6 Bronchial Blockers

Bronchial blockers are positioned in segmental bronchi immediately before the biopsy procedure, and its use is mainly justified to reduce the bleeding. Once in the target place, the blocker has to be fixed to avoid depositioning (e.g. to the endotracheal tube or to the rigid bronchoscope with a sticking plaster).

Two types of bronchial blockers are commonly used in TBLC: the Fogarty catheter (most used, Fig. 5.1) and the Arndt catheter.

The Fogarty balloon (dimensions: 4F, 5F, 6F) consists of a hollow tube with an inflatable balloon attached to its tip. It is available in various dimensions. In its proximal portion, there are two branches, one to inflate balloon with air and the other one for the instillation of fluids, like saline, if necessary.

The Arndt catheter (dimensions: 7F or 9F) has a guide loop in its distal part that has to be tied to the bronchoscope, enabling a more precise placement.

The mechanism of functioning is the same for both devices: they have to be inserted deflated and inflated after the biopsy, immediately after the removal of the cryoprobe, and they have to remain inflated in the biopsy area for 3–5 min. A

check of the bleeding before removing the balloon is suggested.

The majority of the studies reported the use of a bronchial blocker with an expected reduction in moderate-to-severe bleeding [36].

However, in some studies, no bronchial blockers are used, and a second bronchoscope was used in place of them: the biopsy is taken with the first bronchoscope, and subsequently a second one is inserted and wedged to stop the bleeding. For example, Sriprasart et al. [8] reported their experience with two scopes and no bronchial blocker: they reported a diagnostic yield of 87.84%, a 7% of pneumothoraces, 1% severe bleeding and a 4% of death.

5.7 Fluoroscopic Guidance

Once the biopsy area is chosen in the computed tomography (CT) scan, the use of the fluoroscope is a further guidance in the biopsy since its use allows to better evaluate the position of the probe and its distance from the pleura.

Indeed, it is suggested that the probe should be placed in the distal part of the lung parenchyma: if too close to the pleura, the risk of pneumothorax is increased, and on the other side, if too proximal, there is a risk of bleeding since the airways are not entirely protected with cartilage plates and vessels could be damaged whilst taking the biopsy.

Some studies reported a distance from the visceral pleura that varies between 1 and 2 cm, and a distance of around 1 cm has been recently suggested [1]. However, biopsy within 1 cm from the pleura could be necessary in the suspicion of idiopathic pulmonary fibrosis/usual interstitial pneumonia (IPF/UIP), and in those cases, a higher rate of pneumothorax has been reported, also due to the more pronounced fibrotic changes [3]. Dhooria et al. [36] found a lower percentage of pneumothorax in case of fluoroscopic use.

Moreover, the fluoroscopic use allows also a prompt evaluation in case of pneumothorax.

In some other studies, the fluoroscope was not used: in the study of Bango-Álvarez et al. [11], for example, the probe was moved forward until it could not be advanced further and then retracted 1–2 cm following the marks on the probe. They obtained a diagnosis in 86% of patients, and they experienced pneumothorax in 4.7%, no acute exacerbation of IPF and no haemorrhage.

5.8 Cryogenic Gases

Cryogenic gases are the cooling agents that allow the lung tissue to be frozen. They are compressed under high pressure in a tank, and they are released once the probe is activated with the footswitch (Fig. 5.2). The release of the gases generates a rapid temperature drop with a consequent freeze of the surrounding tissue.

Two cooling gases are used, the carbon dioxide (CO_2) and nitric oxide (N_2O): no difference in the mechanism is observed, but the N_2O reaches lower temperatures, could require an aspiration system in the room to be used and is more expensive than CO_2 (see Chap. 4); therefore, CO_2 is the cooling agent core commonly used.

5.9 Cryoprobes

TBLC is performed by the mean of cryoprobes: they are inserted in the operating channel of the flexible bronchoscope and are pushed forward until the biopsy site, in close contact to the lung tissue.

Cryoprobes are flexible probes, 90 cm in length, available in 2 diameters, 1.9 and 2.4 mm (Fig. 5.3). The 2.4 mm probe provides the largest samples with a fewer activation time since there is a positive correlation between the freezing time, the probe's dimension and the cross-sectional area of the biopsy [37].

A freezing time of 5–6 s has to be used with the 2.4 mm probe, whilst 7–8 s is necessary with the 1.9 mm [13], but when the N_2O is used, this freezing time could be reduced [30].

