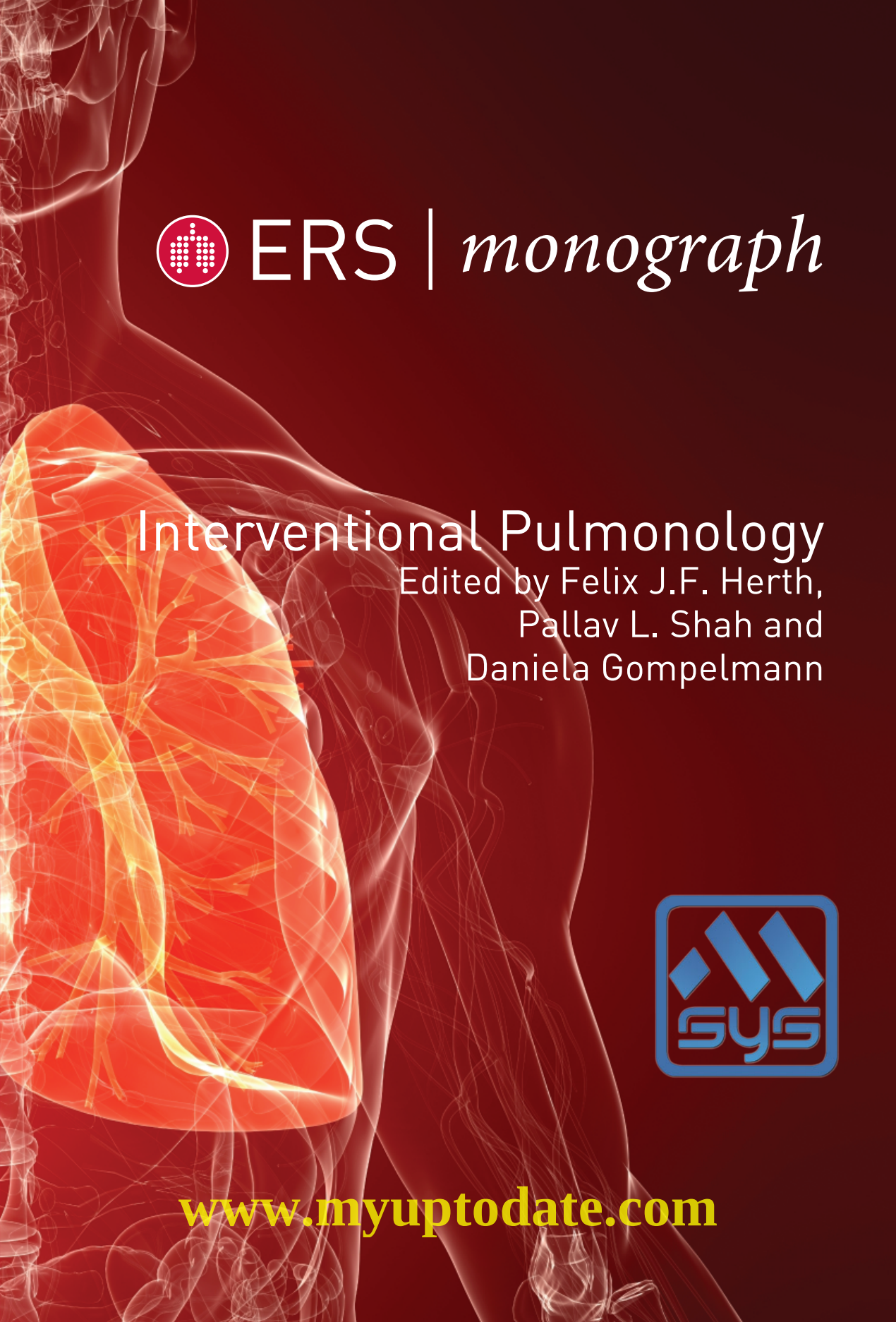

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Interventional Pulmonology

Edited by Felix J.F. Herth, Pallav L. Shah and Daniela Gompelmann

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Interventional Pulmonology

Edited by
Felix J.F. Herth, Pallav L. Shah
and Daniela Gompelmann

Editor in Chief
Robert Bals

This book is one in a series of *ERS Monographs*. Each individual issue provides a comprehensive overview of one specific clinical area of respiratory health, communicating information about the most advanced techniques and systems required for its investigation. It provides factual and useful scientific detail, drawing on specific case studies and looking into the diagnosis and management of individual patients. Previously published titles in this series are listed at the back of this *Monograph*.

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European Respiratory Society, 442 Glossop Road, Sheffield, S10 2PX, UK
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Preface

Robert Bals

Pulmonary medicine is a sub-discipline of internal medicine with several attractive characteristics. The use of endoscopic methods for diagnosis and therapy offers the opportunity to work manually and to improve patient outcomes significantly. In comparison with other specialities, pulmonary interventional methods are still underdeveloped, despite the fact that non-pharmacological treatment often provides favourable outcomes. However, the field of bronchoscopic intervention is developing quickly. In diagnosis, new biopsy techniques and targeting strategies have been developed, with the use of endoluminal ultrasound being an outstanding approach of recent decades. In therapeutics, local cancer control is one of the main fields, while interventional treatment of COPD and asthma has raised significant recent interest. Despite these exciting developments, many methods used in interventional bronchoscopy require careful patient selection and the well-developed skills of the highly trained medical team.

In this *Monograph*, we provide the reader with a broad and detailed overview of the various applications of interventional bronchoscopy. The book begins with a section on Technical Aspects, which summarises standard techniques such as flexible and rigid endoscopy. The Diagnostic Procedures section presents information about novel and targeted biopsy approaches. The final section considers Therapeutic Interventions, providing chapters on the various approaches to the treatment of cancer, haemoptysis, COPD and asthma, amongst others.

Through careful topic selection, the Guest Editors, Felix J.F. Herth, Pallav L. Shah and Daniela Gompelmann, have created a book that successfully summarises current knowledge in this area. Together with the authors, they have produced a practice-guideline publication that provides both background information and hands-on guidance for use in the endoscopy unit. I would like to thank the Guest Editors and all of the authors for their hard work on this excellent book.

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Guest Editors

Felix J.F. Herth

Felix J.F. Herth graduated at the University of Freiburg (Freiburg, Germany) and was trained at Klinikum Karlsruhe (Karlsruhe, Germany) and at the Beth Israel Deaconess Medical Center (Harvard Medical School, Boston, MA, USA).

Felix Herth is Professor of Pneumology at the University of Heidelberg (Heidelberg, Germany). His department (Pulmonary and Respiratory Critical Care Medicine) focuses on: the diagnosis and therapy of respiratory tract diseases (such as lung emphysema, cystic fibrosis, fibrosing alveolitis and pulmonary hypertension); noninvasive ventilatory support for patients with respiratory deficiency or failure; and sleep-related respiratory disorders. His team provides outstanding expertise in all fields of bronchoscopy, and takes a lead position in the development of devices for diagnostic and therapeutic purposes.

Felix Herth's research interest are lung cancer, ILDs and interventional bronchoscopy. He is a European Health Leader (Insead Business School) and works closely with the European Health commission.

Pallav L. Shah

Pallav L. Shah is currently Professor of Medicine at Imperial College London (London, UK). He is a Senior Consultant Physician at the Royal Brompton Hospital (London, UK), and the Chelsea and Westminster Hospital (London, UK). He qualified in Medicine at Guy's Hospital Medical School (London, UK) and trained in pulmonology at the Royal Brompton Hospital.

Pallav Shah is active in both the research and development of new treatments. He has had over 200 papers published and has contributed to several books, including as sectional editor of the Thoracic section of *Gray's Anatomy* (39th & 40th editions) and as sectional editor for the Respiratory section of the *Oxford Textbook of Medicine* (6th edition). He is also the author of the

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Atlas of Flexible Bronchoscopy and Chief Editor of *Essentials of Clinical Pulmonology*. He has also been involved in the HERMES (Harmonised Education in Respiratory Medicine for European Specialists) education programme for the European Respiratory Society (ERS).

Pallav Shah is experienced in the diagnosis and treatment of all aspects of respiratory disease. He is a renowned interventional bronchoscopist and is distinguished in its application in respiratory medicine. He pioneered bronchoscopic lung volume reduction for emphysema with devices such as the Zephyr endobronchial valve (Pulmonx Corporation, Redwood City, CA, USA), endobronchial coils, Vapor treatment and intrabronchial valves. More recently, he has focused on the treatment of COPD with Vapor therapy, targeted nerve ablation and the novel Rejuvinair (cryospray) (CSA Medical Inc., Lexington, MA, USA) procedure for chronic bronchitis. Pallav Shah was involved in the development of bronchial thermoplasty for asthma, and is currently assisting in the development of novel techniques for the ablation of peripheral lung tumours, which perform a range of procedures including cryotherapy and the insertion of gold markers to enable treatment with the CyberKnife.

Daniela Gompelmann

Daniela Gompelmann completed her medical training at the University of Saarland (Homburg, Germany) in 2007. She has been a consultant in the Pulmonology and Critical Care Medicine department at Thoraxklinik (Heidelberg, Germany) since 2015. Her research interests lie in the field of interventional pneumology, particularly endoscopic therapeutic procedures for patients with COPD and emphysema. She is principal investigator and head of the Junior Research Group of Interventional Pulmonology at the Translational Lung Research Center (Heidelberg, Germany), member of the German Center for Lung Research.

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Introduction

Felix J.F. Herth[1], Pallav L. Shah[2,3,4] and Daniela Gompelmann[5]

The role of bronchoscopy in the evaluation and treatment of respiratory disease has evolved dramatically over the last decade. It was initially a tool for examining and sampling the central endobronchial tree, and techniques available included simple suctioning of secretions, bronchial washing, bronchial brushing and bronchial biopsies. The latter two are achieved by inserting either a cytology brush or biopsy forceps through the instrument channel and sampling the area of direct interest. During the 1990s, there was a transition from fibreoptic bronchoscopes to video bronchoscopes. The quality of the imaging systems has improved exponentially thanks to advances in video charged coupled devices (CCDs). Initially, there was the development of fluorescence bronchoscopy and NBI for the early detection of cancer. Although these techniques have the potential to identify lesions early, they have become less important with improvements in image quality. The transition to low tar cigarettes with filters means the natural history of lung cancer has also changed from central airway squamous cell carcinomas to more peripheral adenocarcinomas. Techniques have therefore been developed for sampling peripheral lesions, such as radial ultrasound with a guide sheath and computer-aided navigation bronchoscopy (LungPoint (Broncus Medical, Inc., San Jose, CA, USA) and superDimension (Medtronic, Minneapolis, MN, USA)). With the growth in CT scanning, the identification of peripheral nodules and pulmonary abnormalities will further increase, which will in turn increase the demand for sampling in these peripheral abnormalities.

Endosonography and particularly EBUS-TBNA, with the development of the integrated linear ultrasound bronchoscope, have transformed the staging and diagnosis of lung cancer. These techniques allow sampling of multiple mediastinal and hilar lymph node stations as short day-case procedures under conscious sedation. These techniques are also useful for sampling mediastinal lymph nodes in other conditions such as sarcoidosis, and allow sampling of abnormalities adjacent to the central tracheobronchial tree.

Bronchoscopy has now truly reached its potential as a therapeutic tool. Central obstructing tumours can be debulked using either electrocautery, argon plasma photo coagulation, laser ablation or cryo-extraction. Traditional cryotherapy with repeated freeze–thaw cycles can also be used but requires a follow-up bronchoscopy to clear up necrotic tissue. PDT is a further possibility but this requires a photo-sensitiser to be administered intravenously about 72 h followed by PDT at bronchoscopy and a subsequent procedure to remove the

[1]Dept of Pneumology and Critical Care Medicine, Thoraxklinik Heidelberg, Heidelberg University, Heidelberg, Germany. [2]Royal Brompton Hospital, London, UK. [3]Chelsea and Westminster Hospital, London, UK. [4]Imperial College London, London, UK. [5]Dept of Pulmonology and Respiratory Care Medicine, Thoraxklinik, University of Heidelberg, Heidelberg, Germany.

Correspondence: Pallav L. Shah, Royal Brompton Hospital, Sydney Street, London, SW3 6NP, UK. E-mail: pallav.shah@imperial.ac.uk

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debris and necrotic tissue. Where there is tumour ingress extrinsically or loss of the airway structure, endobronchial stents may be considered. These primarily have a role in supporting the trachea or main bronchi. Stents are available in a variety of forms, from SEMS (which may be bare, partly or fully covered) to silicon stents.

Bronchoscopic lung volume reduction using endobronchial valves has been established as part of optimal medical treatment, as a treatment for severe hyperinflation and for use in the absence of collateral ventilation. Alternative approaches that are being developed include endobronchial coils, vapour therapy (which uses the fibrotic effects of thermal ablation) and chemical fibrotic agents. In COPD, ablation of the vagus nerve using radio frequency ablation of the nerve plexus surrounding the main bronchi is at an advanced phase of development. Cryospray therapy with liquid nitrogen is also in development for the treatment of chronic bronchitis. Bronchial thermoplasty has been shown to be effective in a wide group of asthma patients and has been available for about 10 years.

Bronchoscopy has evolved from a simple visual tool that relies on light, to an imaging tool with integrated ultrasound that allows sampling of parabronchial and mediastinal abnormalities. Its true potential is the increasing number of conditions that may be treated using a bronchoscopic approach.

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List of abbreviations

AFB	autofluorescence bronchoscopy
APC	argon plasma coagulation
BAL	bronchoalveolar lavage
COPD	chronic obstructive pulmonary disease
CT	computed tomography
EBUS	endobronchial ultrasound
EDAC	excessive dynamic airway collapse
ENT	ear, nose and throat
EUS	endoscopic ultrasound
FEV1	forced expiratory volume in 1 s
HRCT	high-resolution CT
ILD	interstitial lung disease
NBI	narrow band imaging
OCT	optical coherence tomography
PDT	photodynamic therapy
PET	positron emission tomography
RFA	radiofrequency ablation
SBRT	stereotactic body radiation therapy
SEMS	self-expandable metallic stents
TBB	transbronchial biopsy
TBLB	transbronchial lung biopsy
TBNA	transbronchial needle aspiration
VATS	video-assisted thoracoscopic surgery

Flexible bronchoscopy

Johannes M.A. Daniels

Flexible bronchoscopy allows visual inspection of the airways and can be used for diagnostic and therapeutic purposes. Indications for diagnostic bronchoscopy are abundant and include evaluation of symptoms such as cough or haemoptysis, evaluation of clinical findings such as suspected malignancy or pneumonia of unknown aetiology and early detection of lung cancer. In addition, several therapeutic modalities are at the disposal of the bronchoscopist and many more are currently under development. Prerequisites for performing flexible bronchoscopy are good knowledge of the patient, equipment and sedation techniques as well as skill in handling the bronchoscope, performing sampling techniques and managing complications. Although bronchoscopy can be performed with only topical anaesthesia, it is an unpleasant examination and sedation should be offered to the patient. Specific precautions are necessary for adequate and safe sedation.

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Technological advances have made flexible bronchoscopy a very effective tool in the diagnosis of many diseases of the respiratory tract and paved the way for many more technological breakthroughs, both diagnostic and therapeutic. Breakthroughs through modifications of the flexible bronchoscope (some of which are covered elsewhere in this *Monograph*) include linear EBUS [1, 2], AFB [3, 4] and NBI [3, 5]. Breakthroughs by adding catheter based techniques (some of which are covered elsewhere in this *Monograph*) include TBNA [6, 7], laser treatment [8], radial EBUS [9–11] navigation [12], bronchoscopic lung volume reduction [13, 14], bronchial thermoplasty [15–17] and transbronchial cyrobiopsy [18, 19].

This chapter will cover the indications and techniques of flexible bronchoscopy. In addition, we will discuss sedation during bronchoscopy and finally the limitations of flexible bronchoscopy.

Indications

Bronchoscopy can be of value in a wide variety of diseases of the respiratory tract, both in a diagnostic and a therapeutic setting. A good indication for performing bronchoscopy

Dept of Pulmonary Diseases, VU University Medical Center, PO Box 7075, Amsterdam, The Netherlands.

Correspondence: Johannes M.A. Daniels, Dept of Pulmonary Diseases, VU University Medical Center, ZH 4F-004, PO Box 7075, 1007 MB Amsterdam, The Netherlands. E-mail: j.daniels@vumc.nl

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Table 1. Indications for flexible bronchoscopy

Diagnostic flexible bronchoscopy
Evaluation of symptoms
Persistent cough
Chronic dyspnoea
Haemoptysis
Hoarseness
Stridor
Evaluation of clinical findings
Suspected malignancy (central or peripheral)
Suspected bronchial obstruction (recurrent pneumonia, persisting atelectasis)
Pneumonia of unknown aetiology or not responding to treatment
Suspected tuberculosis
ILD
Hilar and/or mediastinal lymphadenopathy
Bronchiectasis
Inhalation injury (toxic, heat, smoke)
Trauma with suspected airway injury
Radiation-induced airway injury
Suspected bronchopleural fistula
Dynamic airway obstruction (*e.g.* TBM, EDAC, RP)
Suspected lung transplant rejection or infection
Airway management issues (*e.g.* evaluation of a difficult airway, obstruction of an artificial airway)
Early detection of lung cancer
Therapeutic flexible bronchoscopy
Mucus impaction
Foreign body removal
Blood clot removal
Endotracheal tube placement in patients with a difficult airway
Tumour ablation (*e.g.* electrocautery, cryotherapy, laser, APC, PDT)
Balloon dilatation
Airway stenting
Airway valves in persistent air leak
Bronchoscopic lung volume reduction
Bronchial thermoplasty
Treatment of bronchopleural fistula

TBM: tracheobronchomalacia; RP: relapsing polychondritis.

would be any clinical situation in which a clinician expects that bronchoscopy will have a substantial diagnostic or therapeutic impact. Specific indications are listed in table 1.

Diagnostic flexible bronchoscopy

Bronchoscopy is often used in the evaluation of common clinical symptoms or the evaluation of specific clinical findings. In most cases, bronchoscopy is part of an elaborate clinical work-up and in each individual case it should be decided whether flexible bronchoscopy is of added value, taking specific guidelines and literature into account.

Evaluation of symptoms

Persistent cough

In patients with chronic cough, flexible bronchoscopy can be performed if extensive clinical evaluation for common causes of cough (pulmonary function testing, imaging, *etc.*) shows

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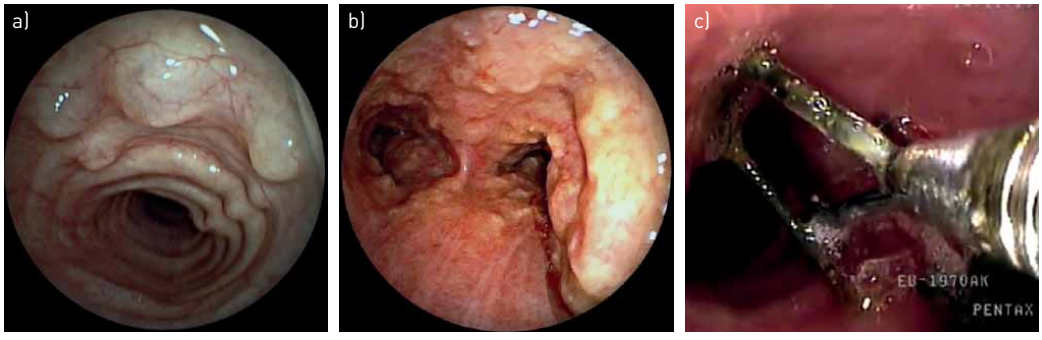

Figure 1. a) Typical appearance of tracheobronchopathia osteochondroplastica in the trachea. Note that the lesions are smooth, covered by normal mucosa and confined to the cartilage rings. This is a spot diagnosis; histological conformation is not required. b) Primary tracheobronchial amyloidosis. Note the characteristic yellowish deposits that seem randomly spread across the airways, while some areas are spared. c) Example of a foreign body, in this case an open safety pin that got stuck in the trachea. A flexible grasping forceps is being positioned for extraction.

no diagnosis or if history taking reveals a specific suspicion of central airway pathology. It is important to realise, however, that the yield of bronchoscopy in chronic cough is low (⩽6%) [20–24]. Occasionally, specific causes of chronic cough can be identified (*e.g.* foreign body, tracheobronchopathia osteochondroplastica, primary tracheobronchial amyloidosis, congenital defects, broncho-oesophageal fistula) (figure 1). Bronchoscopy with biopsies of normal-appearing mucosa performed in patients with cough might explain the mechanisms of chronic cough as part of a research project, but is of no value in clinical decision making [25]. If flexible bronchoscopy is performed in patients with cough, it is important to carefully inspect the oropharynx and laryngopharynx for signs of post nasal drip, inflammation, neoplasm or gastro-oesophageal reflux, or to refer the patient for otolaryngoscopy [26, 27].

Dyspnoea

Flexible bronchoscopy has no place in clinical algorithms for the evaluation of dyspnoea. However, if dyspnoea is suspected to originate from the central airways, bronchoscopy can be of added value. Examples include suspected tracheal stenosis, tracheobronchomalacia, EDAC, malignant airway obstruction or a problem with artificial airways, such as a tracheostomy tube.

Haemoptysis

Haemoptysis can be mild or life threatening. In mild haemoptysis, bronchoscopy can play an important role in localising and identifying the source of the bleeding, even if a CT scan shows no abnormalities [28–30]. If bleeding is significant and the CT scan shows clear location and likely cause (*e.g.* bleeding at site of bronchiectasis), it is preferable to omit bronchoscopy and proceed directly to bronchial artery embolisation. Massive haemoptysis is a rare but life-threatening emergency. The danger of massive haemoptysis lies in asphyxiation. Management of massive haemoptysis requires advanced airway management skills and often bronchoscopic intervention [31]. The evaluation and management of haemoptysis is discussed in more detail in another chapter in this *Monograph* [32].

Hoarseness and stridor

Hoarseness and stridor are less common complaints and are often caused by diseases of the oropharynx, larynx and vocal cords. However, diseases of the trachea, especially in close

proximity to the vocal cords, are also associated with these symptoms. Examples are web-like tracheal stenosis, neoplasms of the proximal trachea and recurrent respiratory papillomatosis.

Evaluation of clinical findings

Suspected malignancy

Bronchoscopy has an important role in the evaluation central and peripheral masses. The positioning of flexible bronchoscopy in the evaluation of pulmonary masses is dependent of many factors. If tissue procurement for histological diagnosis is the primary goal of the procedure then bronchoscopy with biopsies can be an excellent choice. For visible central lesions, the sensitivity of four to five biopsies is >95% [33]. Biopsy techniques are described elsewhere in this *Monograph* [6]. If a lesion is located in the periphery of the lung and especially if small in size, more advanced techniques might be required to obtain adequate samples. Techniques such as navigation and radial EBUS are described elsewhere in this *Monograph* [9]. If lymph node staging is the primary goal then endosonography techniques (EBUS/transoesophageal EUS) [1] or in selected cases TBNA [6] should be used.

Suspected bronchial obstruction

In a patient with persistent atelectasis or recurrent pneumonia, bronchoscopy is an important tool to investigate the cause and, in cases of bronchial obstruction, to re-open the bronchus if possible. Causes of bronchial obstruction causing atelectasis may be mucus plugging, a foreign body, a neoplasm, blood clots, or airway torsion or compression.

In cases of recurrent pneumonia, it is important to analyse the locations of the past pneumonias. If the pneumonia recurs at the same site, bronchial obstruction is suspected, although foreign bodies can sometimes migrate and cause subsequent pneumonias at different sites [34].

Pneumonia of unknown aetiology or not responding to treatment

In the majority of cases, the aetiological agent is not identified and empirical antibiotic treatment is instituted. The patient might not respond to this treatment for several reasons: an unanticipated and untreated pathogen or a non-infectious cause of the pulmonary infiltrate (*e.g.* malignancy, cryptogenic organising pneumonia, eosinophilic pneumonia). For microbiological testing, BAL can be useful for patients who do not expectorate representative sputum samples [35]. For immunocompromised patients (with AIDS or neutropenia, for example), BAL is standard in the diagnosis of opportunistic pulmonary infections (*e.g. Pneumocystis jirovecii*, fungi, viruses). For patients with slowly or non-resolving pneumonia, BAL and optional TBLB is advocated [36, 37].

Suspected tuberculosis

Bronchoscopy can be an important tool in the diagnosis of suspected tuberculosis (TB) of the lung parenchyma, the tracheobronchial tree and the hilar/mediastinal lymph nodes. TB located in the lung parenchyma can manifest as localised disease (pulmonary infiltrate, cavernous lesion, granuloma) or diffuse disease (miliary tuberculosis). Where there is involvement of the lung parenchyma, sputum samples should always be examined first. If a patient does not expectorate sputum or the sputum smear is negative for TB, bronchoscopy can be indicated. The same applies to immunocompromised patients where co-infection with other opportunistic pathogens is possible.

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Interstitial lung disease

In the analysis of ILD, flexible bronchoscopy can be used to perform BAL or TBLB. BAL is a valuable tool in the diagnosis of several specific forms of ILD if used in conjunction with clinical information and HRCT findings. As an example, a high lymphocyte count, in combination with diffuse ground-glass opacities in the mid and lower lung regions, is highly suggestive of cellular nonspecific interstitial pneumonia [38]. For eosinophilic pneumonia, an eosinophil percentage of >25% is considered diagnostic in the presence of a typical HRCT pattern [33]. In many cases, however, BAL and HRCT findings are less specific. In addition, standardisation of the bronchoscopic procedures, cellular analysis and interpretation of the results is still far from optimal. Tissue diagnosis is still the gold standard in many ILDs. TBLB is a minimally invasive method for obtaining lung tissue. An important limitation of TBLB obtained using flexible biopsy forceps is the small amount of alveolated tissue and the presence of artefacts. Transbronchial cryobiopsy was recently introduced for ILD and is clearly superior to forceps TBLB [39]. This promising technique is discussed in more detail elsewhere in this *Monograph* [18].

Hilar and/or mediastinal lymphadenopathy

Lymph nodes in close proximity to the airways can be samples with TBNA, with or without endosonographic guidance. Details for TBNA [6] and EBUS-guided TBNA (EBUS-TBNA) [1] are discussed elsewhere in this *Monograph*.

Bronchiectasis

Indications for flexible bronchoscopy in patients with bronchiectasis may be: the detection of a foreign body; BAL for diagnosis of bacterial, fungal or mycobacterial infection in the absence of representative sputum samples; the removal of sputum plugs; and the diagnosis and management of airway haemorrhage associated with bronchiectasis.

Inhalation injury

Inhalation of heat, smoke or specific chemical substances can cause considerable morbidity and mortality, and airway/lung damage can be permanent [40, 41]. In burns patients, the incidence of inhalation injury is correlated with the size of the skin burn and is associated with poorer outcome, especially if further complicated by pneumonia [42]. Severe inhalation injury is characterised by pulmonary and bronchial oedema and secretions, which can accumulate and cause pneumonia and atelectasis. Bronchoscopic removal of accumulating debris in patients with airway injury is associated with a shorter length of stay in the intensive care unit and a shorter length of stay in the hospital [43].

Trauma with suspected airway injury

Deceleration trauma can cause rupture of the central airways, which is life threatening. Airway rupture can be complicated by pneumothorax, pneumomediastinum or even total loss of airway and death. Only a minority of patients with traumatic airway injury make it to the hospital alive [44]. Bronchoscopic assessment of the exact location, size and extent of the airway injury is crucial. Bronchoscopy should also be used for placement of an endotracheal tube at the correct location (cuff distal to the site of airway defect) [45–48].

Radiation-induced airway injury

High-dose radiation of central tumours is particularly associated with airway injury. Airway injury can include teleangiectatic vascular changes, airway stenosis, airway wall necrosis and airway fistula (figure 2). Airway necrosis or fistula can be complicated by fatal haemoptysis. Prospective data about airway injury in patients who were treated with external beam

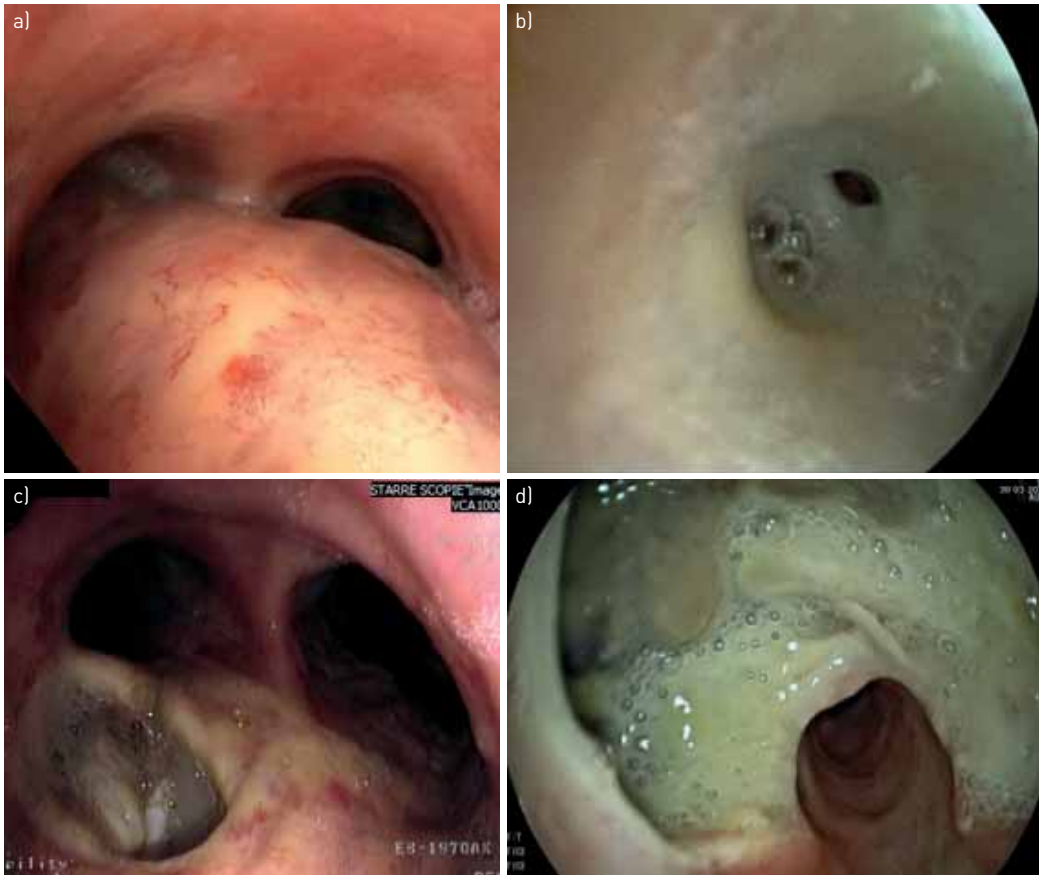

Figure 2. Complications after radiotherapy of the central airways. a) Teleangiectatic vascular changes in the distal trachea. b) Stenosis of the right lower lobe bronchus. c) Tracheo-oesophageal fistula. d) Massive necrosis of the right main bronchus.

radiation is scarce. In a retrospective study of 74 patients who underwent SBRT of a tumour in close proximity to the central airways, Karlsson *et al.* [49] found atelectasis in 24% of patients. A prospective study of 342 patients who were treated with endobronchial brachytherapy reported an incidence of bronchial stenosis of 12% [50]. A Cochrane review about palliative endobronchial brachytherapy for nonsmall cell lung cancer showed that fatal haemoptysis can occur in up to 20% of cases, with similar numbers observed in external beam radiation and endobronchial brachytherapy [51].

Suspected bronchopleural fistula

Bronchopleural fistula most frequently occurs as a complication of stump dehiscence or dehiscence of bronchial anastomosis after lung surgery (figure 3). Timely diagnosis of bronchopleural fistula is crucial to prevent further complications, such as pleural empyema, and to initiate adequate surgical and/or medical management.

Dynamic airway obstruction

Dynamic airway obstruction can be caused by any disease that is associated with loss of stability of the airway. Instability of the airways causes collapse during expiration. The most

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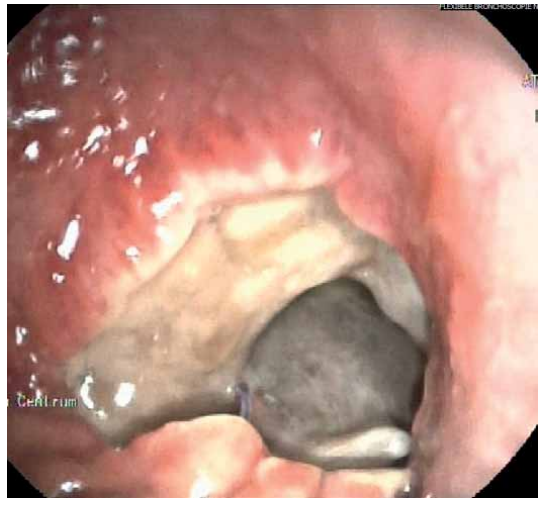

Figure 3. Dehiscence of the bronchial anastomosis after sleeve lobectomy of the right upper lobe. Note the sudden stop of bright pink bronchial wall.

common cause of airway instability is pulmonary emphysema, where loss of lung parenchyma results in loss of airway tethering. Several rare conditions are associated with instability of the central airways. In tracheobronchomalacia (TBM), which has multiple causes, destroyed or damaged cartilage causes central airway collapse and expiratory flow limitation. EDAC is characterised by excessive bulging of the membranous wall while the cartilage is unaffected [52]. Bronchoscopy is the gold standard for the diagnosis of TBM and EDAC, and can distinguish different causes of TBM (*e.g.* primary, tracheal injury caused by endotracheal tube or tracheostomy, or relapsing polychondritis).

The role of bronchoscopy in suspected lung transplant rejection or infection and airway management issues is discussed elsewhere in this *Monograph* [53].

Early detection of lung cancer

Squamous cell lung cancers account for 20–30% of lung cancers and are most common in the central airways. Although a shift toward more peripherally located squamous cancer has been observed in surgical series [54, 55], it is estimated that 15–20% of lung cancers are of the central squamous cell type, which constitutes a major worldwide cancer burden [56]. Regardless of technological improvements that have led to modern video bronchoscopy systems, the sensitivity for detecting early stage central lung cancer is low [57, 58]. AFB uses the spectral differences in fluorescence and absorption properties of normal and dysplastic bronchial epithelium, and enables early detection of centrally located pre-invasive endobronchial squamous lesions [59, 60]. AFB and other early detection techniques are described elsewhere in this *Monograph* [3].

Therapeutic flexible bronchoscopy

Right from the start, bronchoscopy was also intended for therapeutic use. Some of the first rigid bronchoscopes in the 19th century were used for foreign body removal. Nowadays, there is a great variety of therapeutic bronchoscopic applications for many pulmonary diseases. Most of these techniques can be applied through a flexible bronchoscope. Current

Figure 4. Performing flexible bronchoscopy. The bronchoscope is held in the non-dominant hand, while the fine motor skills of the dominant hand are used to advance the bronchoscope and to operate instruments through the working channel.

and near future therapeutic interventions are described elsewhere in this *Monograph* [13, 15, 32, 61–67].

Technique

Handling the bronchoscope

The bronchoscope is high-tech and expensive equipment and should be handled with great care. The tip of the bronchoscope should be protected from trauma because it contains essential, fragile and expensive parts, such the lens and the CCD. After positioning the patient, performing a time-out procedure, applying local anaesthesia and sedation if required, the bronchoscope can be introduced through the mouthpiece, nose or artificial airway. Throughout bronchoscopy, several important issues should be kept in mind, as follows.

Left or right hand?

The flexible bronchoscope was originally designed to be held in the left hand, because Professor Shigeta Ikeda (who invented and developed the flexible fibreoptic bronchoscope in cooperation with Olympus Optical Co. and Machida Endoscope Co.) was left-handed. The reason that modern commercially available bronchoscopes are still designed to be held in the left hand is because many techniques have been added that often require more complex skills than handling the bronchoscope. Steering a flexible bronchoscope clockwise and anti-clockwise and flexing and extending the tip with the lever requires only simple motor skills. Advancing and retracting the bronchoscope and operating instruments through the working channel of the bronchoscope (biopsy forceps, TBNA needles, bronchial blockers, *etc.*) requires fine motor skills (figure 4), which are preferably carried out with the dominant hand. Nevertheless, some bronchoscopists, experts amongst them, prefer to hold the bronchoscope in their right hand. The available literature also shows this to be a matter of controversy [68, 69]. Individual factors such as hand dominance, degree of ambidexterity and existing motor neuron pathways can play an important role in making

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this choice. Therefore, it makes sense that every bronchoscopist should find out for themselves what works best.

Stay in the midline

There are three reasons why centring the bronchoscope in the airway is imperative. First, touching the airway wall will create injury, discomfort and coughing, which will make the procedure more unpleasant for the patient and more difficult for the operator to perform. Secondly, when the bronchoscope is not centred in the airway, inspection will be incomplete and important findings may be missed. Thirdly, the bronchoscopist can become disorientated if important anatomical landmarks are missed. It is therefore crucial to stay in the midline right from the start of the procedure. Once the medial sulcus of the tongue, followed by the hard and soft palate have been identified, the uvula and the epiglottis, the arythenoid cartilages, and the false and true vocal cords become easy to locate. Collapse of the oropharynx and hypopharynx can sometimes hinder correct identification of anatomical structures. In such cases, a head tilt and chin lift can be of help [70].

Keep the bronchoscope straight

The flexible bronchoscope is designed in such a way that the movement of the hand piece and the lever should result in the desired movement at the distal end of the bronchoscope. The more the bronchoscope is bent, the poorer the distal end will respond to the commands of the bronchoscopist. Ensuing contact between the bronchoscope and airway wall will cause cough and discomfort for the patient. Deviation of the bronchoscope from a straight vertical line can be used as a marker for bronchoscopy performance. In an automated motion analysis performed in a bronchoscopy-simulation setting, the total deviation of the bronchoscope from a perfectly straight vertical line correlated negatively with the performance on a simulator [71].

Make small movements

The bronchoscope should be controlled by making small movements. Rotation of the bronchoscope is achieved by gently turning the wrist that holds the hand piece. Deflection of the tip is achieved by gently moving the lever up or down. Making large movements is unnecessary, makes the procedure more difficult and often makes the operator assume ergonomically unfavourable positions, which can cause musculoskeletal complaints for the endoscopist [72].

Proceed slowly

Quick and hasty navigation through the airways can be counterproductive. It increases the chance of bumping into the airway wall which causes injury, discomfort and coughing. Furthermore, the endoscopist can lose orientation more easily and important findings can be missed. A slow, controlled and complete bronchoscopy is preferable and might also save time because there is no need for re-orientation or re-inspection.

Work systematically

A systematic approach to flexible bronchoscopy is an absolute necessity. It allows the endoscopist to remain oriented throughout the bronchoscopy, to perform a complete assessment of all anatomical structures of the central airways and to accurately report findings. An accurate assessment is of vital importance because bronchoscopy can play a crucial role in the decision-making process in patients with thoracic diseases. A systematic approach requires excellent handling skills, knowledge of airway anatomy and an understanding of airway pathology. Learning a systematic approach is part of modern

bronchoscopy education and can be tested with validated tools such as the bronchoscopy skills and tasks assessment tool [73].

Flush the working channel before disconnection

When the procedure has finished, the bronchoscope should be cleaned according to local protocols. Before disconnecting the bronchoscope from the light source, the working channel should be flushed with isotonic saline for 15 s or 100 mL. This will expel 95% of the blood, mucus and other debris [74]. After flushing, the bronchoscope can be disconnected and subjected to local manual and automated cleaning and drying protocols.

Ergonomics

In our efforts to care for our patients and to improve the procedures, ergonomics is often overlooked. Ergonomics is rarely a subject of discussion between (interventional) pulmonologists. Nonetheless, according to an online survey, 39% of pulmonologists experience pain during bronchoscopic procedures [75]. The most common locations for pain were shown to be the back, shoulder, wrist, thumb and neck. 21% of these pulmonologists sought treatment. Sex and height did not correlate with an increased risk of pain. Similar numbers were observed in gastroenterology physicians [72]. In a survey completed by 684 endoscopists, 362 (53%) experienced musculoskeletal injury perceived to be definitely (n=204) or possibly (n=158) related to endoscopy. A higher rate of endoscopy-related injury was related to a higher procedure volume (>20 cases·week^{-1}), a greater number of hours per week spent performing endoscopy (>16 h·week^{-1}) and an increased total number of years performing endoscopy [72].

Simple adjustments can improve ergonomics in the bronchoscopy suite. Adjusting the height of the operating table before the start of the procedure is simple and can significantly improve posture. Optimising the height and position of the monitors in relation to the operator can result in better head and neck alignment over the shoulders. Complaints of discomfort in the left hand and wrist often occur when performing bronchoscopic procedures in the left lung, especially the left upper lobe. If the bronchoscopist is performing the procedure while standing behind the patient and holding the bronchoscope in the left hand, the left wrist will be extended for a prolonged period of time, which can cause pain and tremor. This is easily prevented by positioning an extra monitor to the left of the patient. Upon entering the left main bronchus, the bronchoscopist can step over to the right side of the patient and look at the monitor to the left of the patient. This will keep the left hand and the head in a neutral position while examining the left lung. Alternatively, the bronchoscopist can stand or sit in front of the patient. To enjoy a long and healthy career in bronchoscopy, it is wise to invest in improving ergonomics.

Anatomy

A thorough understanding of anatomy is crucial when performing bronchoscopy. Correct identification of all anatomical structures from the teeth to the subsegmental bronchi is necessary to stay oriented throughout bronchoscopy, to localise pathological findings and to guide procedures such as a targeted bronchial washing or TBB. The bronchoscopist should also be able to correlate the anatomy shown on CT scan/chest radiography images to the anatomy during bronchoscopy. Careful assessment of the CT scan can be used to predict whether a lesion can be seen with the bronchoscope, to determine where it can be

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found and to select the most appropriate method to reach the lesion (*e.g.* forceps, TBNA needle). A comprehensive explanation of anatomy for the bronchoscopist is available elsewhere [76]. Here, we will briefly review normal tracheobronchial anatomy. It is important to realise that there are many variations in bronchial anatomy [76].

The trachea

The trachea extends from the cricoid cartilage to the main carina, and consists of 16–20 incomplete cartilage rings. The length of the trachea is ~110 mm and the internal diameter is 14–20 mm. The posterior or membranous part of the trachea consists of a flat fibromuscular wall that bulges slightly anteriorly during expiration and more so during coughing.

The main carina

The main carina is a largely cartilaginous structure that divides the trachea in the left and main bronchi. Lymph node station 7 is located right below the main carina, as is the left atrium, which can blunt the angle of the main carina upon enlargement.

The main, lobar and segmental bronchi

The main bronchi have a structure similar to the trachea. The right main bronchus is ~15 mm in length and extends from the main carina to the right carina 1 (RC1) (figure 5), which divides the right upper lobe bronchus from the bronchus intermedius (figure 5). The upper lobe bronchus is ~10 mm long and gives rise to the apical segmental bronchus (RB1), the posterior segmental bronchus (RB2) and the anterior segmental bronchus (RB3) (figure 5, table 2). The bronchus intermedius is ~20 mm in length and the right carina 2 (RC2) divides it into the middle lobe bronchus and the lower lobe bronchus. The middle lobe bronchus is approximately 15 mm long and bifurcates into the lateral segmental

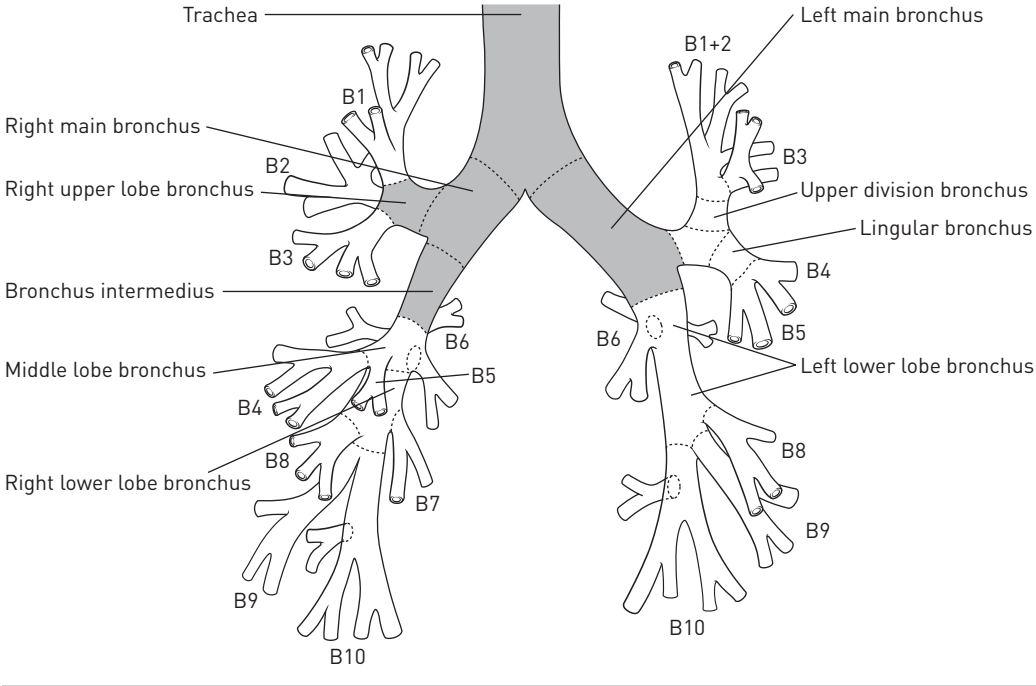

Figure 5. Bronchial anatomy.

Table 2. Segmental bronchial anatomy

	Lobar bronchi	Segmental bronchi
Right main bronchus	Right upper lobe bronchus	RB1, apical segment RB2, posterior segment RB3, anterior segment
	Middle lobe bronchus	RB4, lateral segment RB5, medial segment
	Right lower lobe bronchus	RB6, superior segment RB7, medial basal segment RB8, anterior basal segment RB9, lateral basal segment RB10, posterior basal segment
Left main bronchus	Left upper lobe bronchus	LB1+2, apical posterior segment LB3, anterior segment LB4, superior segment LB5, inferior segment
	Left lower lobe bronchus	LB6, superior segment LB8, anterior basal segment LB9, lateral basal segment LB10, posterior basal segment

bronchus (RB4) and the medial segmental bronchus (RB5). The superior segmental bronchus (RB6) of the right lower lobe originates immediately from the posterior part of the right lower lobe bronchus (RLLB). The medial basal segmental bronchus (RB7) rises just distal from the RB6 on the medial side of the RLLB. Just distal from the RB7, the RLLB trifurcates in the anterior basal (RB8), lateral basal (RB9) and posterior basal (RB10) segmental bronchi.