So far, in terms of complications, no clear data are available proving that a larger dimension of

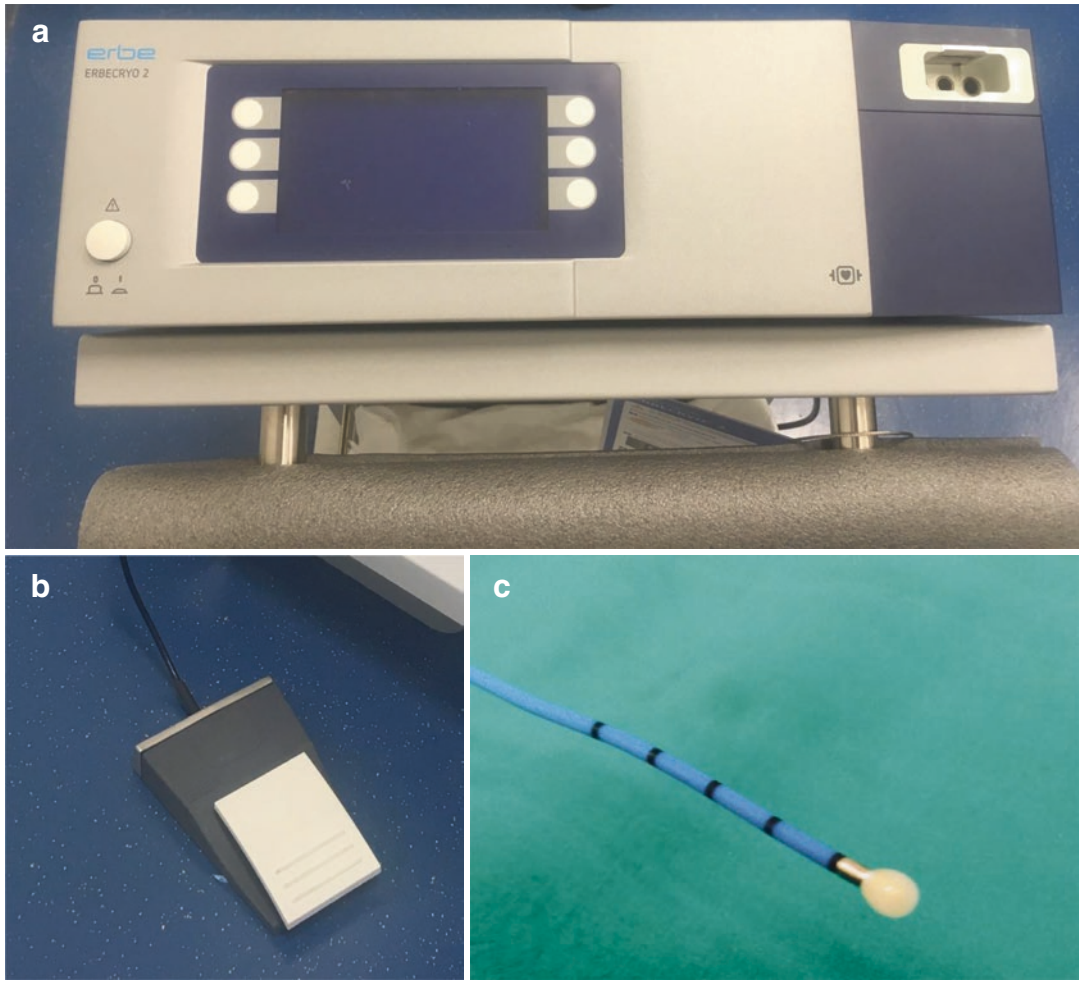

Fig. 5.2 Part of the cryoequipment. (**a**) The console; (**b**) the footswitch; (**c**) the "iceball"

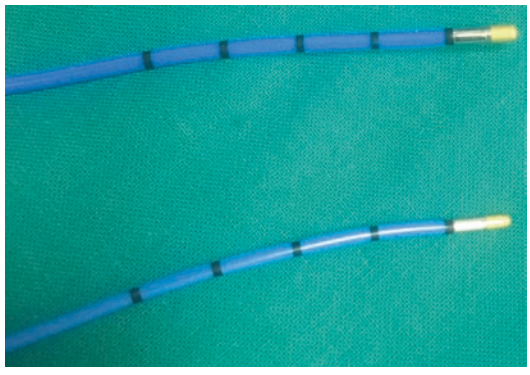

Fig. 5.3 The available cryoprobes

the probe means a higher complication rate; however, a trend towards the rate of pneumothorax was observed in the meta-analysis of Iftikhar and colleagues [38] with the 2.4 mm probe.