The left main bronchus is ∼40-mm long. At the left carina 2 (LC2) it bifurcates into the left upper lobe bronchus and the left lower lobe bronchus (figure 5). The left upper lobe bronchus directly bifurcates at the left carina 1 (LC1) into the upper division bronchus and the lingular bronchus. The upper division bronchus is ∼5-mm long and bifurcates into the apical posterior segmental bronchus (LB1+2) and the anterior segmental bronchus (LB3). The lingular bronchus is ∼10-mm long and gives rise to the superior segmental bronchus (LB4) and inferior segmental bronchus (LB5). The superior segmental bronchus (LB6) of the left lower lobe originates immediately from the posterior part of the left lower lobe bronchus (LLLB). ∼20 mm distal of the LB6, the LLLB trifurcates into the anterior basal (LB8), lateral basal (LB9) and posterior basal (LB10) segmental bronchi. The presence of a medial basal branch is unusual on the left side.

While the segmental bronchi are numbered in a clockwise direction, the subsegmental bronchi indicated with letters in an anticlockwise fashion.

Vascular anatomy

Vascular structures surround the tracheobronchial tree [77]. Knowledge of these structures and their anatomical relation to the tracheobronchial tree is a prerequisite for performing procedures such as TBNA and EBUS. In unusual circumstances, such as severe injury of the bronchial wall, vascular structures can become exposed. Precise knowledge of anatomy

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Table 3. Levels of sedation

Sedation level	Description
Minimal sedation	The patient responds normally to verbal commands. Cognitive function and coordination may be impaired, but ventilatory and cardiovascular functions are unaffected.
Moderate sedation and analgesia	The patient responds purposefully to verbal commands alone or when accompanied by light touch. Protective airway reflexes and adequate ventilation are maintained without intervention. Cardiovascular function remains stable.
Deep sedation and analgesia	The patient cannot be easily aroused but responds purposefully to noxious stimulation. Assistance may be needed to ensure the airway is protected and adequate ventilation maintained. Cardiovascular function is usually stable.
General anaesthesia	The patient cannot be aroused and often requires assistance to protect the airway and maintain ventilation. Cardiovascular function may be impaired.

Information from [79, 80].

and identifying vascular structures on CT images before the procedure can prevent iatrogenic damage and massive haemorrhage.

Sedation

Bronchoscopy is not a pleasant procedure. Symptoms such as nose pain, throat pain, cough, haemoptysis, dyspnoea and anxiety can be experienced during and after the procedure [77, 78]. The willingness to return for another bronchoscopy varies substantially, but can be as low as 53% [78]. Flexible bronchoscopy can be performed without sedation. Informing the patient about the procedure, reassurance and adequate topical anaesthesia can make flexible bronchoscopy tolerable for the patient. However, sedation should always be offered to the patient if there are no contraindications [28]. For several more advanced procedures (*e.g.* EBUS, transbronchial cryobiopsy, bronchial thermoplasty, rigid bronchoscopy, airway stenting) sedation is mandatory.

The American Society of Anaesthesiologists (ASA) has identified different levels of sedation (table 3) [79, 80]. These different stages in practice represent a continuum of sedation. The level of sedation during a procedure can change suddenly. Moderate sedation can easily change to deep sedation. This requires the necessary precautions, knowledge, skills and equipment to manage sedation levels deeper than aimed for. The following general precautions apply in bronchoscopy with procedural sedation. 1) Patients should be screened for comorbidities, contraindications and use of medication. 2) ASA classification should be taken into account [81] because it correlates with the rate of postoperative complications [82]. 3) Electrocardiogram and lung function testing should be performed on indication. 4) Age should be taken into consideration because in general, higher age is associated with an increased complication rate [83–86].

Midazolam

Midazolam is a benzodiazepine with anxiolytic and sedative properties. A useful side-effect is anterograde amnesia, which can last for 1.5 h, but doesn't occur in all patients.

Midazolam can be antagonised with flumazenil. For bronchoscopy, midazolam is usually administered as a single intravenous dose of 0.02–0.05 mg·kg^{-1}, usually 2–5 mg. In several placebo-controlled trials, midazolam was associated with higher patient tolerance when compared with placebo [87–89]. Unfortunately, however, the quality of the evidence on midazolam as a sedative in flexible bronchoscopy is low [90]. Midazolam is often combined with short-acting opioids, such as fentanyl, remifentanil or alfentanyl. Importantly, the addition of opioids increases the chance of respiratory complications. In cases of overdose, midazolam can be antagonised with flumazenil 0.2 mg *i.v.*, followed by 0.1 mg every min, until the desired level of consciousness is reached (maximum cumulative dose 3 mg).

Propofol

Propofol is a phenol derivative that is very lipophilic and therefore crosses the blood–brain barrier quickly. It is used in general anaesthesia but is also an attractive drug for procedural sedation. Propofol has gained popularity in recent years because it can be titrated to a predictable level of deep sedation while the patient is still spontaneously breathing and because the patient regains consciousness shortly after the infusion has stopped. Propofol can be used as an intermittent bolus or a continuous infusion, although in one study, the latter was associated with a higher propofol requirement and a longer duration of bronchoscopy [91]. Propofol is used for deep sedation and overdose can cause respiratory depression and hypotension. Because propofol cannot be antagonised, infusion should be stopped immediately. Because propofol is quickly eliminated, the patient will soon start breathing again. In the meantime, adequate cardiorespiratory management is crucial.

Midazolam *versus* propofol

Three randomised controlled trials have compared midazolam with propofol in bronchoscopic procedures. Clarkson *et al.* [92] compared midazolam (mean±SD 9.3 ±3.1 mg) and propofol (125.4±9.8 mg) in 41 asthmatic patients and found that the required level of sedation was achieved significantly faster with propofol and that patients regained consciousness more quickly with propofol. Stolz *et al.* [93] randomised 200 patients in a non-inferiority trial of *i.v.* propofol *versus* a combination of midazolam and hydrocodone. Propofol was found to be as effective and safe as combined sedation. Clark *et al.* [94] randomised 124 patients that underwent flexible bronchoscopy to either repeated shots of 2 mg of midazolam or 40 mg of propofol. The regimens were equally safe in the hands of a non-anaesthetists and propofol showed quicker neurological recovery and greater patient satisfaction.

Other drugs

Other drugs such as ethomidate, ketamine and dexmedetomidine are also gaining popularity in procedural sedation. They can be used as an alternative or an adjunct to propofol. However, (high-quality) evidence about these drugs in procedural sedation for flexible bronchoscopy is required before any substantial recommendations can be made.

The limitations of flexible bronchoscopy

Flexible bronchoscopy is a very powerful diagnostic and therapeutic tool, but has some limitations. The outer diameter determines how far the bronchoscope can navigate in the

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airways. The majority of bronchoscopes used in daily practice have an outer diameter of 5–6 mm, which allows inspection up to the 3rd–5th generation. Bronchoscopes with a smaller outer diameter (3.1–3.8 mm) are commercially available, but as a consequence the working channel decreases in size (1.2 mm instead of 2.0–3.2 mm), which limits the size of biopsy specimens and suction power. Solutions for reaching the periphery of the lung have been developed (and are discussed elsewhere in this *Monograph*) [9] and interesting new techniques are currently under development.

Another limitation of flexible bronchoscopy is the management of malignant airway obstruction and airway haemorrhage. In malignant airway obstruction, intraluminal tumour tissue should be removed. Rigid bronchoscopy offers a more rapid technique than flexible bronchoscopy. In addition, complications such as airway haemorrhage can be managed in a very safe manner. There is no faster and safer method of airway access, airway blocking and evacuation of blood/clots than with a rigid bronchoscope. When it comes to airway stenting, an interventional pulmonology service should offer both SEMS and silicone stents. Silicone stents in particular require rigid bronchoscopy for placement.

It is also important to take into account that bronchoscopy only informs the operator about the endoluminal structures. This can lead to tunnel vision, which can be dangerous. The bronchoscopist should therefore be aware of the extraluminal world, which is inhabited by lymph nodes, vascular structures and more. Techniques like TBB and TBNA [6] have moved bronchoscopy beyond the airway wall and endosonography has enabled visualisation of extraluminal structures and real-time procedures such as EBUS-TBNA [1].

A final consideration is that flexible bronchoscopes are very vulnerable. Great care should be taken when handling flexible bronchoscopes and whilst performing procedures, especially if needles are involved (TBNA, EBUS, percutaneous tracheostomy). Not only are repair costs often high but the equipment can also be out of service for several weeks.

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Rigid bronchoscopy

Maren Schuhmann

Rigid bronchoscopy was first introduced in the late 1890s, but its use declined in the 1960s with the development of flexible bronchoscopy. However, due to its many new applications and indications, it has seen a revival in recent years. Management of severe haemoptysis, stent placement and recanalisation are some of the many indications for rigid bronchoscopy, often used in combination with a flexible bronchoscope. Its main disadvantages are the need for general anaesthesia and limited opportunities for training due to a relatively low number of departments worldwide performing rigid bronchoscopy on a regular basis.

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In 1897, the ENT surgeon Gustav Kilian from Freiburg, Germany, was the first person to perform a rigid bronchoscopy to remove a piece of pork bone from the right main bronchus of a patient [1]. At the time, he used a Mikulicz–Rosenheim oesophagoscope combined with a rigid forceps and was able to avoid a tracheotomy for the patient. Aspiration of foreign bodies at that time meant falling ill because of atelectasis, chronic pneumonia or haemorrhage.

In 1904, Chevalier Jackson was able to use a rigid bronchoscope with a small light source for the first time in the USA. The development of rigid lenses led to further development of the technique and its use in foreign body retrieval and to treat central airway obstruction [2].

In the 1970s, the flexible bronchoscope was developed and has seen rapid development and improvements in recent years. Several techniques were adapted and invented to be used with the flexible bronchoscope. In many areas, this has led to a reduction in rigid bronchoscopy procedures, but more recently, the technique has seen a revival due to its advantage of securing a large airway, and allowing ventilation and the introduction of large instruments into the central airways [3]. The bronchoscopist Jean-Francois Dumon in Marseille, France, in particular developed the technique and the rigid scope further, and in combination with silicone stenting, laser vaporisation and photocoagulation brought the technique back to the general interest of pulmonologists worldwide [4]. In larger respiratory centres in particular, the ability to perform rigid bronchoscopy is invaluable for

Dept of Respiratory and Critical Care Medicine, Thoraxklinik at University of Heidelberg, Heidelberg, Germany.

Correspondence: Maren Schuhmann, Dept of Respiratory and Critical Care Medicine, Thoraxklinik at University of Heidelberg, Röntgenstrasse 1, 69126 Heidelberg, Germany. E-mail: maren.schuhmann@med.uni-heidelberg.de

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diagnostic as well as all available therapeutic procedures within the airways, often in combination with a flexible bronchoscope. The increased performance of cryobiopsies has also led to an increased interest in rigid bronchoscopy, as the procedure can be performed in a safe fashion with a rigid bronchoscope in place. More junior interventional bronchoscopists now have a keen interest in learning and applying this technique again, and guidelines indicate the need for training in rigid bronchoscopy [5].

This chapter focuses on the indications for and technique of rigid bronchoscopy, and will also discuss the aspects of sedation for rigid bronchoscopy and the limitations of the technique.

Equipment

Briefly, there are three main components to a rigid bronchoscope. The first is the scope itself, which is a straight, hollow, metal tube with a bevelled distal tip. This allows atraumatic intubation through the vocal cords, as well as through a stenosis or when used for recanalisation. Depending on the manufacturer, the length varies between 33 and 43 cm with an outer diameter of 6–14 mm. Thinner bronchoscopes facilitate reaching the main bronchi, whereas the larger scopes allow larger instruments to be passed through, as well as the placement of silicone stents. The choice of bronchoscope depends on the planned intervention. The use of scopes ascending in diameter also allows the dilatation of central stenoses.

There are generally two different types of scopes, the longer bronchoscope and the shorter tracheoscope (figure 1a and b). The bronchoscope is intended to be used all the way to the main bronchi, with slits in the distal end to facilitate ventilation as the bronchoscope is advanced into the contralateral main bronchus. The tracheoscope is shorter and is used instead for interventions in the trachea and at the level of the vocal cords. There are no ventilation fenestrations in the tracheoscope. The EFER-Dumon (La Ciotat, France) and the Dutau-Novatech (La Ciotat, France) rigid scopes are modular systems that allow smaller rigid scopes to be passed through the introducing tracheoscopes. This is particularly useful in the dilatation of stenosis and for recanalisation (coaxial bronchial dilatation).

The second component is an adapter head at the proximal end, which is made up of a central opening, as well as differing side ports, depending on the manufacturer (figure 2).

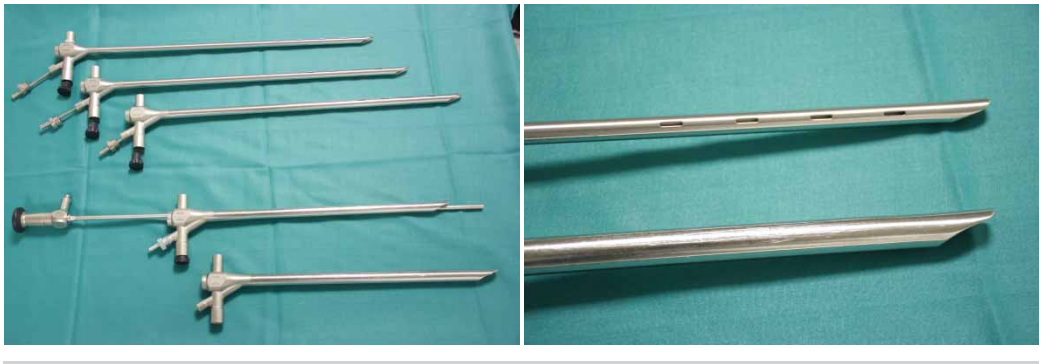

Figure 1. A selection of bronchoscopes and tracheoscopes of differing diameters, showing the ventilation slits in the rigid bronchoscopes.

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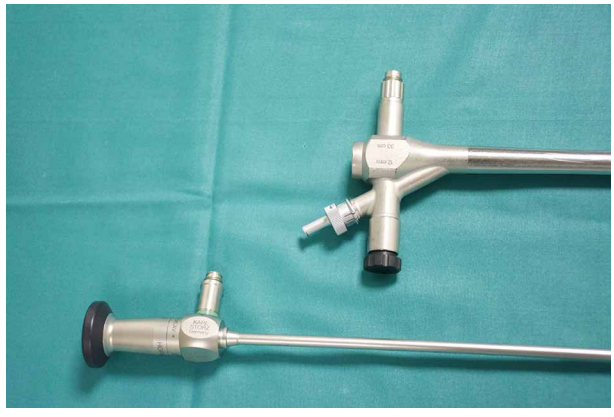

Figure 2. Adapter head of a Karl Storz (Tuttlingen, Germany) bronchoscope.

The light source can be attached to the proximal end or to the telescopic lens. The illumination is usually provided by a xenon light source with a light deflector. On one of the lateral ports, the jet ventilation can be attached; otherwise, it is also possible to attach continuous mechanical ventilation. Manufacturers of the currently available rigid scopes include Karl Storz (Tuttlingen, Germany), Richard Wolf (Knittlingen, Germany), EFER-Dumon and Dutau-Novatech.

For intubation, the operator can look either directly down the bronchoscope through the eyepiece or through an optical lens with an attached chip video camera for easier intubation. These rigid lenses can be attached to a camera, which transmits the picture to a monitor in order to demonstrate the intubation to observers.

Ventilation during bronchoscopy is delivered by either conventional or jet ventilation. The rigid scope is uncuffed, thus leading to a significant amount of air leakage during the procedure. The Richard Wolf bronchoscope has been further developed into the so-called Hemer bronchoscope, allowing the measurement of inspiratory and expiratory pressures, as well as carbon dioxide and oxygen concentrations.

When the airway is secured with the rigid scope, the rigid camera can be advanced further into the main bronchi for inspection, or rigid forceps can be mounted on the camera for biopsy. Alternatively, the bronchoscopist can use a flexible bronchoscope *via* the rigid scope for inspection of the entire bronchial tree prior to any planned intervention.

Technique

When using a rigid bronchoscope, the bronchoscopist, as well as the assisting nursing team and anaesthetist, should be familiar with this technique and trained accordingly. Usually, the rigid bronchoscope is inserted under direct vision, but a laryngoscope can additionally be used. Using the telescope and camera facilitates the view and allows a more comfortable body position for the examiner. It is mandatory that the camera always remains within the barrel of the rigid scope to avoid damage to the airways (figure 3).

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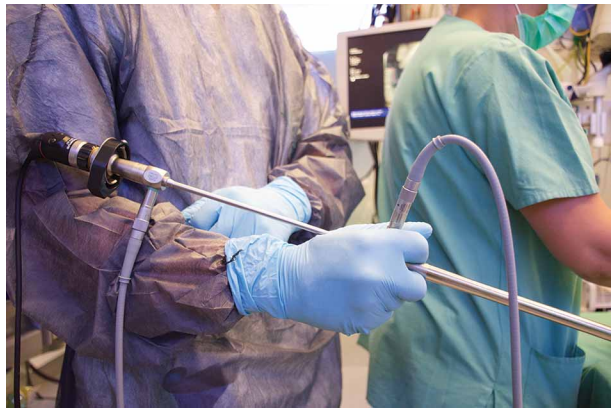

Figure 3. Hand position for a rigid bronchoscope for intubation.

The patient is positioned on their back in an improved Jackson position (slight head elevation for improved laryngeal exposure). The mouth of the patient is opened with one hand and the rigid scope is inserted with the other. The middle finger rests on the hard palate, while the index finger opens the lower jaw and pushes the lower lip out of harm's way. Care must be taken to avoid damage to the teeth and other structures, and the rigid scope should always be guided by the thumb of the opposite hand, acting as a fulcrum. By pushing up the thumb, the upper teeth and upper lip are protected (figure 4). An additional tooth guard can be placed in the mouth; however, this significantly limits the

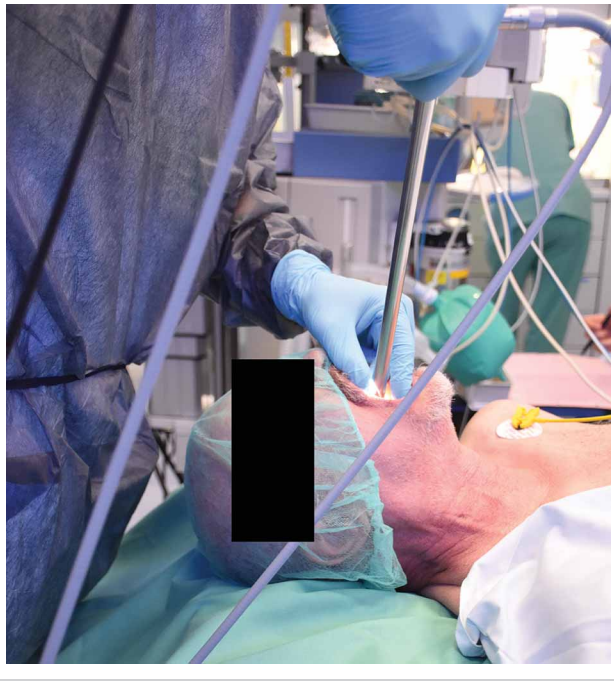

Figure 4. Initiation of intubation, with the thumb protecting the teeth and the index finger opening the mouth.

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opening area of the mouth, sometimes making intubation more difficult. The scope is inserted centrally over the tongue until the uvula is reached (figure 5a). At a steeper angle, the epiglottis is visualised (figure 5b). The epiglottis is subsequently lifted up with the longer end of the distal tip to fully view the vocal cords (figure 5c). The scope is now rotated 90° to the right and the right vocal cord is gently pushed aside while passing through the vocal cords (figure 5d). Once the cords have been passed, the scope is rotated another 90° and advanced to the mid-trachea. The ventilation can now be attached.

Rigid bronchoscopy can also be performed through a tracheostoma, bypassing the anatomical structures described above.

If the right main bronchus needs to be reached with the rigid scope, the patient's head must be tilted to the left in order to align the trachea with the main bronchus. The left main bronchus can also be reached, but the patient's head will need to be turned to the right. While advancing the scope in the trachea, care needs to be taken to lift the scope off the posterior tracheal wall to avoid a laceration or perforation. The position of the rigid scope is stabilised by the patient's trachea and mouth, and rests on the teeth.

Setting

In order to perform rigid bronchoscopy, a dedicated endoscopy suite with an advanced care set-up is required, as well as qualified staff. In many centres, bronchoscopy suites also act as endoscopy suites for gastroenterologists. Alternatively, rigid bronchoscopies are performed in operating theatres. This always implies competition for theatre time and may be a significant impediment. Rigid bronchoscopy does not require a sterile setting, so a dedicated operating theatre is not necessary. A dedicated bronchoscopy unit has the advantage of immediate availability of all necessary equipment at short notice.

Enough space should be available for anaesthetic equipment and fluoroscopy, laser, cryotherapy and navigation systems, as well as ROSE (rapid onsite evaluation) equipment. A stretcher or surgical table is essential in any interventional bronchoscopy suite. It must have full C-arm access, a head end travers for easy intubation, and the possibility of performing the Trendelenburg and reverse Trendelenburg position as well as lateral tilt.

Most importantly, adequate staffing is required in order to perform rigid bronchoscopy safely. Nurses need training in assisting in rigid bronchoscopy, and doctors need to have experience in this technique in order to perform it safely in an emergency setting. An anaesthetist experienced in rigid bronchoscopy and an anaesthetic nurse are also important parts of the team. Coordination and communication with the whole team, but especially with the anaesthetist, are essential to secure a safe airway at all times during the procedure.

Sedation

Adequate monitoring of the patient, as occurs during general anaesthesia, with oxygen pulse oximetry, blood pressure and heart rate monitoring is essential. End-tidal carbon dioxide measurements can be performed during prolonged procedures but may be unreliable due to the open circuit when the patient is jet ventilated.

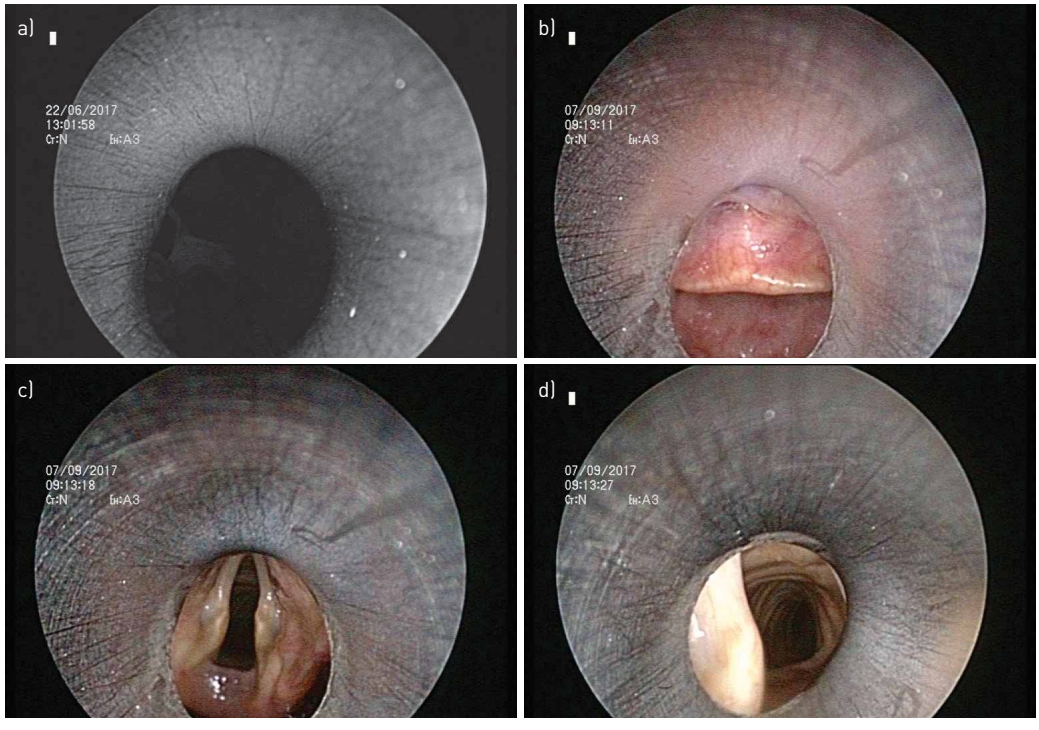

Figure 5. a) View with a rigid camera during intubation. The camera should always remain within the rigid scope. b) View of the epiglottis. c) View of the vocal cords. d) Passing the rigid scope through the vocal cords.

Anaesthesia requires a combination of analgesia, hypnosis and muscle relaxation. Ideally, the onset and offset of the anaesthetic should be rapid, as the patient is often compromised from a respiratory point of view.

Rigid bronchoscopy is usually performed under general anaesthesia using a combination of mostly propofol and an opioid, together with a short-acting muscle relaxant such as succinylcholine. Other agents used during the sedation for rigid bronchoscopy include short-acting opioids such as fentanyl and alfentanil, as well as etomidate or ketamine. Longer-acting opioids are avoided, as post-procedure pain is rare and they may cause prolonged respiratory depression after the intervention. However, some centres may use deep sedation without muscle relaxation, local anaesthesia and spontaneous breathing of the patient, but larger doses of the hypnotic agent are required for the patient to tolerate the rigid tube.

In all cases, an anaesthetist is required who is experienced in different ventilation strategies that may be unfamiliar for some. Due to the open circuit, volatile gases need to be avoided and only intravenous anaesthesia is used.

A rigid bronchoscope can be inserted into a nonparalysed patient but only under deep sedation. This may mean higher doses of analgesic or sedative agents, risking cardiovascular instability.

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The total *i.v.* anaesthesia often consists of a combination of propofol and a short-acting opioid such as remifentanil. Longer-acting opioids may induce respiratory depression following the procedure.

During rigid bronchoscopy, different ventilation strategies can be applied such as high-frequency jet ventilation, manual jet ventilation, controlled ventilation and spontaneous assisted ventilation, as well as apnoeic ventilation. There are reported cases of barotraumas associated with jet ventilation, but these are rare [6].

Indications

Advantages of rigid bronchoscopy

Inspection of the airways and a purely diagnostic bronchoscopy is currently performed with a flexible bronchoscope in most centres under local anaesthesia and with either no or moderate sedation. The use of a rigid bronchoscope under deep sedation or general anaesthesia can only be justified with increased complexity or duration of the intervention, or for specific interventions. In most diagnostic procedures, a combination of rigid and flexible bronchoscopy is performed, the rigid bronchoscope allowing a secure airway for ventilation and oxygenation of the patient and for the flexible bronchoscope in order to reach smaller and more distal airways. Most diagnostic instruments are advanced *via* the working channel for the flexible bronchoscope.

The advantage of the combination of rigid and flexible bronchoscopy is to secure the airway with a large ventilating lumen and with little airway obstruction. The large lumen of the rigid scope allows a variety of larger tools and devices to be inserted, as well as offering the possibility of advancing a large suction catheter in the case of a larger haemorrhage. Instruments can be changed quickly, and complications such as haemorrhage after endobronchial biopsy or TBB can be managed more quickly than with just a flexible bronchoscope. A rigid bronchoscope can also be advanced into the right or left main bronchus, isolating one lung for ventilation in case of a major bleed.

For the removal of foreign bodies, rigid bronchoscopy is often required, although smaller foreign bodies can also be removed using flexible bronchoscopy *via* an endotracheal tube.

Indications for rigid bronchoscopy

The indications for the use of a rigid bronchoscope are varied. Management of significant haemoptysis can only safely be dealt with when a rigid bronchoscope is available. The causes and treatment of haemoptysis are discussed in more detail elsewhere in this *Monograph* [7].

Central airway obstructions can be dealt with quickly by mechanical coring ("apple" coring) of the lesion with a rigid bronchoscope. This allows rapid recanalisation of large airways prior to placing a stent to maintain the airway. The scope itself can also compress the bleeding surface of the tumour after debulking, and haemorrhage can be partially controlled. With the aid of rigid forceps, large tissue samples can be obtained quickly during the procedure, and other large rigid instruments such as rigid scissors can be advanced *via* the rigid scope.

Other interventional instruments such as a laser, argon plasma coagulator, electrocauteriser, cryoprobe or microdebrider can also be inserted *via* a rigid bronchoscope, either directly or through the working channel of a flexible scope.

Although metallic stents can be placed *via* a flexible bronchoscope, their insertion and management can be made easier with the availability of a rigid scope. The placement of silicone stents will always require a rigid scope as they cannot be inserted using only a flexible bronchoscope.

Dilatation of benign strictures with scopes of progressively increasing diameter is also an indication for rigid bronchoscopy.

Newer techniques for endoscopic lung volume reduction (valves, coils, bronchial thermal vapour ablation and targeted lung denervation), as well as thermoplasty for the treatment of severe asthma, can also be performed *via* a rigid scope.

Limitations of rigid bronchoscopy

Training

Rigid bronchoscopy is limited mainly by the experience of the bronchoscopist. Not all pulmonologists are fully trained in performing rigid bronchoscopy safely and efficiently. Adequate training in order to deal with complications that may arise during the procedure is mandatory to offer a full service to patients. In the UK and USA, for example, rigid bronchoscopy is not performed routinely, and training centres are limited, whereas in Europe, and particularly Germany, more endoscopies use rigid bronchoscopy on a regular basis, although the numbers are still low in comparison with the number of centres performing flexible bronchoscopy [3].

National and international guidelines may also not agree on the number of rigid bronchoscopies needed to be performed on a yearly basis to remain competent at this technique [5]. Obviously, the learning curve will vary from person to person, as discussed in more detail elsewhere in this *Monograph* [8]. Some trainees may never perform rigid bronchoscopy during their pulmonology training, but even within specialised interventional fellowships, the amount of exposure to rigid bronchoscopy varies widely. There is also no universally accepted curriculum to teach this technique. Most trainees are taught on low-fidelity models to practice the careful intubation required prior to patient contact, and virtual-reality simulators for rigid bronchoscopy are currently not available. Once the technique has been mastered on a model, most trainees have their first patient experience in patients without teeth.

Contraindications

In cases of life-threatening airway stenosis or haemoptysis, there is no contraindication for rigid bronchoscopy if it can alleviate the source of bleeding or obstruction.

The contraindications for rigid bronchoscopy relate mainly to the necessity for a general anaesthetic. If the patient is unable to have a general anaesthetic, the alternative of local anaesthesia and flexible bronchoscopy needs to be evaluated. It must be noted, however,

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that sedation and flexible bronchoscopy may not necessarily be safer for the patient, particularly if staffing limitations require the bronchoscopist also to administer and monitor the sedation of the patient.

Impaired reclination of the neck due to, for example, unstable metastases of the spine or ankylosing spondylitis can present a contraindication to rigid bronchoscopy. Otherwise, contraindications as for flexible bronchoscopy similarly apply, such as clotting disorders or cardiac instability. These have been described in the British Thoracic Society (BTS) guidelines for flexible bronchoscopy [9].

Complications

Overall, rigid bronchoscopy performed by an experienced bronchoscopist is a relatively safe procedure [10]. However, complications can occur, similarly to with flexible bronchoscopy. Due to the necessary drugs used to induce general anaesthesia or deep sedation, the effects on the cardiovascular system can be pronounced, especially during the induction phase [11].

During intubation with a rigid bronchoscope, there is a risk of damage to the teeth if they are not adequately protected by the thumb or if the mouth opening is limited. A tooth guard can be used, but this reduces the mouth opening further. During intubation, the vocal cords as well as the posterior wall of the trachea can be lacerated, particularly if not enough care is taken, and hence during intubation the vocal cords need to be clearly visualised and the scope must be elevated off the posterior wall under full vision at all times. The patient also needs to be made aware of and consent to possible side-effects, such as hoarseness, sore throat, infection, cough and bleeding, as well as complications that might arise due to the planned intervention.

Complications related to rigid bronchoscopy quoted in the literature often refer to the procedures performed, such as massive haemoptysis, foreign body retrieval or stent placement. Insertion of a rigid bronchoscope and a simple diagnostic procedure carries no more risk than flexible bronchoscopy.

Conclusion

Rigid bronchoscopy is a well-established technique that has been neglected in some centres since the invention of the flexible bronchoscope. However, in recent years, it has seen a revival and is now mostly used in combination with flexible bronchoscopy. Its varied diagnostic and therapeutic options make it a valuable technique in the hands of an experienced bronchoscopist. More training centres need to be established to assure adequate learning opportunities for future interventional pulmonologists.

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Chapter 3

Bronchoscopy in intensive care

Suveer Singh

Bronchoscopy in the intensive care unit developed in the early 1970s. Its flexibility and versatility provide a crucial diagnostic and therapeutic tool. Indications are commonly to facilitate placement of a definitive airway, airway sampling for infection and clearance of secretions. More complex situations such as airway haemorrhage, percutaneous tracheostomy insertion, foreign body removal, burns inhalation injury, tracheal tears and persistent air leaks in mechanically ventilated patients are amenable to therapeutic bronchoscopy. Single-use portable bronchoscopes are important in the emergency setting, where a fast response, rapid visualisation and prevention of decontamination delays are essential. Bronchoscopy of the acutely sick awake patient is a valuable skill, requiring expertise and experience. An understanding of working endobronchial anatomy, physiological effects, and the risks and complications of bronchoscopy in this setting is necessary. Protocols for preparation, documentation and World Health Organization-style "time outs" should be encouraged. Training programmes still require significant development to ensure maintenance of satisfactory contextual and experiential skills.

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This chapter focuses on the use of bronchoscopy, specifically flexible bronchoscopy, in the intensive care unit (ICU) and other emergency settings. More general aspects of bronchoscopy are discussed elsewhere in this *Monograph* [1, 2].

History of bronchoscopy in intensive care

The first use of the fibreoptic bronchoscope in the ICU was reported by Marvin A. Sackner and colleagues in 1971 [3]. He described obtaining a flexible bronchoscope from Olympus, having attended a lecture by Dr Shigeto Ikeda in 1970. While the thoracic surgeons who performed rigid bronchoscopy were not initially impressed by the potential of the flexible scope, Sackner placed it through the endotracheal tube (ETT) of intubated patients, allowing a view of the effects of the inflated cuff on the tracheal mucosa. This engaged the thoracic surgeons in considering it as a tool for assessing airway integrity in their long-term ventilated postoperative patients. Sackner went on to demonstrate transnasal insertion of

Respiratory and Intensive Care Medicine, Royal Brompton and Chelsea and Westminster Hospitals, Imperial College London, London, UK.

Correspondence: Suveer Singh, Respiratory and Intensive Care Medicine, Chelsea and Westminster Hospital, 369 Fulham Road, London, SW10 9NH, UK. E-mail: suveer.singh@imperial.ac.uk

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the flexible fibreoptic bronchoscope through a nasopharyngeal airway, a route that had gained acceptance for reliable tracheobronchial suction in the nonintubated patient [4]. Other applications of flexible bronchoscopy use in pulmonary medicine were described, including facilitation of intubation in the difficult airway of a patient with obstructive sleep apnoea (the first reported such interventional case in the USA [5]), selective aspiration of mucus plugs, observation of local tumours, lung collapse and stenosis, localisation of haemoptysis, and selective sampling of the lower airways [6].

Equipment

The flexible bronchoscope provides an image of the distal view either directly through an eyepiece, or as a processed video image projected onto a small screen connected to a video bronchoscope or to an external monitor connected to a processor unit. Disposable, single-use bronchoscope systems are invaluable in the ICU and other emergency settings. They are easily accessible, quick to use and relatively inexpensive. While the optics and image quality are inferior to the traditional videostack systems, they are being increasingly utilised for urgent therapeutic bronchoscopy and for luminal visualisation during percutaneous tracheostomy. Disposable systems contain a distal mounted camera illuminated by a light-emitting diode rather than fibreoptic cables. The image is transmitted *via* a cable in the device to the monitor screen. This arrangement combines quality of image, although inferior to conventional systems, with low manufacturing costs. Disposable systems eliminate the need for disinfection between procedures, and potentially reduce cross-contamination and infectious outbreaks, so long as they are discarded rather than reused.

Rigid bronchoscopy is rarely used in the critical care unit and will not be discussed further in this chapter.

Indications

The common indications for bronchoscopy in the critical care setting are diagnostic and therapeutic. Bronchoscopic surveillance is also important, either as part of optimising the endobronchial environment (*e.g.* prior to planned re-extubation in complex cases) or following certain therapeutic procedures (*e.g.* to reassess patency after relief of lobar collapse or post-endobronchial valve placement). A list of common indications is given in table 1.

Infection

Suspected respiratory infection, and the need for microbiological sampling, is the commonest reason for diagnostic bronchoscopy in this setting. Sampling modalities include nondirected bronchial lavage (NBL), bronchial washings, BAL, TBNA and protected catheter brushing.

Ventilator-associated pneumonia

Ventilator-associated pneumonia (VAP) develops in ~5–20% of critically ill patients receiving mechanical ventilation, although published rates from observational studies are subject to variation, with attributable mortality suggested to be 2–27% [7, 8]. Symptoms are a combination of fever, purulent secretions, new, progressive or persistent radiographic appearances and worse inflammatory markers. The previously adopted convention of a

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Table 1. Indications for bronchoscopy in the critical care setting

Indication	Diagnostic	Therapeutic	Surveillance
Infection (*e.g.* VAP)	✓ (BAL)		✓ (bronchial wash)
Intubation/airway (bronchoscopic)		✓	
Lobar collapse	✓	✓	
Inhalation injury	✓	✓	✓
Persistent air leak	✓ (balloon isolation)	✓ (endobronchial valves)	
Airway haemorrhage	✓	✓	
Percutaneous tracheostomy		✓	
Airway stent insertion		✓	
Severe or persisting respiratory failure	✓	✓	
Upper airway obstruction and clearance	✓	✓	
Suspected malignancy, lymphadenopathy	✓ (biopsies, TBNA)		
Aspiration (gastrointestinal or foreign body)	✓	✓	
Tracheobronchial injury/trauma	✓	✓	✓

VAP: ventilator-associated pneumonia.

minimum of 48 h mechanical ventilation to distinguish pre-ventilatory infection from that considered to be contributed or caused by the mechanical ventilation is losing favour, and moves to change terminology to infective (or noninfective) ventilator-associated complications are gaining credence. Ventilator care bundles are aimed at reducing these risks of VAP development. Inappropriate initial empirical antibiotic therapy is an independent predictor of increased mortality.

The diagnosis of VAP depends on the criteria used [9]. Accepted current systems include the Centers for Disease Control and Prevention criteria and the HELICS (Hospital in Europe Link for Infection Control and Surveillance) system, which allows various sampling methods (NBL or bronchoscopic washings) and semiquantitative microbiology [10, 11]. The diagnostic superiority of BAL over less invasive sampling techniques such as bronchial washings, NBL or blind catheter brushings is dependent on the protagonists and study design. Thus, a bronchial wash of 20 mL from a segment corresponding to a new or persisting area of radiological opacification, or from where purulent secretions emanate, is the standard practice for evaluation of suspected new pulmonary sepsis. However, BAL and semiquantitative microscopy may reduce the overdiagnosis of infection based upon the presence of any organisms in a NBL or bronchial wash, which may be colonisers or contaminants.

BAL involves serial insertion of 40–50 mL aliquots of up to 120–180 mL of warm saline into the relevant bronchial segment (depending on tolerance and oxygenation), through the wedged bronchoscope. The first 20 mL is discarded to reduce contamination from any components of bronchial secretions and as much of the remainder as possible is retrieved by suction. While there is no evidence of mortality difference in VAP [12], when comparing qualitative (presence or absence of pathogens in the culture) and quantitative

(with a threshold CFU count of bacterial growth to differentiate between infection and colonisation of the lower airways) cultures obtained by bronchoscopic *versus* nonbronchoscopic techniques, the possibility of reducing unnecessary antibiotic prescriptions favours bronchoscopic sampling. This may further be relevant through the development of concomitant rapid biomarker sampling to rule out pulmonary sepsis [13–15].

Pulmonary infection in the immunocompromised patient

Pulmonary infection in the immunocompromised patient may be viral, bacterial, fungal, tuberculous, due to other organisms or copathogenic. The diagnostic value of bronchoscopic sampling in this setting is gaining in importance, not least as a clinical decision-making tool in rationalising multiple anti-infective medications.

The diagnosis of viral pneumonia is challenging. Sampling is important, particularly in the context of immunocompromise due to haematological malignancy. Once again, the challenge is pathogenicity or the "bystander" effect. A move to real-time PCR is emerging [16]. *Pneumocystis jirovecii* pneumonia (formerly *Pneumocystis carinii* pneumonia) is effectively diagnosed by BAL. Sensitivities of up to 98% are reported in treatment-naive patients. In those on prophylaxis, this is reduced when using indirect immunofluorescence staining [17]. In the diagnosis of tuberculosis, bronchoscopic sampling in the mechanically ventilated patient and its diagnostic accuracy are influenced by the clinical likelihood of disease and radiographic "targets". Bronchial washes are usually sufficient for mycobacterial tuberculosis (MTB) diagnostics. PCR-based rapid diagnostic MTB and rifampicin resistance platforms such as the MTB/RIF (Xpert) assay provide high diagnostic accuracy in low- and high-prevalence cohorts, even when smear negative [18, 19]. The use of other sampling modalities such as TBNA may increase diagnostic yield. Invasive respiratory fungal infection is difficult to diagnose, with a high mortality (>80%) if untreated. Haematological malignancy, acquired and iatrogenic immunosuppressed patients most frequently require rapid diagnostics, often in the critical care setting. Diagnostic criteria are determined by the revised European Organization for Research and Treatment of Cancer/Mycoses Study Group guidelines [20]. The sensitivity of cultures is low. Current diagnostic methods are optical density assays to identify fungal cell wall elements (β-D-glucan for any fungi and galactomannan for invasive pulmonary aspergillosis) or PCR. The diagnostic accuracy of BAL galactomannan and/or PCR-based assays depends on the likelihood of disease. In likely or probable disease, using optical density cut-offs of 1.0 or 1.5, BAL galactomannan has shown sensitivities between 70% and 92%, with specificities up to 98% [21]. BAL β-D-glucan and serum galactomannan are as sensitive but less specific, while PCR has similar diagnostic accuracies. Combining BAL galactomannan and PCR provides the current best diagnostic accuracy [21, 22], although it should be noted that empirical treatment with antifungal agents reduces the accuracy of these tests.

Airway management

The bronchoscope is an invaluable tool in various situations, including the difficult airway, percutaneous tracheostomy, lobar collapse, foreign body removal, placement of double-lumen tubes (DLTs) or endobronchial balloon blockers, airway haemorrhage control and isolation of air leaks.

Difficult airway

Provision of bronchoscopes as part of difficult airway protocols has been established for many years. Awake fibreoptic intubation is the anaesthetic gold standard for the anticipated

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difficult airway. Failed intubation in the operating room is reported at <1%, whereas up to 25% of airway complications reported in hospitals in the UK were in the ICU or emergency department [23]. Here, a combination of unpreparedness or lack of a backup plan and lack of appropriate airway skills, including bronchoscopy, were identified [23]. The pre-placement of an ETT over the bronchoscope allows the ETT to be advanced into the trachea under direct vision. This may be done with or without sedation/neuromuscular blockade, the latter requiring communication, anticipation and cooperation of the patient. The access point (oral or nasal) will determine the size of the outer diameter of the bronchoscope (and the ETT).

By definition, access to the trachea and visualisation of the entry point (*i.e.* the vocal cords) is difficult, and often the use of multimodality tools can improve the chances of success. For instance, the flexible tip of the bronchoscope may not be easily manoeuvred through the vocal cords due to distortion or excess soft tissue/debris. Furthermore, advancing the ETT may be difficult. In these situations the use of a laryngoscope (direct or indirect viewing) or a supraglottic airway device (*e.g.* i-gel airway (Intersurgical, Wokingham, UK), laryngeal mask airway, Berman/Guedel airway or "Magic" airway) to allow better and quicker controlled direction of the bronchoscope to its target can be helpful (figure 1). The numbers and types of video laryngoscope continue to increase. All have particular characteristics providing improved visualisation of the vocal cords over conventional laryngoscopy. However, insertion of the ETT through the cords may in itself not be straightforward despite the view of the larynx. As such, bronchoscopy and these devices should be immediately available as part of a difficult airway protocol [24]. However, their order of use must be governed by the level of expertise and familiarity of the user, adopting published guidance and protocols (*e.g.* those of the Difficult Airway Society; www.das.uk.com). Indeed, there is no direct comparison of video laryngoscopy and bronchoscopy-assisted intubation in the critical care setting. A hybrid technique, using the channel of the video laryngoscope to direct the ETT-sheathed bronchoscope towards the larynx, has been used. Here, the bronchoscope is used as a manoeuvrable end-viewing bougie.

There is now an increasing recognition of awake fibreoptic intubation being a training requirement by several international anaesthesia training programmes. Further information

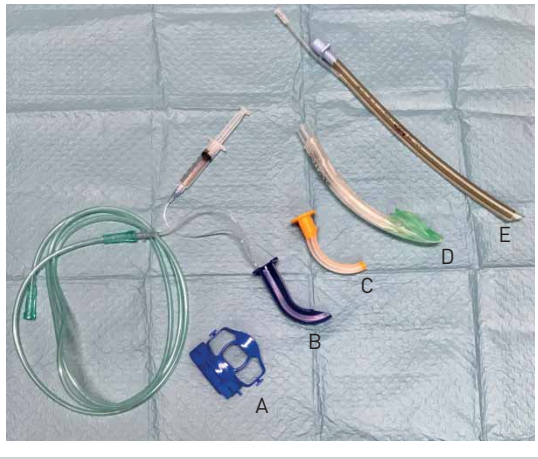

Figure 1. Supraglottic airway adjuncts through which the bronchoscope can be directed towards the larynx. A) Mouth guard. B) "Magic" airway. C) Guedel airway. D) i-gel airway. E) Armoured endotracheal tube (uncuffed) with paraxial channel.

can be sought from agencies such as the Difficult Airway Society or the Airway Management Academy (www.airwaymanagementacademy.com).

Percutaneous tracheostomy

Direct visualisation of the endotracheal airway during tracheostomy has several inherent advantages over "blind" insertion. These include accurate percutaneous needle insertion, observation of cartilaginous ring integrity during dilatation and tracheostomy insertion, prevention of posterior membranous tracheal wall damage, confirmation of accurate final placement, and post-procedure bronchial segmental therapeutic lavage. While randomised studies have not shown an outcome difference with ultrasound guidance *versus* bronchoscopic guidance, the TRACHUS randomised noninferiority controlled trial has demonstrated the benefit of bronchoscopic guidance in reducing complications and its use is increasingly recommended [25, 26].