5.10 Where to Take a TBLC and How Many Samples Should Be Taken

The choice of the biopsy site is up to the operator, where the most representative radiological abnormalities are present, avoiding the

most fibrotic areas. In case where there is a diffuse heterogeneous lung disease, biopsies from different lobes or different segments are preferred.

A significant variability is observed among the studies about this point: some are performed in a single segment, some in more than one segment and in others in different lobes [5, 26], but in most of the cases, no subgroup analyses were performed.

To better evaluate the potential advantages of taking biopsies in different segments rather than in a single segment, Ravaglia et al. [13] conducted a randomized trial in which a significant increase in the diagnostic yield from 69 to 96% was demonstrated when biopsies from a different segment of the same lobe were added. A part from this randomized study, no other data are available that elucidates whether taking biopsy from multiple segments or multiple lobes results in an increase of diagnostic yield; moreover, the impact of this approach on complications is poorly understood.

About the number of biopsies that needs to be taken, in the literature, it ranges from 1 to 7 samples [3]; however, three to five biopsies are the optimal number suggested [1].

5.11 How to Manage the TBLC Samples

Once the tissue is collected, it has to be processed for pathological evaluation.

Comparable to other lung biopsy techniques, TBLC specimens have to be (1) fixed in formalin, (2) embedded in paraffin, (3) orientated in the way to maximize the surface area and finally (4) stained with haematoxylin-eosin (or other stains) or prepared for immunohistochemical analysis.

Attention should be paid in all these phases of tissue manipulation, starting from the removing of the tissue from the probe to the formation of slides in order to minimize tissue damages and artefacts. For example, thawing in hand-warm water may render the tissue removing easier.

Moreover, the TBLC specimens are suitable for investigations such as immunohistochemical and molecular studies [39].

5.12 Learning Curve

The need of standardization is not only expected for technical issues but also for establishing the learning process for TBLC. Nowadays, there is no validated learning protocol for TBLC, and very few studies addressed this point. A relative high complication rate is described with the starting experience of TBLC [20] by unexperienced pulmonologists: out of 25 patients, serious haemorrhage was reported in 3 patients (1 of them life-threatening), pneumothorax in 2 cases and hypercapnic respiratory failure in 1. These results suggest that a high caution should be done with the introduction of TBLC in clinical practice.

Also in the report of Kronborg-White and colleagues [12], the first experience with TBLC was described, and interestingly they specified the learning process of the operator: one of them attended a large experienced centre, and on return, the other two pulmonologists were trained to perform the procedure. Out of 38 patients, complications were seen in 18 cases: 1 has haemoptysis, 6 have moderate bleeding, 10 have pneumothoraces and two has signs of infections on blood tests with fever.

Finally, Almeida et al. performed a retrospective study investigating the diagnostic yield and the complications related to the experience of the operator [24]. Mastering of the procedure was achieved after 70 procedures, in terms of better diagnostic yield, bigger specimens and fewer complications.

Thus, further studies are needed to establish that the learning procedure of TBLC could be with a positive impact on the success and safety of the procedure.

5.13 What Happens After the Biopsy: Writing the Report, Post-procedural Monitoring and Management of Complications

Once the TBLC is performed, there are few more aspects that have to be managed.

First of all, a report of the procedure has to be done, in which the procedure is described.

The description of the technical aspects of TBLC is the responsibility of the operator that has to specify the following details in the report: airway management device (if any), bronchial blocker used (if any), fluoroscopic guidance (if so), probe's size, number of biopsies taken and biopsy site (single/multiple segment(s) or lobe(s)).

Also the pathologist has to write a report to propose the final diagnosis, specifying the specimens' dimension, the percentage of alveolated tissue, the pattern recognition, the immunohistochemical or molecular analyses (if any) and the level of confidence in the proposed diagnosis.

As a second point, after the TBLC, the patient has to be monitored for some hours. The procedure could be performed in both out- [6, 8] and in-patient setting [40]: patients have to be monitored to work off the anaesthesia and to better manage potential complications. In the literature, a minimum of 2 h of monitoring [8] is suggested to evaluate the possibility of escalation of care or to evaluate if further examinations are needed, such as chest X-ray in the suspicion of pneumothorax. Viglietta et al. [41] found a percentage of pneumothorax of 23% (11/43) diagnosed by concordance of chest X-ray and chest ultrasound in the first 3 h: in 10 cases a diagnosis was made by chest X-ray and in 11 cases with chest ultrasound, thus suggesting a potential role of ultrasound in the detection of pneumothorax after TBLC. Moreover, in one patient, a massive pneumothorax occurred immediately after the TBLC, and in only one case, a pneumothorax was detected after 5 h. Kropski et al. [5] found that among the 33 patients that underwent TBLC in an out-patient setting, only one was readmitted for a mild haemoptysis, and no fatal complications occurred.