A few practical points should be highlighted. 1) The procedure may require a third operator, separate from the tracheostomist and assistant holding the ETT. 2) The bronchoscope tip should be within the distal end of the ETT at the time of needle insertion, so as to prevent damage to the bronchoscope. The use of disposable bronchoscopes may find a useful role in this setting. 3) An awareness of the partially occluded airway during withdrawal of the ETT and intraprocedurally should necessitate ongoing assessment of the airway pressure/volume and oxygen/carbon dioxide (CO_2) profiles.

Lobar collapse

The cause of lobar collapse in the critical care setting is often multifactorial (table 2). A combination of predisposing disease-related risks, procedural impact on the lung, nonphysiological impacts of sedation, position, inadequate airway clearance mechanisms and lack of spontaneous ventilatory effort all contribute to lobar collapse. High inspiratory oxygen fraction (FIO_2) can in itself lead to reabsorption atelectasis through nitrogen washout.

Bronchoscopy is commonly used in lobar and complete lung collapse during mechanical ventilation, where physiotherapy or recruitment manoeuvres have been unsuccessful. It may identify migration of the ETT as a cause of the collapse. Directed suction is usually combined with forced saline flushing. Repeated episodes may be necessary, with intermittent periods of re-recruitment following temporary removal of the bronchoscope from the ETT. Concurrent mucolytics (*e.g.* nebulised *N*-acetylcysteine) can be used to treat airway plugging when nonpurulent mucus is tenacious (*e.g.* in COPD). It is considered not

Table 2. Causes of lung collapse in the critically ill patient

Obstructive	
Large airway	Mucopus, migrated endotracheal tube, inflammatory (tuberculosis, sarcoid), foreign body
Small airway	Mucopus, inflammatory, foreign body
Nonobstructive	
Compression	Air trapping (COPD), lymphadenopathy (tumour, sarcoid, tuberculosis), malignancy
Passive	Supine position, neuromuscular weakness, pleural effusion, pneumothorax, abdominal distension
Adhesive	Post-cardiopulmonary bypass, smoke inhalation injury, acute respiratory distress syndrome (surfactant loss)

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to be useful when there are purulent secretions or if F_{IO_2} >40%, at which its activity is reduced.

The use of endobronchial DNase has been reported to improve the success of bronchoscopic lobar re-expansion in resistant paediatric cases [27]. DNase has been used safely and shown to improve chest radiography appearance compared with hypertonic or normal saline, but with no difference in other outcomes [28].

Foreign body removal

The removal of foreign bodies bronchoscopically in the critical care setting is uncommon. The nature of the foreign body, its location, potential impact, bronchoscopic tools and expertise available are factors in this setting [29]. A range of retrieval devices including grasping forceps, wires and baskets may be needed.

Cryoadhesion and extraction, using a through-the-bronchoscope probe, whose tip freezes on the foreign body by delivering high-pressure CO_2 or nitrous oxide, is safe and effective in the bronchoscopy clinic [30, 31]. Its use in mechanically ventilated patients has not yet been formally evaluated.

General aspects of foreign body removal and the specifics of cryoadhesion/extraction are discussed in more detail elsewhere in this *Monograph* [32, 33].

Balloon blocker and DLT placement

Single-lung ventilation, through endobronchial isolation, can be achieved with accurate placement of bronchial blockers or DLTs by bronchoscopic visualisation. This may be for indications such as isolation of bronchopleural fistulas or alveolopleural fistulas, airway haemorrhage control, lung resection, transplantation, or differential lung ventilation.

Balloon blockers may be endobronchial (*e.g.* lumen <2 mm for subsegmental isolation) or paraxial, passing alongside the bronchoscope. This may be through the ETT, if space allows, or by passage outside the ETT, with bronchoscopy through the lumen of the ETT. Accurate positioning of the balloon blocker may require twisting it round at the proximal end and use of the tip of the bronchoscope to feed it down, either manually or by lassoing the loop wire of the balloon blocker onto the end of the bronchoscope. Certain balloon blockers have tip-deflecting ends allowing a certain degree of control over the direction of placement. Balloon blockers that fit through the working channel of the bronchoscope are used for various procedures such as assessment of collateral ventilation in COPD, (sub)segmental isolation of air leaks due to an alveolopleural fistula or temporary bronchial tamponade as part of airway haemorrhage control (no suction is possible while this balloon blocker occupies the working channel of the bronchoscope).

DLTs are conventionally inserted with bronchoscopic confirmation of positioning post-insertion. The endobronchial cuff should be identified in the appropriate bronchus, just below the carina and the patency of the upper lobe bronchus checked, noting the distal position of the tracheal lumen. The size of the bronchoscope needs to fit the inner lumen diameter of the smaller bronchial tube of the DLT. Bronchoscopic reassessment of position should occur if the patient is moved into a lateral position or if a change in ventilatory parameters suggests possible tube migration and obstruction. Common bronchoscope, ETT and DLT sizes are listed in table 3.

Table 3. Bronchoscope, endotracheal tube (ETT) and double-lumen tube (DLT) sizes

Type	Broncho-scope (OD) mm	Channel diameter mm	ETT (ID) mm	DLT size (OD) mm	DLT bronchus (ID) mm	DLT trachea (ID) mm
Ultrathin fibreoptic or hybrid	2.8	1.2	⩾4	12–13.5 (35 Fr)	4.3	4.5
				13.3–14 (35 Fr)	4.5	4.7
Paediatric fibreoptic	3.6	1.2	⩾5	12–13.5 (35 Fr)	4.3	4.5
				13.3–14 (37 Fr)	4.5	4.7
Paediatric hybrid	4.2	1.2	⩾5			
Adult diagnostic	4.4	2.0	⩾7			
fibreoptic	4.9	2.2	⩾7.5			
Adult diagnostic	4.9	2.0	⩾7.5			
hybrid	5.5	2.1	⩾8			
Adult therapeutic fibreoptic	5.9	2.8	⩾8			
Adult therapeutic	6.0	3.0	⩾8			
hybrid	6.3	3.2	⩾8			
EBUS	6.9	3.2	⩾8.5			

OD: outer diameter; ID: inner diameter; Fr: French.

Airway haemorrhage

In the critical care setting, airway haemorrhage must be acted upon quickly from a diagnostic and therapeutic perspective. Major haemorrhage is fortunately rare, but may quickly become catastrophic. The clinical situation (*e.g.* medical or surgical patient, iatrogenicity, risk factors for coagulopathy and likely source of bleeding) needs to be considered when planning the strategy for haemorrhage control and patient management. Likely causes of haemorrhage may be local mucosal, tumour related, from cavitatory lung disease, anomalous vessels (either from fragile vessels in distorted endobronchial submucosa or from the higher pressure bronchial circulation), diffuse alveolar haemorrhage or traumatic. The risk of hypoxaemia and asphyxiation must be managed alongside haemodynamic control. Systematic approaches for control have been published, but there is no formal training in these strategies beyond various training workshops [34]. The use of endobronchial techniques or devices for the control of haemoptysis is well established, as part of a multidisciplinary approach.

Definitions of severity based upon volume of haemoptysis retrieved are not helpful beyond documentation. More useful is a change in the rate of bleeding and the time from intervention to control. Once bleeding is settling, it is imperative to survey the other airway segments and clear spillover blood that will quickly form a tenacious clot. Bronchoscopy is performed to identify the source of bleeding, isolate the remaining lung and create a tamponade until there is control of the bleeding.

Haemorrhage management involves suction above the point of bleeding, administration of cold saline, diluted adrenaline (1:100 000 to 1:200 000; although up to 1:10 000 has

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been used, there is concern about cardiovascular risks at higher doses) and tamponade of the source segment with the bronchoscope. If necessary, tamponade with a through-the-bronchoscope (loss of suction) or paraxial balloon blocker are options.

Other options such as endobronchial tranexamic acid or surgical gauze packing have been proposed as further measures for controlling the bleeding [35]. Methods such as turning the patient onto the side of the bleeding, DLTs and the use of noncontact strategies such as endobronchial APC have also achieved success in isolated reports, but outside the critical care setting [36]. The use of Watanabe spigots or endobronchial inspiratory-only one-way valves to control recurrent bleeding by isolating the source has been reported in selected situations. However, acute haemorrhage control would have to be established first by alternative means and the technique cannot be recommended in the acute setting [37, 38].

Use of antifibrinolytic agents, specifically tranexamic acid administered intravenously for haemoptysis in tuberculosis, may shorten the duration of bleeding, but remission is unclear from limited studies. Tranexamic acid may also be delivered endobronchially. In the specific situation of diffuse alveolar haemorrhage, due to vasculitides, post-haemopoietic stem cell transplant, drugs or toxins, untreated mortality is >50%. Serial instillation of endobronchial recombinant factor VII at doses of 30–50 $mg \cdot kg^{-1}$ in addition to systemic glucocorticoids and aminocaproic acid (an antifibrinolytic agent) resolved this in a small case series [39]. The airway haemorrhage literature appears to confirm that some form of tamponade is the most effective way of controlling immediate local endobronchial bleeding.

The patient's cardiorespiratory status, source and rate of control of bleeding will determine the need for sequential actions. A multidisciplinary approach is essential with rapid recourse to alternatives such as rigid bronchoscopy, interventional radiology or surgery if initial bronchoscopic strategies fail. The role of bronchial artery embolisation *via* interventional radiology is well documented, with low complications when good pre-embolisation anatomy is definable [40]. Surgical resection must also be available if necessary and feasible, with good reported success rates of bleeding control related to mycetoma.

The interventional pulmonology management approaches to haemoptysis are discussed further elsewhere in this *Monograph* [41].

Air leak isolation and resolution

Persisting pneumothorax may result from thoracic surgery, chest trauma or as a complication of underlying pleuroparenchymal lung disease. The air leak is either due to a bronchopleural fistula, usually following surgery, or an alveolopleural fistula. In some cases the air leak does not seal and alternative treatments are needed such as surgery or inserting a foam/gel to seal the leak. Endobronchial (inspiratory-only) valves can be used for patients with air leaks for whom the usual treatments have not worked or for those unable to undergo surgery. Insertion of endobronchial valves for persistent air leaks aims to reduce or eliminate airflow through the leaks so that the rest of the lung can function normally. They may also allow the tissues around an air leak to heal so that the leak stops. In the critical care setting, they have reported success rates up to ~50% [42].

The first stage is to identify and isolate the bronchial segment(s) involved. This involves placing a through-the-bronchoscope balloon blocker into and occluding the suspected segment(s) (having first adjusted ventilatory and oxygenation settings for the procedure and cleared the airways of mucus and debris). The balloon blocker is then fully inflated

while monitoring the airflow reduction/cessation at the external pleural flow device (*e.g.* underwater seal bottle). Having removed the balloon blocker, a one-way valve mounted on a flexible catheter is passed through the bronchoscope and inserted into the target airway(s). Several valves may be placed and are generally removed some weeks/months after resolution. Serial bronchoscopic surveillance is necessary to check the position of the valve and clear away mucus, which may occlude the valve and limit its effectiveness.

General therapeutic interventions for airway fistulas are discussed in more detail elsewhere in this *Monograph* [43].

Airway assessment

Assessment of the airway, both upper and lower, can be diagnostic, therapeutic or for surveillance in certain situations.

Smoke inhalation injury

This occurs in at least 5% of patients with major burns (>20% total body surface area) and contributes to their mortality. It may increase mortality by 20% alone and up to 60% if also complicated by pneumonia [44]. Moreover, it increases the risk of pulmonary sepsis [44]. It is the most frequent cause of death at the scene of a fire. Injury to the airway and tracheobronchial tree may also result from inhalation of chemicals (*e.g.* chlorine gas), drugs and biological weapons. Systemic disturbances are common, but depend on the nature and toxicity of the inhaled substance.

Airway swelling/obstruction is progressive and may be exacerbated during fluid resuscitation, emphasising the need for constant reassessment [45]. Hoarse voice, carbonaceous sputum on deep cough, singed facial and nasal hair, and erythema and oedema of the mucosa in the mouth should raise suspicions of potential airway compromise. Swelling may not reach its maximum until 24 h after injury and may occur rapidly during fluid resuscitation. Early bronchoscopy is recommended to record the level and degree of injury.

Careful evaluation of the upper airways, especially in patients who present no evidence of more distal injury, is extremely important during bronchoscopy. Severe oedema in the supraglottic area or a large quantity of upper airway secretion may indicate that these patients are more likely to present acute airway obstruction and this is an indicator for the early intubation of patients suspected of having upper airway injury.

The diagnosis of inhalation injury is clinical, based upon a history of smoke inhalation and physical findings of facial burns, singed nasal hairs, oedema, erythema and soot from the upper or proximal lower airways. Bronchoscopic visualisation identifies soot, erythema, oedema or ulcerations in the upper and lower airways. Of note, severe vasoconstriction from hypovolaemia may mask significant injury initially in the absence of soot. Apart from this exception, bronchoscopy has a high accuracy in confirming the diagnosis of established inhalation injury.

A macroscopic grading system allows standardisation of observed findings (table 4) [46]. However, there is only weak evidence to suggest a correlation between this measure of endobronchial inhalation injury and subsequent outcomes [47]. This is likely due to the

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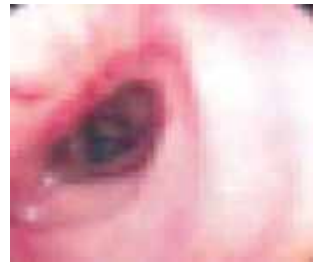
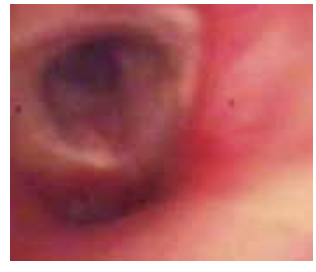
Table 4. Burns inhalation injury: bronchoscopic grading system

Grade	Severity	Endobronchial features	Image
0	No inhalation injury	Absence of carbonaceous deposits, erythema, oedema, bronchorrhoea or obstruction	
I	Mild injury	Minor or patchy areas of erythema, carbonaceous deposits in proximal or distal bronchi (any or combination)	
II	Moderate injury	Moderate degree of erythema, carbonaceous deposits, bronchorrhoea, with or without compromise of the bronchi (any or combination)	
III	Severe injury	Severe inflammation with friability, copious carbonaceous deposits, bronchorrhoea, bronchial obstruction (any or combination)	
IV	Massive injury	Evidence of mucosal sloughing, necrosis, endoluminal obliteration (any or combination)	

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variable distal effects of the less soluble inhaled injurious gaseous agents, which bypass the upper airways [48].

Bronchial lavage should be performed if pulmonary contamination is present; however, consideration should be given to the fact that excessive saline lavage may induce lung injury. Its value may be mainly in clearing airway debris developing later on [49].

Regular administration of aerosolised bronchodilators should be considered. Nebulised heparin and *N*-acetylcysteine have been used to reduce cast formation, distal airway obstruction and atelectasis [50]. Antibiotic and steroid therapies have no proven prophylactic role, but may be required in specific situations. Pneumonia is the most common cause of death in hospitalised patients suffering from inhalation injury. Serial bronchoscopy can help remove debris and necrotic cells in cases with aggressive pulmonary hygiene, or when suctioning and positive pressure ventilation are insufficient. The use of bronchoscopy in patients with inhalation injury complicated by pneumonia has been associated with a decrease in the duration of mechanical ventilation, length of ICU stay and overall hospital costs [51].

Tracheobronchial injury

Patients with chest trauma have potential bronchial injury. Another cause of tracheal injury is following traumatic intubation. Clinical manifestation of tracheobronchial injuries is variable, and depends on the site and size of any air leak. Lesions may not always be clinically evident. An air leak or unexplained pneumothorax in the presence of high-impact blunt trauma, or in the absence of upper airway, rib fracture or oesophageal tear, should warrant bronchoscopy for possible tracheobronchial rupture. Once identified, treatment algorithms based upon a multidisciplinary discussion with thoracic surgeons are reported; management may be conservative, associated with serial bronchoscopic surveillance and lavage [52].

Preparation and safety

Physiological effects of bronchoscopy

The physiological effects of bronchoscopy may be considered as: 1) increased airway resistance, 2) reduced lung compliance, 3) hypoxaemia and hypercapnia, and 4) cardiovascular effects.

A standard 5.7 mm outer diameter bronchoscope will occlude ~15% of the trachea. However, this increases serially to ~40% and ~66% in size 9 and 7 mm ETTs, respectively. The airway resistance will increase accordingly and flow will reduce by the fourth power of the reduced airway radius, as well as by a longer ETT and nonlaminar flow (Poiseuille's law).

Positive end-expiratory pressure will increase, as will peak airway pressures, theoretically increasing the risk of pneumothorax. The distal airway collapse caused by repeated suction and the effect of saline lavage on denuding the alveolar surfactant layer will contribute to (usually) temporary changes in static and dynamic lung compliance post-bronchoscopy. This should be considered in case recruitment manoeuvres are needed thereafter. During suctioning, positive end-expiratory pressure and delivered tidal volume

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will decrease; as much as 200–300 mL of the volume can be lost. Reduced tidal volume and functional residual capacity produce alveolar collapse. This, together with the likely further loss of surfactant by saline lavage, will reduce lung compliance. This can be noted as a reduction in tidal volumes for the corresponding delivered pressure. Lung compliance will recover variably, but in certain situations may warrant post-procedural recruitment manoeuvres.

Hypoxaemia is expected by reduced alveolar oxygen, due to multiple factors of reduced inspiratory flow and volume, alveolar collapse by suctioning, and flooding of alveoli during BAL. Hypercapnia is a result of hypoventilation caused by airway obstruction. The end-tidal CO_2 will rise quickly and may necessitate adjustment of the set minute ventilation or temporary removal of the bronchoscope if haemodynamic consequences ensue, although this is clinically infrequent.

Patient, staff and equipment

Patient safety and crisis risk management dictate the need for appropriate planning and preparation. Concurrent with World Health Organization (WHO) perioperative guidance, bronchoscopy in the ICU should use a WHO-like checklist and "time outs" (*i.e.* planned pauses). Standardised documentation of findings is surprisingly inconsistent when compared with other procedures performed in the ICU (*e.g.* echocardiography, gastroscopy, radiography, *etc.*). International authorities are increasingly recommending such preparation advice. A suggested bronchoscopy checklist is provided in table 5.

The staff member(s) assisting should have the required equipment available and have determined the inner diameter size of the ETT, so as to request the appropriate sized bronchoscope, adaptor for the ETT and suction tubing. This should minimise the need for

Table 5. Checklist items for bronchoscopy

Preparation for bronchoscopy	Bronchoscopy procedure	After bronchoscopy
Indication and imaging	Ventilator settings	Ventilator settings
Risks	Oxygenation adjustment	Sterilisation and leak test
Correct reversible risks	Monitoring	Documentation: technical quality, location, tube position, anatomy, mucosa, secretions, abnormalities
ETT or tracheostomy size (>2 mm of bronchoscope size)	Emergency drugs	Chest radiograph
Feeding stopped	Airway haemorrhage control (cold saline, adrenaline, *etc.*)	Recovery reassessment
Consent/assent	"Time out"	
Equipment: bronchoscope type/size	Light source on, white balance, suction on	
Monitor position (opposite side)	Knowledge of anatomy	
Consumables	Thorough airway and segmental assessment	
Drugs	Surveillance: ETT position, mucosa, segments, carina, abnormalities	
Staff: designated roles, experienced operator, assistants	Sampling/interventions	

ETT: endotracheal tube.

interruptions due to missing paraphernalia. Having emergency drugs, an airway haemorrhage kit (*i.e.* ice-cold saline, 1:100 000 adrenaline in 2–5 mL aliquots) and a pneumothorax kit to hand is part of the preparation. Once a "time out" has occurred and the ventilator settings have been adjusted appropriately (sedation with or without neuromuscular blockade), it is helpful to have one assistant holding the ETT and calling out the cardiorespiratory parameters and whether action thresholds are reached, while another provides the consumables and handles the samples.

Ventilatory settings can be adjusted according to the anticipated length of the procedure, physiological changes occurring and the likely adverse clinical impact. Ventilators should be in an adaptive support ventilation (ASV) or mandatory mode as a result of the sedation and neuromuscular blockade. Volume-controlled, pressure-limited modes may facilitate volume maintenance during and after the procedure.

Procedure

Practical aspects of bronchoscopy involve checking the light source is on, white balance is performed, and the suction is connected and on (also see [1, 2]). Centring the bronchoscope within the lumen and withdrawing to a recognised point of reference require learned handling dexterity. The flexible bronchoscope is designed such that the main body is held in the left hand and the right hand can manipulate the distal end of the bronchoscope (although bronchoscopes do permit the alternative hand configuration). In the ICU, bronchoscopy is performed from the side of the semirecumbent patient or from the head end of the patient. The video monitor is placed on the opposite side to the operator, who can adjust his/her position as needed.

The pre-procedure checks and "time out" are performed, and F_{IO_2} is increased to 100%. As the patient is adequately sedated and, if appropriate, paralysed, the ventilator should be in an ASV mode, either volume- or pressure-controlled. Changes to the ventilator rate and/or delivered volumes are not usually necessary during the procedure if short periods in the airway are adopted. De-recruitment will occur when breaking the closed circuit to introduce the elbow-shaped bronchoscopy adaptor and during suction through the bronchoscope. If this is clinically important then the well-known clamp–unclamp technique is used at the circuit break point. Adjustments to ventilator set volumes or pressures must only be made during the procedure by experienced staff, cognisant of the risks and management of volutrauma/barotrauma. More likely, if the oxygen saturations are trending down by >4% from baseline or <90%, then the bronchoscope is withdrawn and unobstructed ventilation resumes until reoxygenation allows continuation of bronchoscopy. End-tidal CO_2 traces will usually become flat during the procedure while the airway is effectively obstructed by the bronchoscope. This is expected and usually tolerated. End-tidal CO_2 will likely rise following the procedure for a period of time as a consequence of the hypoventilation during the procedure. Ventilatory and oxygen settings can be adjusted thereafter. An assistant should constantly observe, report and alert the operator to changes and stop-thresholds being reached for oxygen saturations, blood pressure and heart rate or rhythm.

Anatomy

Segmental radiological anatomy by CT is important. The adult trachea is ~12 cm long and 1.6–2 cm in diameter, and has 16–20 cartilaginous rings. The cricoid cartilage is the only

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complete ring and serves as an important bronchoscopic landmark during percutaneous tracheostomy insertion. The main carina is at the T4/T5 level, corresponding to the surface mark of the sternomanubrial junction in a supine patient. The bronchopulmonary segments are numbered 1–10, descending by origin off the bronchus. The right named segments are: upper lobe: A (apical, 1), P (posterior, 2), A (anterior, 3); middle lobe: L (lateral, 4), M (medial, 5); lower lobe: A (apical, 6), M (medial, 7), A (anterior, 8), L (lateral, 9), P (posterior, 10) (acronym: APALM AMALP). The left named segments are: upper lobe: upper division: AP (apicoposterior, 1+2), A (anterior, 3); lingula: S (superior, 4), I (inferior, 5); lower lobe: A (apical, 6), A (anterior basal, 8), L (lateral basal, 9), P (posterior basal, 10) (acronym: APAL ALP) (note that there is not usually a left medial basal segment, or the medial and anterior are combined, due to the evolutionary position of the heart).

A helpful rule of thumb for remembering the segmental anatomy is to consider the endobronchial tree as two descending corkscrews. When approached from the back, the right endobronchial corkscrew descends rotating clockwise (the caveat being middle lobe lateral, 4 then medial, 5) and the left endobronchial corkscrew descending anticlockwise. "Broncho" (www.bronchoscopy.nl) is a useful app that contains bronchoscopy images and videos of the bronchial anatomy.

Infection control/decontamination

Decontamination and disinfection prior to and following the procedure will minimise cross-infection. Manual cleaning, brushing and flushing with enzymatic or low-foam detergent soon after bronchoscopy removes organic particulates from the working channel, facilitating disinfection. Thereafter, chemical disinfection (no longer aldehyde based) occurs in automated processors and the bronchoscope then stands in an airtight, vacuum storage cupboard until use. Guidance on how long bronchoscopes should be left out prior to use is advisable. Single-use-only accessories should be used where possible to prevent cross-contamination. Disposable systems eliminate the need for disinfection between procedures.

Complications

While bronchoscopy is safe (mortality rate 0.01%; major complication rate 0.08–2% [53]), certain factors will increase these risks in the ICU. Thus, severe respiratory failure, hypercapnic acidosis, poorly controlled bronchospasm, ETT <8 mm, pneumothorax, haemodynamic instability, arrythmogenic potential and raised intracranial pressure should all be recognised, managed and accounted for with regard to the timing and duration of bronchoscopy interventions. Bronchospasm is rare. This may become of clinical relevance in patients with known obstructive airways disease, who may require appropriate additional medication. The impact of hypoxaemia on cardiovascular stress and workload should be anticipated. ECG changes have been reported in 15% of patients periprocedurally (including atrial fibrillation, ST and conduction abnormalities) [54]. Unexpected ST changes can occur in 20% of awake patients aged >60 years [54]. A 5% mortality within 30 days of acute myocardial infarction is associated with patients who still have ischaemia at the time of bronchoscopy and a risk assessment is always warranted [55]. In those with raised intracranial pressure, appropriate sedation, neuromuscular blockade and blood pressure control is crucial. Major bleeding is rare (1:500–1000 cases) and dependent on factors described earlier. Haemoglobin, platelet and coagulation studies should be performed, and corrected if clinical bleeding is anticipated. Preparedness for bleeding control is part of the preparation.

Bronchoscopy in the nonintubated patient

Bronchoscopy can be performed in the emergency setting without a definitive airway (*i.e.* ETT or tracheostomy tube). The indications are usually for airway clearance of tenacious secretions causing acute airway obstruction/collapse. The aim is generally to prevent intubation/re-intubation. For example, in patients with infective exacerbations of COPD and difficult-to-clear secretions, noninvasive ventilation (NIV) with early therapeutic bronchoscopy can prevent intubation and reduce tracheostomy in a proportion, although duration of ventilation, hospital mortality and stay are unchanged [56].

Bronchoscopy of the awake patient in the emergency setting may be undertaken with various forms of adjunctive oxygenation or assisted ventilation. High-flow nasal oxygen (HFNO), up to 70 $L \cdot min^{-1}$, has superseded the need for bronchoscopy through the cut-out mask of the non-rebreather bag at 15 $L \cdot min^{-1}$. It provides a number of theoretical benefits, such as increased oxygen reservoir, longer time to desaturation and some increase in pharyngeal pressure, up to 1 cmH_2O per 10 $mL \cdot min^{-1}$ increase in flow in healthy individuals. Even in apnoeic anaesthesia, the high flows provide sustained oxygenation in the unobstructed airway [57]. NIV masks, either oronasal or full face, can be modified to accommodate a bronchoscope. This will usually require a bronchoscopic elbow adaptor with two orifices (for ventilation and for the bronchoscope) and a mouth guard, unless the nasal approach is used.

In a randomised controlled trial of hypoxaemic patients in the ICU, bronchoscopy by the nasal approach through a continuous positive airway pressure mask and high-flow device source, with entrained oxygen, maintained better oxygenation [58]. Despite the same F_{IO_2}, the group with high-flow-generated continuous positive airway pressure had reduced falls in oxygen saturations and no post-procedural respiratory failure at 6 h. A recent Cochrane review has reported a lack of advantage of HFNO over NIV in the high-dependency setting [59]. However, the practicalities of bronchoscopy through an NIV mask device are challenging and therefore use of HFNO in this situation is gaining wider acceptance. Indeed, while bronchoscopy through NIV masks in patients with mild acute respiratory distress syndrome is technically feasible, one-third of patients were subsequently intubated within 24 h, although obtaining positive microbiological results was enabled in ~60% of patients [60]. Thus, caution and preparation for intubation is advised in the ICU setting [60].

Bronchoscopy in the ICU may also be performed through supraglottic airway devices, armoured ETTs placed into the posterior oropharynx, or through a mouth guard and airway adjuncts such as Berman and "Magic" airways, allowing bronchoscopy-guided access to the larynx. Nasal intubation through an appropriately sized ETT (size 6 mm) with a smaller bronchoscope (4.8 mm external diameter) is feasible. Also see the earlier section of this chapter on difficult airway management (figures 1 and 2).

Potential deterioration must be considered in all these situations. A plan of escalation to a definitive airway or limit of care must be established beforehand. Having an ETT sheathed over the bronchoscope may facilitate this. The type of sedation used is crucial in order to ensure acceptable patient tolerance, technical adequacy and safety. Experience in the use of sedatives and their side-effects is important, particularly in this setting. Short-acting, quickly reversible agents, such as propofol, short-acting benzodiazepines and synthetic narcotics (*e.g.* fentanyl, alfentanil or remifentanil) are considerations. Relaxation of the

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Figure 2. Bronchoscopy through a noninvasive ventilation mask. A) Mask (oronasal; full face mask alternative). B) Mouth guard (blue). C) Elbow bronchoscopy ventilation adaptor. D) Bronchoscope insertion cord. Head straps are used once the mask is positioned effectively by hand, as shown here.

vocal cords for introducing the ETT through deep sedation and paralysis is often necessary for a safe definitive airway.

Training

Many international training schemes specify bronchoscopy as a required competency skill, including for percutaneous tracheostomy [61]. However, the processes for acquiring and assessing procedural competency vary, and there is a move away from a target number of procedures in order to address this [62]. The European Society of Intensive Care Medicine has recommended formal training competencies through its link with CoBaTrICE (www.cobatrice.org), the international competency training programme in intensive care medicine. An increasing number of standalone training courses exist, providing knowledge and hands-on workshops.

The value of computer-based virtual bronchoscopy modules, bronchoscopy simulators, dexterity tools and high-fidelity simulation scenarios is recognised as a valuable part of skills acquisition, compared with no training. However, the evidence base for outcomes in which bronchoscopy simulation may be beneficial beyond conventional clinical instruction is lacking [63]. Simulation-based bronchoscopy training is effective for tasks such as inspection and foreign body removal (and also EBUS-TBNA and rigid bronchoscopy), and can bridge learning transfers to patient contact. It is suggested that such simulation-based training be complemented by simulation-based assessment, done using tools such as the Bronchoscopy Skills and Tasks Assessment Tool and the Mastery of Learning model, whereby progression to the next level requires demonstration of proficiency [64, 65]. There is further need to increase accessibility to all trainees, utilising cheaper low-fidelity

simulation tools and contextual structured scenarios, and for more frequent refresher courses in order to allow maintenance of skills.

Training in interventional pulmonology is discussed further elsewhere in this *Monograph* [66].

Conclusion

Bronchoscopy in the intensive care setting is an essential aspect of the management of the sickest, critically ill patients. Since its development in the 1970s, the key diagnostic aspects remain sampling for pulmonary infection and therapeutic bronchial lavage for segmental lobar collapse. However, further indications such as part of difficult airway placement, percutaneous tracheostomy, persistent air leak isolation and correction, inhalation injury management, and airway haemorrhage control are now established. Bronchoscopy in the nonintubated acutely sick patient can be valuable. However, it provides challenges and risks, and requires training, planning and the appropriate adjuncts for airway and oxygenation support. Technological advances now allow single-use flexible bronchoscopes that can be deployed quickly with good quality images. WHO-style checklists and "time outs" are recommended. Patient safety aspects such as maximum flow oxygen delivery, adjustment and monitoring of the ventilation and physiological changes are important in reducing complications. A knowledge and appreciation of the patient, equipment and staff requirements allows more efficient procedures. As with other critical care procedures, skills-based training programmes, advanced-level mentorship and assessments will need to incorporate the elements discussed in order to promote excellence.

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Chapter 4

Imaging

Sebastian Ley[1] and Claus Peter Heussel[2]

Many tracheobronchial, parenchymal and mediastinal diseases can be assessed by interventional pulmonology procedures. Imaging of the thoracic structures is the most important prerequisite before intervention. The tasks are manifold and include detailed visualisation of the anatomy, risk assessment and definition of the target. In this context, CT plays a major role, as it allows fast, highly spatial and three-dimensional imaging of the pathologies to be addressed. CT enables virtual bronchoscopies in order to plan the actual intervention, or serves as database for navigated EBUS or biopsy. CT also allows assessment of the lung parenchyma and thus determination of the eligibility of a patient and the target lobes for endobronchial lung volume reduction treatment. However, CT is only a morphological imaging technique, and functional assessment of tissue (*i.e.* lymph nodes) must be done by PET or magnetic resonance imaging. Post-treatment follow-up can be done by radiography for regular post-treatment assessment or by CT imaging for suspected complications.

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Various mediastinal, bronchial and lung diseases can be treated by interventional bronchoscopic techniques, which can be summarised as: tissue probing (lymph nodes, lung nodules), treatment of tracheobronchial bleeding, treatment of airway stenosis and endoscopic lung volume reduction (ELVR) [1, 2]. This chapter will focus on the radiological, or noninvasive, diagnostic modalities, which can also be used for further planning and guiding of interventions, leading to fast diagnosis with low risk, including the control and management of possible complications and success.

Patients usually present with a clinical syndrome, and (radiological) imaging is performed to further evaluate the underlying disease. Imaging therefore plays a vital role in the clinical assessment of patients with mediastinal and thoracic diseases. In particular, three-dimensional (3D) imaging techniques such as CT are frequently used techniques for assessment of tracheobronchial and pulmonary diseases. Although still more at an experimental stage, magnetic resonance imaging (MRI) is also used to address these issues and may be used for planning of interventional procedures.

[1]Diagnostische und Interventionelle Radiologie, Chirurgisches Klinikum München Süd, München, Germany. [2]Diagnostische und Interventionelle Radiologie mit Nuklearmedizin, Thoraxklinik Heidelberg gGmbH, Heidelberg, Germany.

Correspondence: Sebastian Ley, Diagnostische und Interventionelle Radiologie, Chirurgisches Klinikum München Süd, Am Isarkanal 30, 81379 München, Germany. E-mail: ley@radiologie-ley.de

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Imaging techniques

For tailoring and planning interventions, high spatial resolution and/or functional information are helpful [3]. Various radiological imaging techniques are available for the assessment of pathologies of the mediastinum and lung parenchyma.

Radiography

The initial imaging procedure to work up a patient is usually a radiograph of the chest in two orientations, providing an overview of the thoracic and mediastinal structures and any pathologies to exclude severe acute comorbidities. However, this kind of projection imaging suffers from superimposition and is insufficient for guidance or planning of an interventional procedure. It is therefore used mainly as a baseline comparator for the post-interventional detection of complications (*e.g.* pneumothorax, effusion) and an estimation of treatment success (*e.g.* atelectasis, mediastinal shift, implant location) (figure 1).

Computed tomography

CT is routinely and widely used for detailed visualisation of the mediastinum, tracheobronchial tree and lungs. The spatial resolution of one CT image is typically 512×512 pixels in the x–y axis. The z-axis resolution is determined by the resolution of the detector used; usually it is in the range of 0.625 mm. Reconstruction of overlapping images is recommended (*e.g.* 20%) to allow optimal 3D post-processing. However, different examination protocols are applied to specific clinical situations.

Lung cancer screening

Within the European Union, lung cancer is the most frequently fatal cancer, leading to over 266 000 deaths per year and accounting for 20.8% of all cancer deaths [4]. Low-dose CT

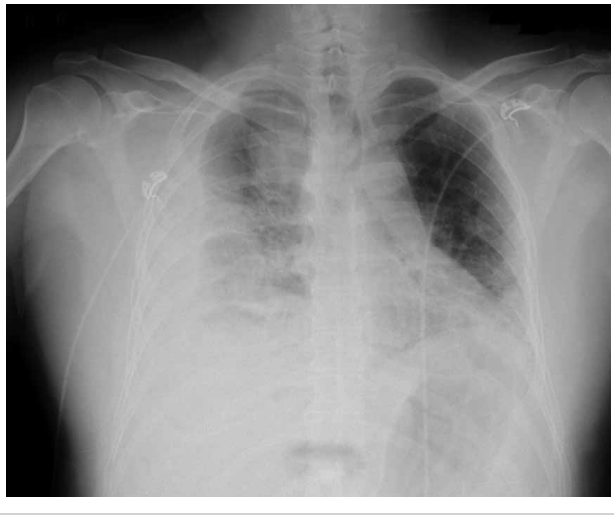

Figure 1. Post-interventional chest radiograph of a patient with ILD. A cryobiopsy was performed for diagnostic purposes, and a right-sided haemothorax occurred as a complication, as shown.

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screening/scanning has evolved as the modality of choice for assessing high-risk populations [5]. These low-dose CT protocols, with a recommended dose of 0.1–0.6 mSv, aim to provide excellent visualisation of the nodular structures within the lung parenchyma (*i.e.* a high-contrast scenario) [6, 7]. However, these low-dose datasets inherit a lot of image noise, making evaluation of interstitial and mediastinal (low-contrast) structures difficult or even impossible. This technique is always carried out without application of intravenous contrast material. Therefore, these image datasets are often not suitable for 3D planning software tools, such as for electromagnetic navigation bronchoscopy (ENB), or as quantification tools for emphysema [8] or fibrosis [9].

While the sensitivity of CT is relatively high for detecting pathological structures, the specificity is relatively low. Infectious diseases in particular can mimic neoplastic pathologies, requiring further investigation. In a recent study, 116 patients were scheduled for navigational bronchoscopy for the diagnosis of a pulmonary lesion [10]. Of these, 7% had a decrease in size or resolution of their lesion at the CT done at the time of planned intervention, leading to cancellation of their procedure. For cancelled cases, the average time from initial CT prompting referral for bronchoscopy to the day of procedure scan was 53 days. Therefore, a follow-up scan before an intervention is recommended.

Standard-dose CT examination

A CT examination performed with a standard dose carries a higher radiation burden than the low-dose CT examinations used in the screening setting, usually between 2.6 and 4.3 mSv [11, 12], but allows assessment of the mediastinum, hilar and lung parenchyma structures. Use of a standard dose offers the possibility of scanning with or without *i.v.* contrast medium, including a CT angiogram.

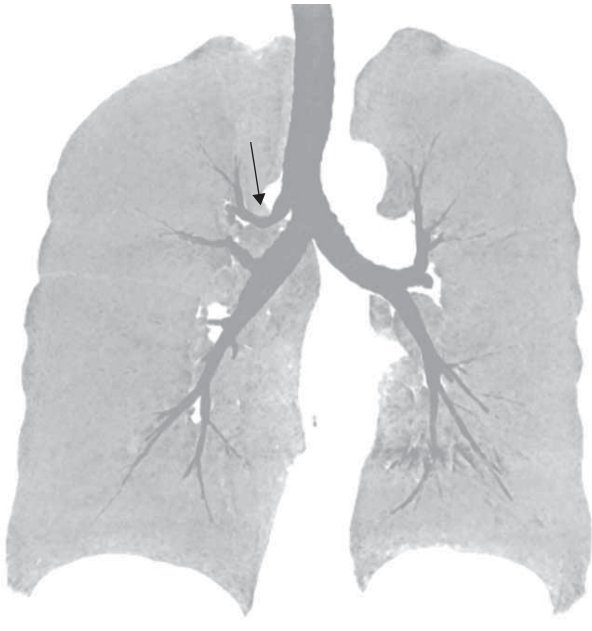

Figure 2. Routine CT for evaluation of ILD. The minimum intensity projection clearly demonstrates a separate origin of the right upper-lobe bronchus (bronchus suis) as a normal variant (arrow).

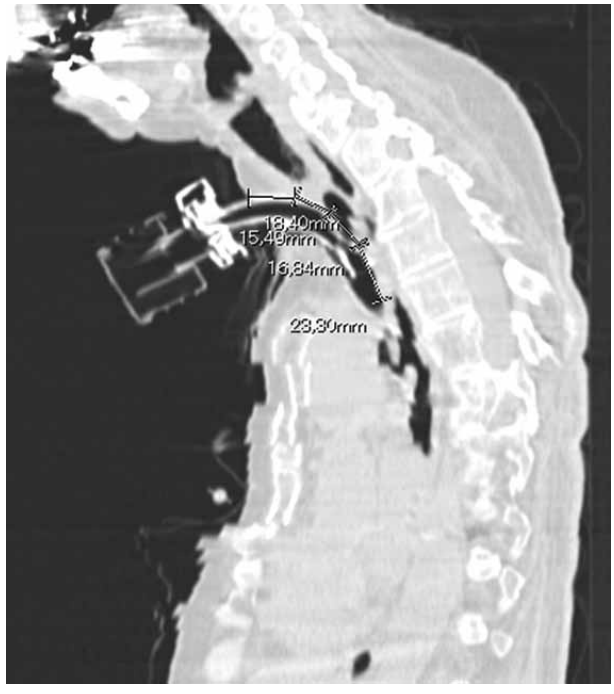

Figure 3. A sagittal reformated chest CT in a patient with a tracheal cannula. CT allows exact visualisation of the tracheal geometry and subsequent design of individualised tracheal cannulas.

An *i.v.* contrast-enhanced CT is recommended for mediastinal tumours/lesions or processes that infiltrate the chest wall. Contrast-enhanced CT should also be performed for assessment of haemoptysis or pulmonary embolism. The bolus timing must be chosen depending on the suspected vessel system, since the short acquisition time (*e.g.* 4 s) of modern scanners allows a low amount of contrast medium and therefore selective pulmonary–arterial, selective aortal or combined phases. This information must be provided to the CT technician prior to the CT scan, since individual bolus triggering enables optimal individual vessel opacification.

Mediastinal lymph nodes

Staging and evaluation of mediastinal lymph nodes by CT is based mainly on size: a node is deemed pathological with a short-axis diameter of >10 mm (sensitivity 60% and specificity 70% for malignancy) [13]. However, the excellent visualisation of CT allows precise localisation of the lymph node to plan the interventional biopsy of an enlarged lymph node [14–16].

Tracheobronchial tree

It is known that tracheobronchial variations and abnormalities occur in ~2% of the population, although more are now being identified using CT [17] (figure 2). For almost two decades, CT imaging has been the best technique for noninvasive visualisation of the tracheobronchial tree [18]. CT datasets of the trachea can be used to plan and design individual tracheal cannulas, especially in cases of anatomical variants or previous surgical modifications (figure 3).

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From the trachea to the terminal bronchioles, an airway tree consists of approximately 17 generations of branches, beyond which alveoli begin to appear, ultimately terminating at the alveolar sacs.

Given the 3D nature of CT datasets, these datasets are perfectly amenable for automatic segmentation and data extraction. This is especially true for the central airways in humans, which branch in a dichotomous manner. Automatic segmentation of the tracheobronchial branching is possible down to the ninth generation (and partially down to the 11th generation) with standard PC hardware [19–21] (figure 4).

These 3D datasets form the basis for ENB, an image-guided approach that uses 3D-reconstructed CT scans and sensor location technology to guide a steerable endoscopic probe to peripheral lung lesions that may be beyond the reach of conventional bronchoscopes [22]. While actual bronchoscopy offers inherent valuable options for treatment and tissue assessment, virtual bronchoscopy based on CT image

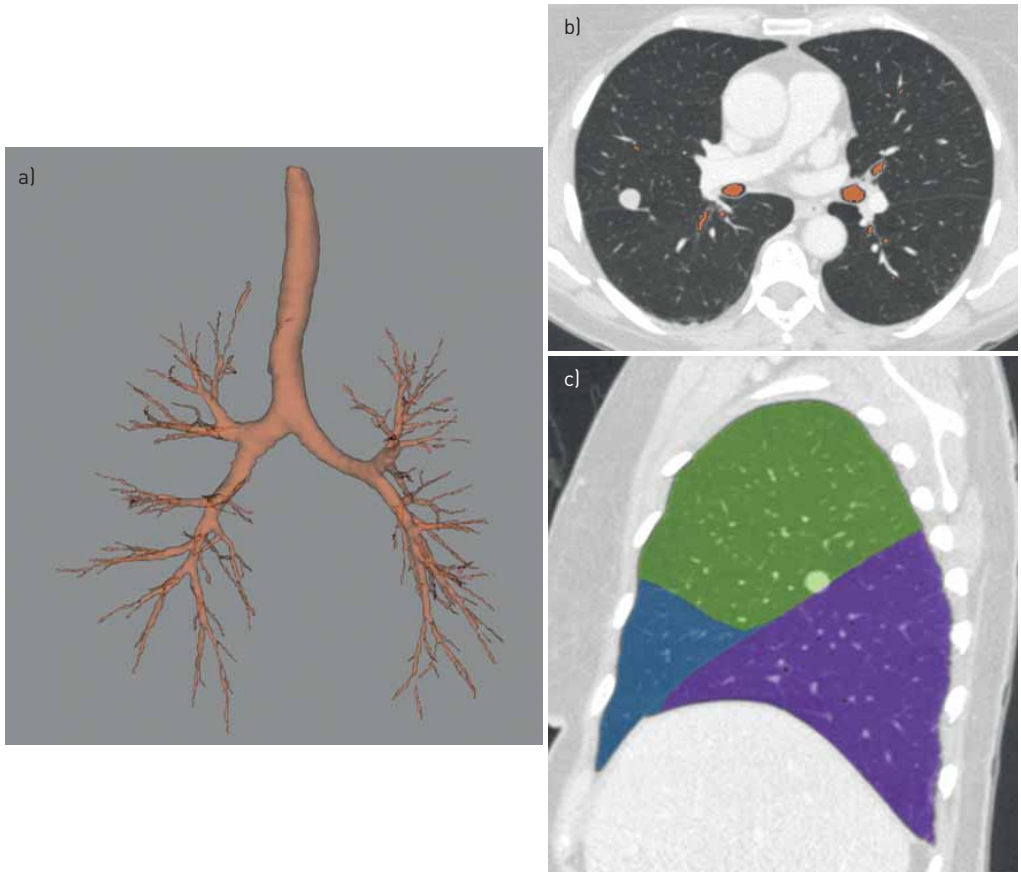

Figure 4. a) Automatic segmentation of the trachea and central airways. Visualisation in three-dimensional volume rendering is available as standard software (this example was generated with the Philips IntelliSpace Portal, COPD; Philips, Guildford, UK). b) An axial CT slice with segmented airways and a large nodule in the right upper lobe. c) Automatic lobar segmentation is also available for easy visualisation of the localisation of pathologies.

datasets provides several additional advantages: 1) the ability to pass stenoses virtually, 2) the view of the stenosis is not limited to a central-to-peripheral view but is also possible from a peripheral-to-central view, and 3) extralumenal organs such as lymph nodes, and tumours, vessels, struma and atelectasis, for example, can be displayed in the same procedure, enabling direct assessment of a mass causing a compression or obstruction; a multiplanar reformat orthogonal to the bronchial centre line can be useful in this situation.