Finally, it has to be remembered that TBLC needs to be performed in an endoscopic suite, fully accessorized for the management of the potential complications such as the treatment of bleeding or pneumothorax and even where there is a rapid access to the intensive care unit.

In Table 5.3 a suggestion is provided on how to perform TBLC and which equipment should be used.

In Fig. 5.4 a summary of the procedure is shown.

Table 5.3 Performing TBLC: which technique and which equipment should be used

Topic	Technique	Equipment
Sedation/anaesthesia	Deep sedation or general anaesthesia	Intravenous administration
Airway management	Intubated patient	Rigid trachea—bronchoscope or endotracheal tube
Ventilation	Spontaneous	Oxygen supply
Bronchial blocker	Suggested	Fogarty or Arndt catheter
Fluoroscopic guidance	Distance from the visceral pleura: = or <1 cm; early detection of pneumothorax	Suggested
Cryoprobes and freezing times	2.4 mm → 5–6 s 1.9 mm → 7–8 s	
Where to take TBLC	In the "most affected area"	
How many samples	3–5	
Procedural and post-procedural monitoring	Suggested	SpO_2, heart rate, blood pressure

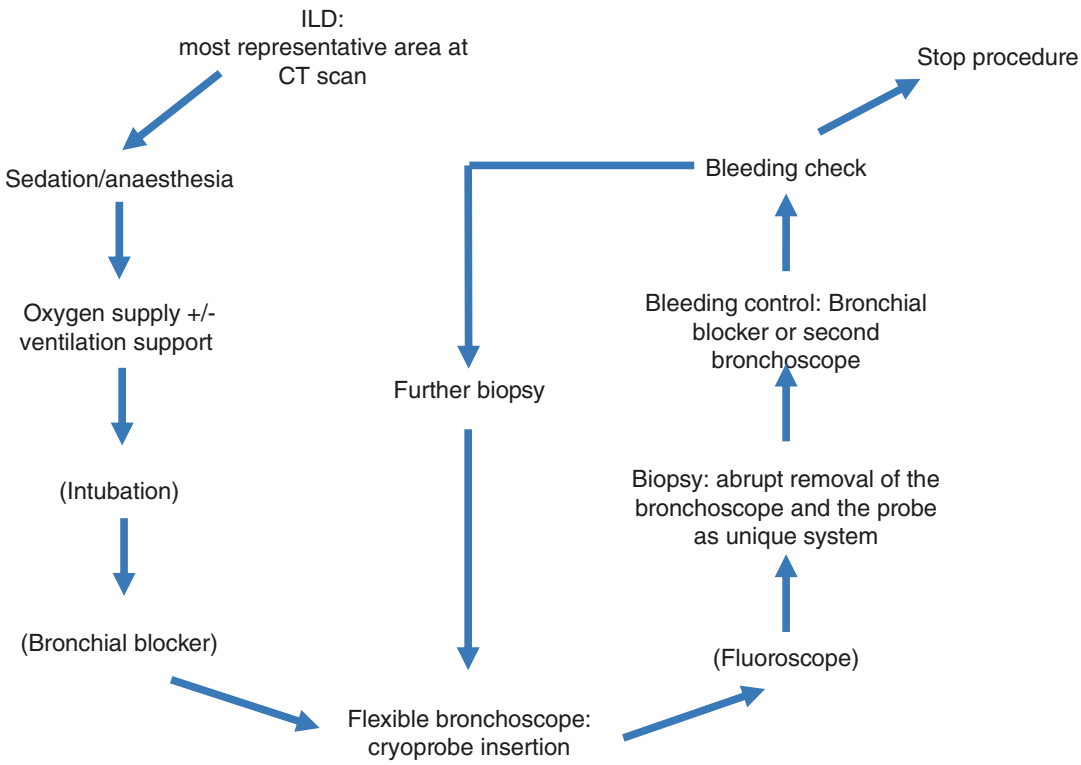

Fig. 5.4 A summary of TBLC technique

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