With respect to malignant bronchial stenosis, squamous cell carcinoma, accounting for ~25–30% of all lung cancers, is the most common cause arising in central airways. The progression from normal bronchial epithelium to squamous metaplasia followed by dysplasia, carcinoma *in situ* and finally invasive carcinoma has been well described. Approximately 11% of patients with moderate dysplasia and 19–50% with severe dysplasia will develop invasive carcinoma. Therefore, reporting of central airway obstruction on radiology reports can have an impact on bronchoscopic airway interventions and patient outcomes [23] (figure 5). Herth *et al.* [24] compared CT assessment of thoracic tumour invasion into the bronchial wall *versus* EBUS assessment of the same condition in 131 patients and concluded that EBUS had a far better specificity (100%), sensitivity (89%) and accuracy (94%) compared with a CT scan (28%, 75% and 51%, respectively). The ability of chest CT and EBUS to distinguish between compression and infiltration was measured against the histology results [24].

Prior to an actual bronchoscopic intervention, rendering of a virtual bronchoscopy based on the CT dataset is possible to plan the procedure [25]. This might help to identify features such as lymph nodes for TBB, which might be relevant in staging purposes. In 32 patients with thoracic malignancies, CT scans and virtual bronchoscopy were performed and compared with actual bronchoscopy [26]. The sensitivities of CT scanning and virtual

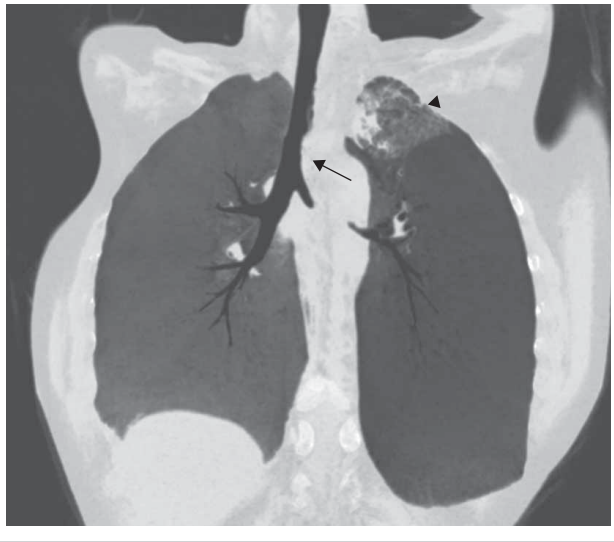

Figure 5. Minimum intensity projection of a CT dataset in the coronal orientation. Narrowing of the trachea (arrow) has resulted from tuberculosis infection. The tuberculosis is also located in the left upper lobe (arrowhead).

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bronchoscopy for the detection of endoluminal, obstructive and mucosal lesions were 90%, 100% and 16%, respectively.

Prior to stent placement, thin-section CT with both 2D and 3D reconstructions along the bronchial centreline are helpful to evaluate the relationship of the airway to adjacent structures such as major vessels [27, 28].

Multiplanar reconstruction and 3D volume-rendered images aid diagnostic interpretation and help in communicating results to referring physicians. CT can accurately evaluate the aetiology, location and length of airway obstruction, and can determine the type, length and sizing of airway stents. Landing zones can be accurately defined, and anatomical variations (*e.g.* tracheal bronchus) can easily be considered.

The CT protocol utilised for stent evaluation should be tailored to the specific patient. In cases of malignant central obstruction, *i.v.* contrast should routinely be administered to delineate the relationship between the obstructing mass, bronchi and central vascular structures.

CT is also the modality of choice for planning of any endobronchial volume reduction treatment. In this setting, CT allows combined visualisation of the lung parenchyma and airways. Many factors are now recognised as needing to be evaluated for estimation of success of ELVR [2]. First, it was shown that heterogeneous emphysema is a better predictor for outcome than bullous or other forms of emphysema [29]: a target lobe is destroyed by emphysema. Second, the lung lobe must be affected by emphysema in a fixed manner, meaning that there is no change in air content during inspiration and expiration [30]. This information can be achieved by imaging the patient in both respiratory settings and comparing visually, or preferably quantitatively, the density changes between both examinations. Furthermore, treatment with obstructive endobronchial valves is only successful if there is no collateral ventilation to the treated lobe. The major contributors to the integrity of the lobes are the lobar fissures (figure 6). A computer-assisted analysis of 573 CT examinations recently showed that ~90% of all examined persons had incomplete fissures regardless of whether COPD was present or not [31]. Optionally, functional information, including lung lobe perfusion, provides additional information on which lobe to treat as a target.

Taking all this information together, an individualised plan for placement of the ELVR can be determined (figures 7 and 8). Combined emphysema destruction, complete fissure, air trapping and reduced perfusion indicate atelectasis induction of the target lobe.

There are numerous conditions where ELVR is contraindicated, which can be depicted by CT. For example, bronchiectasis, repeated infections of the lower airways and frequent exacerbations of COPD, as well as a greater amount of sputum and bronchial secretions, are unfavourable and are contraindications for ELVR [32]. In addition, large pleuroparenchymal scars indicate the possible development of atelectasis of the treated lobe.

Vessels

Another area for interventional treatment is haemoptysis. Haemoptysis is a frequently seen issue in patients with chronic respiratory diseases (10% of patients affected) and with an incidence of 0.1% in outpatients and 0.2% in hospitalised patients.

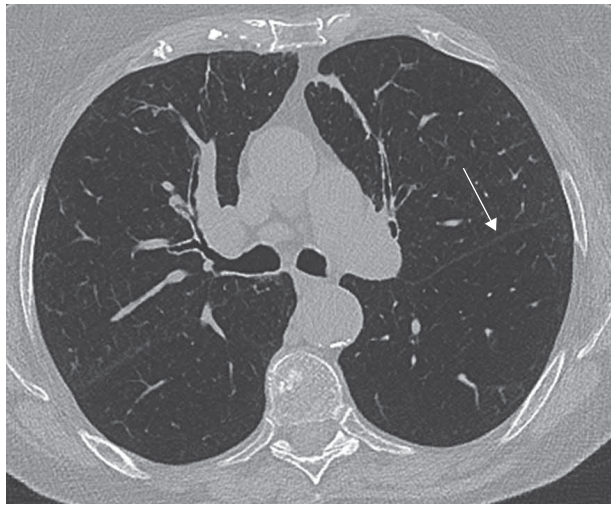

Figure 6. A patient with emphysema worked up for endobronchial lung volume reduction therapy. Note that the left fissure is intact (arrow), which is one important finding excluding major collateral ventilation.

In the majority of cases, the bleeding originates from the vasa privata of the lungs, the so-called bronchial arteries. These originate from the aorta, extend along the bronchi and subdivide into supplying branches to the trachea, the bronchi, and the vasa vasorum of the pulmonary arteries and veins, as well as to the aorta, the small bronchopulmonary branches of the lung, the diaphragmatic and mediastinal visceral pleura, and the central oesophagus and subcarinal lymph nodes [33]. About 70% of the bronchial arteries emanate from the descending thoracic aorta between the end plate of the fifth thoracic vertebra and the base of the sixth thoracic vertebra, frequently at the height where the aorta crosses the left main bronchus. The remaining 30% of bronchial arteries originate from other vascular territories, such as the subclavian artery, the internal thoracic artery, the pericardiacophrenic artery, the inferior phrenic artery, the thyrocervical trunk, the brachiocephalic artery, the vertebral artery, the front of the aortic arch, the abdominal aorta or, in rare cases, the left gastric artery.

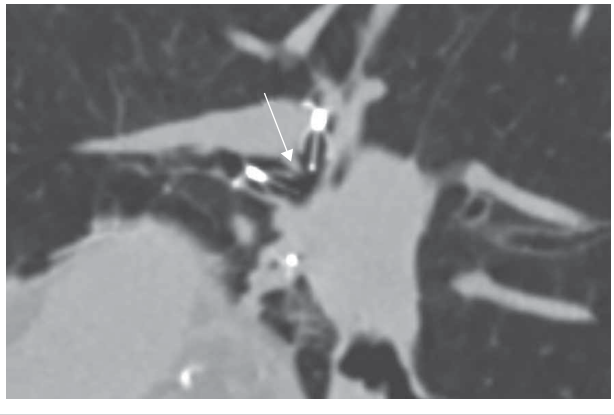

Figure 7. The same patient as in figure 6 approximately 5 months after endobronchial valve placement. The patient did not show adequate clinical improvement and thus a CT was performed for localisation of the valves. A multiplanar reformat is shown indicating the localisation of the valves. One segmental valve showed leakage (arrow). This dataset was used for planning the correction of the placement.

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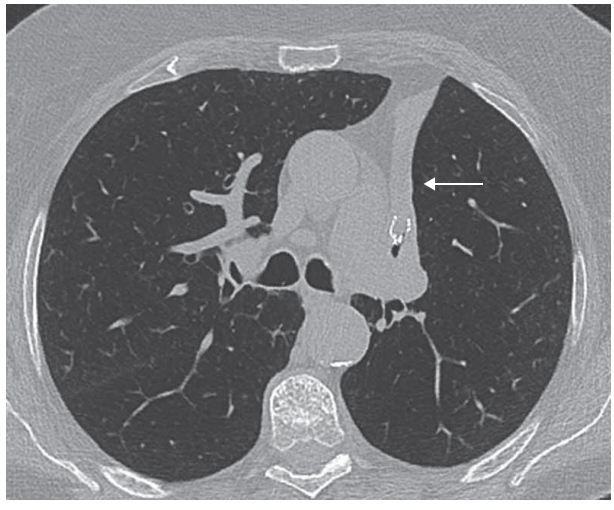

Figure 8. The same patient as in figures 6 and 7. After correction of the endobronchial valve, a follow-up CT was performed. With complete closure of the bronchus, atelectasis of the treated segment (arrow) occurred after 3 months.

For diagnostic purposes, contrast-enhanced CT angiography and bronchoscopy can be performed. Using contrast-enhanced CT angiography, localisation of the bleeding is possible in 63–100% of cases and discloses the cause in 60–77%. For bronchoscopy, localisation of the bleeding is possible in 73–93% of cases, while the cause often remains unclear with a detection rate of 2.5–8%.

For further management, interventional catheter-based embolisation of the bleeding vessel can be performed. In the case of bronchoscopy, vasoactive substances can be applied to staunch the bleeding [34].

PET/CT

Fludeoxyglucose-PET/CT imaging combines functional tissue information and morphological imaging. Given the technical restrictions, the PET readout must be performed during free breathing, while the CT part is subsequently also acquired in free breathing, resulting in limited accuracy for planning interventions. Respiratory triggering helps to reduce respiratory artefacts; however, full inspiratory inflation of the lung resulting in the best tracheobronchial depiction is not reached.

Despite the functional information, the sensitivity and specificity of PET for assessment of mediastinal lymph nodes in lung cancer patients is reported to be 78–93% and 82–95%, respectively [13, 35]. In the case of a PET-positive lymph node, PET/CT can be used for guidance as to which node is best to biopsy, using EBUS or VATS for example.

Magnetic resonance imaging

MRI allows morphological and functional assessment of the mediastinum and hilar structures. Morphological imaging using MRI shows the same sensitivity and specificity as

CT for mediastinal pathologies as T2- and T1-weighted imaging, with and without contrast, based mainly on the same characteristic of lesion size as used by CT [36]. Recent studies have demonstrated the clinical value of diffusion-weighted imaging, with significantly different values between malignant and benign mediastinal lesions [37]. Therefore, this technique can be used for indicating malignant lesions to be biopsied and, more specifically, regions within a lesion most likely to result in a representative or non-necrotic specimen (figures 9–11).

Visualisation of the trachea and main bronchi is possible using MRI but is inferior to CT [38]. In addition, visualisation of the lung parenchyma is limited in patients with emphysema, with correct classification of the leading type of emphysema in only 55–68% [39]. Using 3D perfusion techniques, MRI allows regional assessment of pulmonary perfusion [40]. This information is helpful in planning ELVR therapy, as perfusion is a strong surrogate for lung parenchyma destruction and thus is a target for EBVR [41, 42].

Imaging of complications

With the increase in use of interventional pulmonology techniques, some specific imaging findings after intervention should be mentioned.

Complications after TBNA are rare but include bleeding, pneumothorax and pneumomediastinum. Bacteraemia, fever and, rarely, mediastinitis have been reported following this procedure [43]. In a large series of patients undergoing mediastinal staging for lung cancer with linear EBUS, only one major complication (pneumothorax requiring a chest tube) was reported [43], while in a meta-analysis study of patients undergoing biopsy of peripheral nodules with radial EBUS, the pooled pneumothorax rate was 1% (11 out of 1090 patients), with 0.4% of patients requiring a chest tube [43]. Haemorrhage was rare, with no patients requiring intervention. Similar to EBUS, complication rates of ENB are low, although higher than EBUS. In a pooled meta-analysis of patients following ENB, the pneumothorax

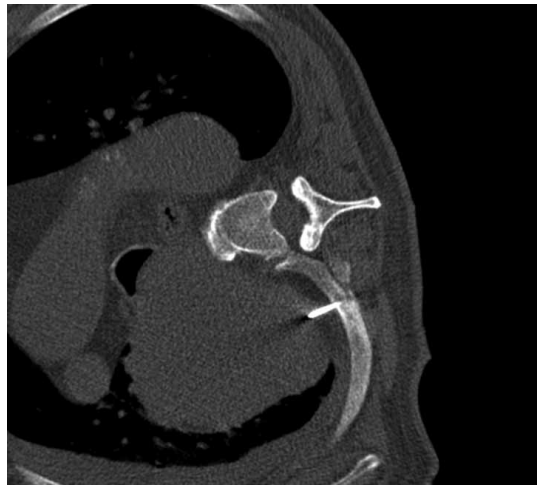

Figure 9. CT-guided biopsy of a large lung mass. The needle (bright linear object) is pointing towards the lesion centre. The result of the biopsy was necrosis.

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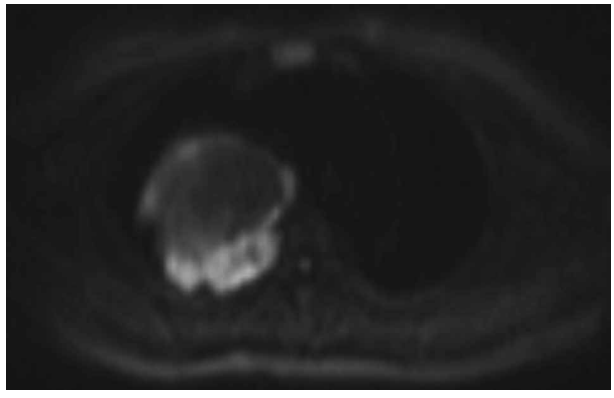

Figure 10. The same patient as in figure 9. For assessment of vital tumour tissue, magnetic resonance imaging was performed with diffusion imaging. The bright areas indicate active tumour located primarily at the rim of the lesion. The centre of the lesion is dark, representing avital or necrotic tissue. This information was used for further planning of a second biopsy.

rate was 3.1% (32 out of 1033) with 1.7% of patients requiring chest-tube placement (17 out of 1033), and pulmonary haemorrhage (either mild or moderate) was present in 0.9% of patients [43].

In a series of 1235 bronchoscopic biopsies in patients following lung transplant, the most common complications were bleeding (4%) and pneumothorax (1.5%) [44].

The imaging appearance following forceps biopsy in patients after lung transplantation has a distinctly different appearance from that of TBNA and generally appears as a small air-filled cavity with or without fluid (haemorrhage), which decreases in size and resolves within 1–2 months [43].

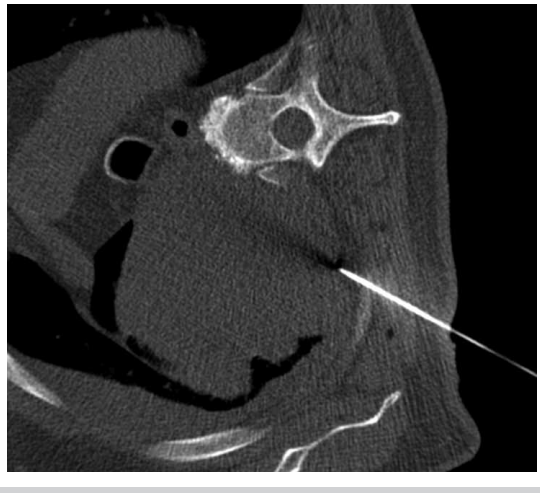

Figure 11. Second biopsy on the same patient as in figures 9 and 10. Based on magnetic resonance imaging diffusion information, the biopsy was taken from the outer parts of the lesion with subsequent diagnosis of a small cell lung cancer.

Tracheal stenosis can be treated by balloon dilatation using flexible or rigid bronchoscopy. Complications include laceration of the airway (in 52% after dilatation of benign strictures) with subsequent pneumomediastinum, bleeding, pneumothorax and mediastinitis. In very rare cases, massive haemoptysis secondary to rupture of a pulmonary artery branch and rupture of the tracheobronchial tree requiring surgical repair can occur [45].

Following stent placement, complications include stent narrowing, malpositioning, migration and fracture, with more rare complications including airway perforation and stent erosion into adjacent structures. In a series of 309 procedures, stent complications occurred in 42% [46]. The most common complications included partial stent occlusion by secretions or granulation tissue (36%), pneumothorax (8–18%), stent migration (5%) and airway perforation (1%). A significant number of patients (41%) required multiple stent procedures or revisions [46, 47].

A number of risk factors have been found to be significant CT predictors for the development of pneumothorax, including emphysema volume of the untreated ipsilateral lobe, the ratio of the volume of the untreated ipsilateral lobe to the volume of the hemithorax, the emphysema type and pleural adhesions [47]. Usually patients were followed up by bronchoscopy, but it was suggested that CT could be used as a primary surveillance tool. Only if CT shows signs of complications should flexible bronchoscopy be performed [48]. For the initial follow-up after stent placement, a chest radiograph may be sufficient, as it allows counting of the number of valves/stents *in situ* and their location, as the short-term complications are displacement or even exhalation of the valve due to coughing (figure 12).

Following endobronchial valve placement, the major complications are pneumonia (4.2%), pneumothorax and COPD exacerbation (7.9%) [29]. Device migration can occur, and deaths have been reported secondary to pneumothoraces due to contracting lung, resulting in rupture of a bullous area of the lung.

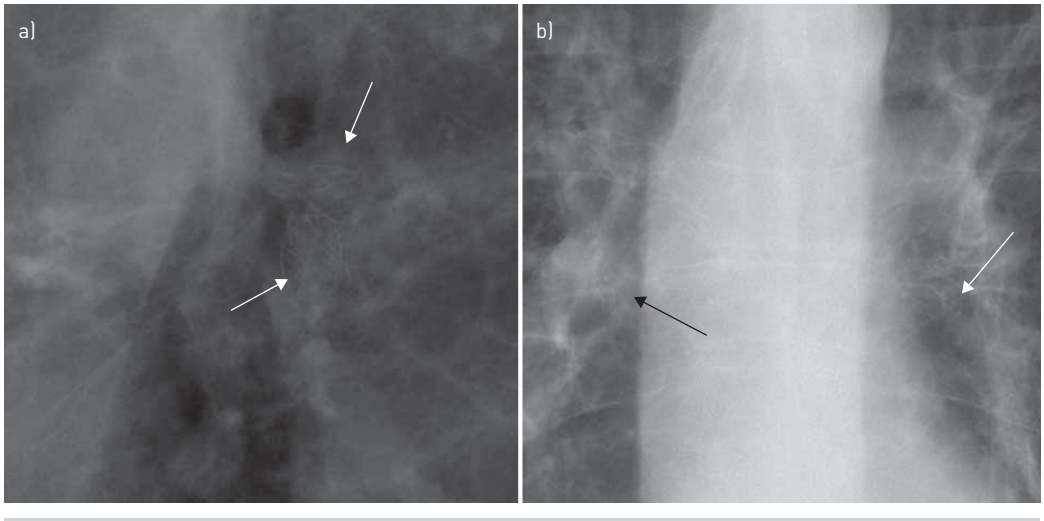

Figure 12. Patient following endobronchial valve placement in the left lower lobe. a) Two valves (white arrows) are indicated on the lateral and enlarged plain film. b) 6 weeks later, the patient returned after severe coughing. The enlarged frontal view shows displacement of one valve (black arrow) to the right side.

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The main goal of endoscopic valve placement is to reduce the volume and ideally generate atelectasis of the treated lobe. In the case of unsuccessful treatment, thin-section CT should be performed, and orthogonal and centreline reformations should be carried out for each individual valve to check for leakage (figure 7), misplacement or any other reason for incomplete obstruction.

Conclusion

Imaging is an important tool for guidance of any interventional pulmonology technique. Specific clinical scenarios require different imaging techniques and therefore detailed questions for ordering imaging need to be provided. The mainstay imaging technique is CT, allowing fast, highly spatial and 3D imaging of the pathologies to be addressed. CT enables virtual bronchoscopies in order to plan the actual intervention, or serves as a database for navigated EBUS or biopsy. CT also allows assessment of the lung parenchyma and thus determination of the eligibility of a patient and the target lobes for ELVR treatment. Functional imaging regarding tumour/metastatic activity must be done by PET or MRI.

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Chapter 5

Training

Leizl Joy Nayahangan[1], Paul Frost Clementsen[1,2] and Lars Konge[1]

Interventional pulmonology has evolved dramatically to include more complex procedures. For example, the use of fibreoptic bronchoscopes has been transformed by advanced video bronchoscopes with new image-acquisition systems that allow access to difficult areas, such as structures outside the bronchial tree. With advancing technology and innovation, the challenge is how to train and develop proficient interventional pulmonologists. Training has traditionally been by apprenticeship under expert clinicians, in which residents learned procedural skills through direct observation and eventually performing the procedure under supervision. However, this training approach is discouraged in the modern healthcare system. The future of interventional pulmonology depends on proper training and certification, without practical testing on patients. Competency-based education is efficient for learning technical skills and ensuring competency before moving to the next level. Efficient instructional strategies should include rigorous approaches, such as mastery learning and deliberate practice, well-described objectives, predefined benchmarks and valid, reliable assessment tools.

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Procedural competency is conventionally achieved through supervised residency in clinical wards. This happens over time, during which knowledge and technical skills are acquired according to credit hours from courses or number of procedures performed. However, the range of diseases is expanding, and new therapies are being introduced. This increases the demands for interventional pulmonology [1]. Residents have limited training time in light of increased focus on production, which is defined as patients per unit of time, work-hour restrictions and increasing emphasis on patient safety. Interest in more advanced, safer training venues, such as simulation centres, has increased dramatically in response to the confluence of challenges that the medical community is facing.

Teaching pulmonologists of the new century

Today's healthcare environment has undergone many modifications, fuelled by the surge in new technology that is transforming delivery and practice, especially in minimal invasive medicine and surgery. Interventional pulmonology has been at the vanguard of this

[1]Copenhagen Academy for Medical Education and Simulation, University of Copenhagen and the Capital Region of Denmark, Rigshospitalet, Copenhagen, Denmark. [2]Dept of Internal Medicine, Zealand University Hospital, Roskilde, Denmark.

Correspondence: Leizl Joy Nayahangan, Copenhagen Academy for Medical Education and Simulation, Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen, Denmark. E-mail: leizl.joy.nayahangan@regionh.dk

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innovation. It has expanded rapidly to diagnose and treat a wide range of pulmonary diseases [2]. These advances are attracting trainees, clinicians and the industry, because of the unique skill sets and expertise that distinguish interventional pulmonology from other well-established subspecialties of pulmonary medicine and thoracic surgery. Consequently, extensive training beyond the traditional pulmonary and critical-care fellowship to acquire advanced technical expertise is now required. Professional organisations across Europe and North America have started to recognise these unique skill sets and are pursuing major reforms to define curricular requirements, including indications and desired patient outcomes [3, 4]. In the USA, a dedicated, 12-month fellowship training programme has been established to prepare trainees in procedural practice, advanced knowledge, skills and research [5]. Other current venues offer short courses and extended sabbatical training in different interventional pulmonology centres across the world [6]. Despite these initiatives to formalise dedicated training pathways and define competencies, interventional pulmonology is still in its infancy and continues to evolve, alongside new technologies. There is a need for formal, standardised interventional pulmonology training programmes measured by valid, reliable competence metrics [7]. Educational leaders must take responsibility for exploring new training modalities and incorporating these into the armamentarium of education in interventional pulmonology [5].

Approaches to training

Traditional apprenticeship method

Formal training for interventional pulmonologists focuses on diagnosing and managing pleural diseases, lung cancer, central airway obstruction, and many other diverse and specialised procedures. Residency training is traditionally achieved through the standard apprenticeship method, which has been the cornerstone of medical and surgical training for over a century [8]. This follows the long-established adage of "see one, do one, teach one", wherein trainees observe experienced practitioners and are expected to acquire the necessary skills and competencies. Patients have played a central role in residency training for decades. Silvestri [9] described his first bronchoscopy in 1993:

"I practiced for a while on an inanimate tracheobronchial tree, convinced that I would be observing this first procedure and proud to have not damaged the bronchoscope in the process. When the attending physician arrived, a highly regarded bronchoscopist in his own right, he proceeded to take the teaching head (at the time there were no videoscopes) and hand me the bronchoscope, which he never took back. What followed can only be described as incompetence of the highest order. While the procedure only took 30 min, it seemed like days. Sweat poured from my gloves while the room shrunk in around me. I felt every emotion from anger at my attending physician, to sympathy for my patient, to fear for my career, believing it would end in disgrace when I could not enter the superior segment of the right lower lobe."

Nowadays, we are experiencing major changes in healthcare delivery and exploring new technologies.

New dimension of training simulation

Simulation provides trainees with a forgiving, safe environment in which to develop and refine technical skills before working in the clinical environment with patients. Modelled

from the aviation industry, simulation in healthcare includes different models, such as live animals, human cadavers, ask trainers, manikins, computer-based models and virtual-reality simulators. This training approach is modelled on Fitts and Posner's three-stage theory of motor-skills acquisition [10]. When presented with a task, the trainee attempts to understand the mechanisms of the task and consciously attempts to produce a specific result. In this cognitive stage, the performance is slow and inefficient, and errors are evident. For example, when performing flexible bronchoscopy, the trainee must initially understand the principles behind how the scope works, how to insert and manoeuvre it, and how to systematically explore the bronchial tree. After subsequent practice and feedback sessions, the trainee reaches the integrative stage, in which movements are more efficient and accurate. The trainee still thinks about how to manoeuvre the scope, but now does so fluidly, with fewer interruptions. In the autonomous stage, the tasks are precisely and consistently executed, and the movements are automatically controlled, with little or no cognitive input. The trainee inserts the scope and manoeuvres through the bronchial tree in an automated fashion. At this stage, the trainee also focuses on refining the skills associated with the task. The first stages should be accomplished in a simulation-based environment, in which trainees can safely practise, learn from errors, and potentially achieve the skills and confidence to perform the task autonomously.

Simulation is highly resource intensive. Return of investment can be achieved when equipment and training are centralised in a local centre, shared by different hospitals [11]. This allows flexibility, making the centre available for trainees to practise according to their availability. They can practise individually, guided by training assistants or in pairs. Figure 1 shows a simulation centre with different equipment for practising various procedures in interventional pulmonology.

Following the evolution of equipment in interventional pulmonology, simulation equipment also proliferated. Physical models and virtual-reality simulators are the most common equipment currently used. Konge [12] compared these modalities (table 1).

The curriculum of training programmes is one of the challenges that must be addressed. Simulation will only be effective if it is integrated into a well-designed curriculum. Generally, simulation programmes are developed in a predictive approach without

Figure 1. Endoscopy room at the Simulation Centre at the Copenhagen Academy for Medical Education and Simulation, Copenhagen, Denmark. Reproduced from [12] with permission.

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Table 1. Comparative overview of physical models and virtual-reality simulators

	Physical models	Virtual-reality simulators
Training efficacy	High trainee satisfaction; no randomised trials performed	Randomised trials showing higher efficacy than apprenticeship approach at the beginning of the learning curve
Price	Relatively cheap but will need real equipment, which will require repair costs	Expensive; return on investment is improved if training is centralised and shared by several departments/ hospitals
Portability	Mobile; not too heavy to move around	Heavy and fragile to move
Different cases/ difficulty	No, only fixed cases	Yes, several cases of simulated patients
Simulates pathologies	Only enlarged lymph nodes for EBUS-TBNA	Cases with bleeding, visible tumours or enlarged lymph nodes
Simulates use of tools	Real tools can be used with caution to avoid damaging the model	Varied simulated tools can be used to instil lidocaine, remove foreign bodies, perform biopsies, *etc.*
Provides feedback	No, an instructor is needed for feedback	Automatically delivers a multitude of performance metrics; several of these must be used with caution due to lack of evidence-based validity

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systematic objectives [13], according to experiential notions [14] or availability of equipment [15]. We must know the current needs of residents in training prior to buying equipment and developing training programmes. Developing an efficient curriculum should start with identifying the problem and performing a general needs assessment [16]. In Denmark, a systematic, national needs assessment was conducted among key opinion leaders in pulmonary medicine to identify procedures for simulation training. This resulted in a prioritised list of 11 technical procedures that are clinically relevant and should be integrated in a simulation-based curriculum. Flexible bronchoscopy was the most important, followed by pleurocentesis, EBUS-TBNA, EUS-guided fine-needle aspiration biopsy (EUS-FNA), noninvasive ventilation, transthoracic biopsy of pleural or lung tumour, focused ultrasound scanning of the lungs, chest-tube insertion, needle biopsy of visible lymph node/tumour of the skin, focused ultrasound scanning of the heart and thoracoscopy [15]. Educational directors are encouraged to use this list to develop training programmes.

Establishing competency

Time- and volume-based approach

The current educational approach in interventional pulmonology has followed the traditional time- and volume-based framework, in which the vast majority of trainees successfully complete a fixed amount of time and curricula [17]. When these are met, it is crudely assumed that the trainee can apply what they have learned to deliver patient care. This method does not take into account the fact that individuals learn at different paces, resulting in a wide variation of skill levels among trainees at the end of their education [13].

For example, individuals with outstanding technical dexterity require less time to master a skill compared with an average individual, who needs more time to practise to achieve the same results.

Practice guidelines, such as those from the American College of Chest Physicians (ACCP) and the European Respiratory Society and American Thoracic Society (ERS/ATS), have outlined the desired objectives, structures and outcome of training, including recommended volume thresholds for different procedural skills to demonstrate competence [3, 4]. How were these numbers derived? These numbers are arbitrary and should be taken as suggestions, rather than absolute regulations [18]. The focus must shift to quality, rather than quantity, of training. This can be achieved by establishing standardised training curricula in the field of interventional pulmonology.

Competency-based education

Advocating for expertise rather than experience is the driving force for educational organisations, such as the Accreditation Council for Graduate Medical Council (ACGME), the American Board for Medical Specialties (ABMS) and the Royal Colleges in the UK, to establish competency-based training for all doctors [19, 20]. Recently, the Association for Medical Education in Europe (AMEE) also developed guidelines promoting a new training paradigm called competency-based education [21]. This contemporary training approach is fundamentally orientated towards outcome abilities, with greater emphasis on accountability, flexibility and centring on the learner [22]. Training is tailored according to the individual's needs and abilities to progress from the beginning to advanced technical tasks [23]. Effective, evidenced-based medical education should include mastery learning, deliberate practice and rigorous outcome measures [24]. Mastery learning is a specific, rigorous approach towards achieving proficiency in a particular task [25]. Trainees must acquire the knowledge and skills to reach a predefined proficiency level before moving to the next learning objective.

According to Ericsson [26], it takes extensive experience to become outstanding at something but does not necessarily lead to expertise. Achievement of expert performance requires engaging in deliberate practice. This involves focused, repeated practice on a representative task to learn from errors and improve, according to immediate feedback. This approach is followed by other professionals, such as chess masters, Olympic athletes and scientists to become world-class performers. Maintaining superior performance also takes constant practice. McGhagie *et al.* [27] underscored the use of deliberate practice in medical education by outlining nine features: 1) highly motivated trainees with good concentration, 2) engaging with a well-defined learning objective or task, 3) an appropriate level of difficulty, 4) focused, repetitive practice, 5) rigorous, precise measurements, 6) informative feedback from educational sources (*e.g.* simulators, teachers), 7) trainees who monitor their learning experiences and correct strategies, and errors and levels of understanding, and who engage in more deliberate practice, 8) evaluation to reach a mastery standard and 9) advancing to another task or unit.

Deliberate practice is a viable solution to training limitations, such as scarcity of clinical educators. However, unsupervised practice could lead to developing bad habits and misunderstandings [28]. Directed, self-regulated learning allows trainees to practice autonomously but access directed guidance when needed. The trainee can be metacognitively, behaviourally and motivationally active [29]. Another way to train is dyad

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practice, in which two individuals learn a task collaboratively instead of individually. Bjerrum *et al.* [30] explored dyad practice as a simulation training strategy in bronchoscopy and concluded that practising in dyads can increase efficiency for novice learners. Educators should consider these two ways of learning to conserve time without sacrificing efficiency and effectivity in developing technical skills.

At the end of residency training, interventional pulmonologists are expected to have reached a predefined level of competency, allowing them to perform procedures safely and efficiently. Information about performance and competence depends on effective, accurate, timely and meaningful assessment [31]. In 1990, Miller [32] presented his pyramid of competence to define the framework for assessing clinical skills (figure 2). This ground-breaking conceptual model outlines the different facets of competence, starting with the base "knows" (knowledge of basic facts), followed by "knows how" (knowing how to use the learned knowledge), "shows how" (applying this knowledge) and finally "does" (performing the acquired skills in the clinical environment). Each facet of the pyramid should be assessed by valid, reliable assessment tools. There is increasing focus on "shows how" and "does". Simulation plays a vital role, especially in the "shows how" stage. Inspired by Miller's pyramid, Konge *et al.* [12] outlined a three-step approach to achieve competency in endoscopy, in which step 2 tackles hands-on training to practise and master procedural skills away from patients (figure 3). It is important to acknowledge that simulation does not aim to create experts but helps novices go through the steepest part of the learning curve.

Practical applications of simulation in interventional pulmonology

Bronchoscopy

Bronchoscopy is a defining skill for a practising pulmonologist. It is imperative that the skill set is acquired and maintained to optimally deliver healthcare, and to minimise errors and complications. Currently, there are no guidelines defining competence in either diagnostic or therapeutic bronchoscopy. Several assessment tools have been developed, but

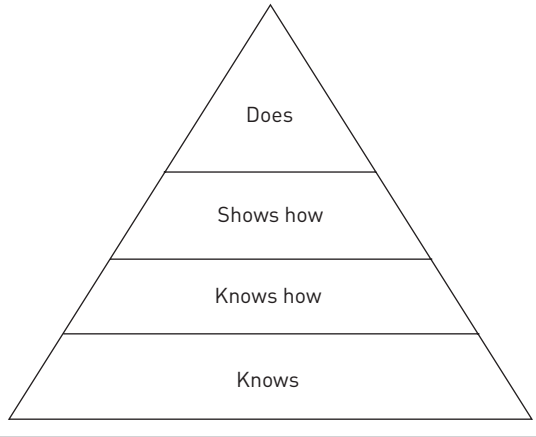

Figure 2. Miller's pyramid of competence.

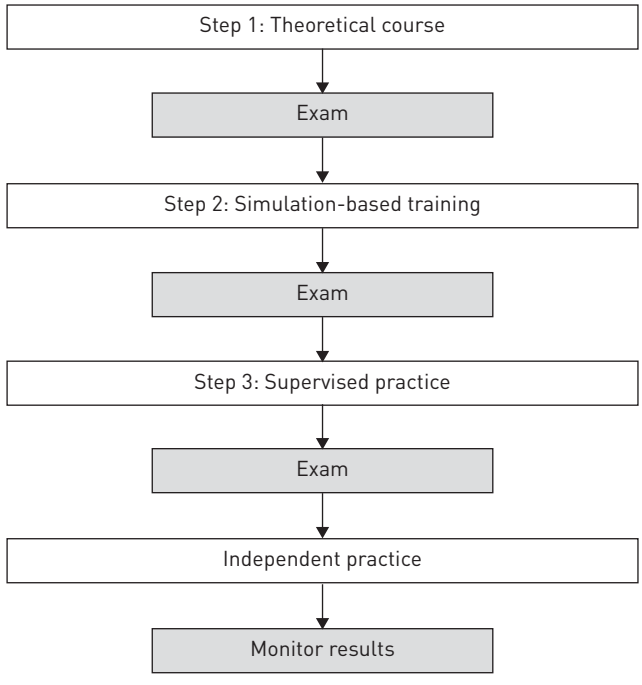

Figure 3. A three-step approach to competency in endoscopy. Reproduced and modified from [12] with permission.

most institutions still rely on sheer volume as the measure of competence. The ACCP proposed that trainees should perform at least 100 flexible bronchoscopies under supervision to attain basic competency and 25 bronchoscopies per year for maintenance [4]. Other educational guidelines, such as those of the ACGME and ERS/ATS, propose different arbitrary numbers [3, 33]. Bronchoscopy encompasses several heterogeneous components, including knowledge of thoracic anatomy, scope of diagnostic and interventional treatment, technical aspects of the procedure and acquiring practical skill sets, so should not be limited to procedural-based training. The skill sets associated with bronchoscopy can be taught in a simulation-based environment, with measurable, competence-based assessment tools to ensure cognitive and technical acquisition [34]. Simulation-based training in bronchoscopy has been around for many years, with the proliferation of available equipment ranging from low- to high-fidelity simulators. High-fidelity systems, such as virtual-reality simulators, contain clinical cases of virtual patients who can cough, breathe and present complications [35]. They also provide real-time feedback on objective metrics, such as percentage of segments entered, wall collisions and sampling efficiency. Examples include the GI-Bronch Mentor from Simbionix (3D-Systems Healthcare, Littleton, CO, USA) and the EndoVR Endoscopy Training Simulator (CAE Healthcare, Montreal, Quebec, Canada). Low-fidelity simulators, such as physical models, are low cost and provide an opportunity for trainees to use real bronchoscopes on moulded, realistic tracheobronchial trees. The trainees learn airway anatomy and enhance their eye–hand coordination [36]. Simulation centres are encouraged to develop dedicated training programmes that include both systems, in which trainees practise basic psychomotor skills on low-fidelity simulators and then work on different cases in virtual-reality simulators, repeatedly performing the procedure in a systematic way, and managing complications and learning sampling techniques [37].

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Several researchers have developed assessment tools to measure competency [38–41], including two reliable, valid tools developed by Konge *et al.* [42, 43] to assess competence in bronchoscopy in the clinical setting and on a virtual-reality simulator. To validate usability of assessment tools, a credible pass/fail criterion must be identified. A pass/fail score was established using an instrument that tested manual dexterity, knowledge of anatomy and endobronchial-image recognition. It was possible to set standards that would relay meaningful consequences when applied to bronchoscopy operators with varying degrees of experience. This objective assessment tool, with a pass/fail score, may aid in certifying and recertifying pulmonologists [44].

The use of rigid bronchoscopy has resurged with the growth of interventional pulmonology. It manages malignant and benign central-airway disorders. One of the advantages includes allowing simultaneous procedures, such as ablation, debulking and suctioning, without limiting ventilation [45]. Current dedicated interventional pulmonology programmes include formal training in rigid bronchoscopy as fundamental. However, recent surveys have demonstrated that most trainees do not have many opportunities to achieve the required basic competency [46, 47]. Furthermore, there are no standard approaches to performing the procedure. To address this, Mahmood *et al.* [48] developed a competency-orientated assessment tool called the Rigid Bronchoscopy Tool for Assessment of Skills and Competence (RIGID-TASC) to objectively score operators in basic rigid-bronchoscopic intubation and navigation. This checklist-based tool comprises the important steps in performing rigid bronchoscopy, such as assembling the bronchoscope, upper- and lower-airway navigation, and the time to complete the procedure. The RIGID-TASC was found to be valid and could discriminate according to level of experience. However, a pass/fail criterion has not been established, which calls for further research. Rigid bronchoscopy also plays a vital role in stent placement, repositioning, maintenance and removal [49]. The large working channel of a rigid bronchoscopy is beneficial in stent placement, as it allows direct visualisation, revision or removal of stents [45]. Technologically advanced airway stents are now available, but stenting success depends on operator experience. Training opportunities are scarce and vary across centres [50]. There is a clear need to define a competency-based training programme for rigid bronchoscopy, including stent placement.

A recent report recognised the need to establish quality systems for improving the assessment and certification processes. It was suggested that multiple training modalities, including simulation, should be incorporated in bronchoscopy training. An optimal, multimodality training programme for bronchoscopy should include didactic lectures, web-based learning, case-based reviews and hands-on training [36].

EBUS and oesophageal ultrasound

EBUS-TBNA is a useful technique for obtaining biopsies for diagnosing and staging patients with lung cancer. The techniques associated with this advanced procedure are challenging to master and are time-consuming [51–53]. Previous studies have shown that the diagnostic yield greatly depends on operator competence [54, 55]. There is sparse evidence on training requirements for EBUS. International guidelines recommended different volume requirements to achieve basic competency, stating 40 or 50 supervised procedures [3, 4]. The recent British Thoracic Society (BTS) guideline recognises that these numbers are usually arbitrary, so decided not to quote a specific number [56]. A study examining the learning curves of interventional pulmonology trainees suggested that there is a need for further

improvement, even after performing 200 procedures. In addition, there was a significant variation in the rate of learning, the number of cases required to reach a performance threshold and the highest skill level that can be achieved. These results underscore the paucity of only setting a number of procedures as a determinant for competency [57]. A survey of pulmonology trainees in the UK reported that only a few considered themselves competent to perform interventional diagnostic or therapeutic procedures at the end of training. Overall, 36% regarded themselves competent to undertake simple TBNA; however, only 2.8% felt competent to perform EBUS-TBNA or endobronchial diathermy [58]. New technologies and simulation-based training, such as in bronchoscopy, have provided similar venues for practising EBUS prior to supervised training in the clinical environment [59]. The BTS supports attendance of courses to gain knowledge, practise on inanimate objects such as phantoms or virtual-reality simulators, and gain hands-on experience in the clinical environment under the supervision of an expert operator. Furthermore, the use of objective, validated tools to assess technical skills and competency should be established. A number of studies have explored the efficiency of simulators as training tools for EBUS. Konge *et al.* [60] performed a series of studies exploring the validity and reliability of simulator metrics to differentiate between experts and novices, and established a pass/fail standard. They established validity evidence for an assessment tool, the EBUS assessment tool (EBUSAT) [61]. In this randomised controlled trial, the EBUSAT assessed the competency of trainees after undergoing apprenticeship training with patients compared with trainees who trained in virtual-reality simulators as a supplement to apprenticeship training. The trainees in the latter group scored higher on the EBUSAT, which assessed both anatomical knowledge and biopsy techniques. Competency was assessed in the clinical setting with patients, rather than in a simulator. Other studies investigated training modalities such as wet laboratories, computer-based simulation and the traditional apprenticeship method. Collectively, these studies concluded that simulation-based training is more efficient and can replace the apprenticeship method at the beginning of the learning curve (figure 4).

The ERS recently launched a structured training programme on EBUS, comprising a three-part comprehensive process [62] (figure 5). Part 1 is a theoretical introduction

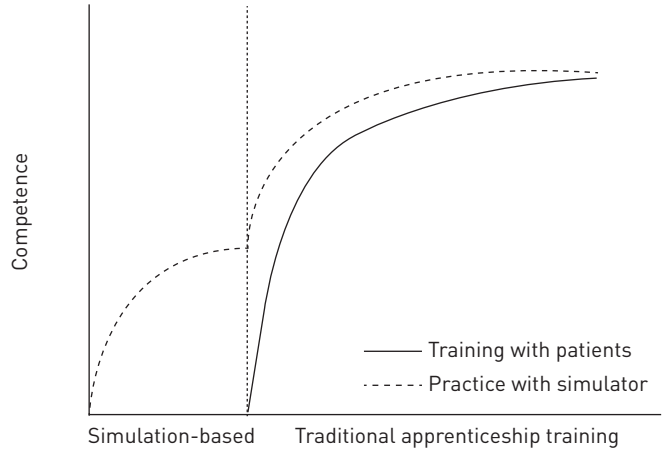

Figure 4. A graphic illustration of two training approaches: practising on simulators before patients, and the initial training on patients. Reproduced from [61] with permission.

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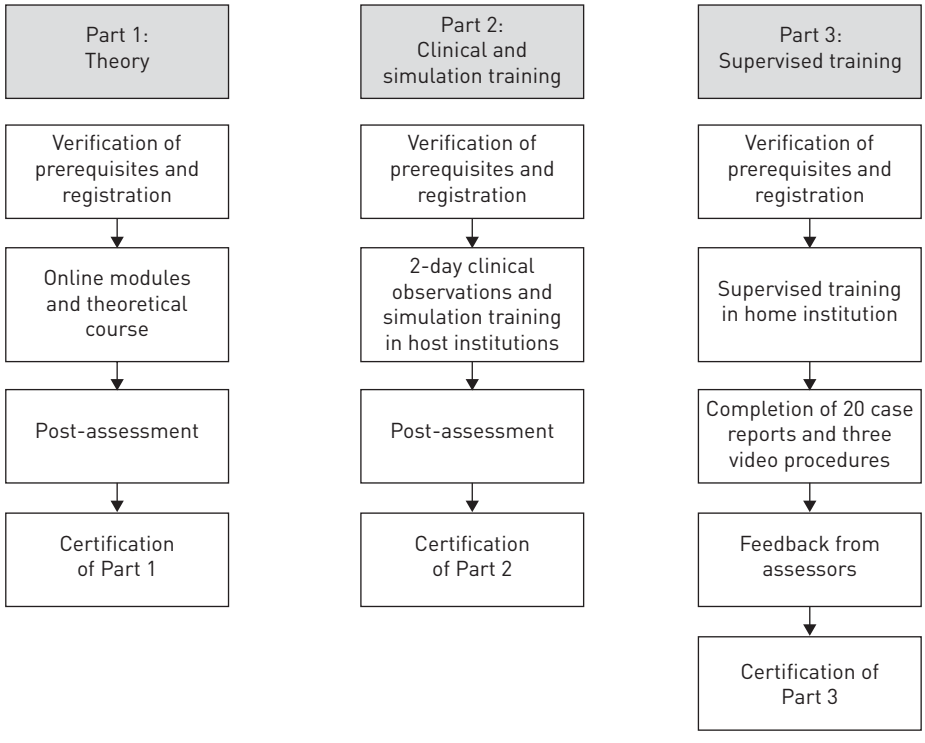

Figure 5. The ERS EBUS training programme. Reproduced and modified from [62] with permission.

comprising self-directed online modules and a course, including lectures and live transmissions of procedures. Part 2 is intensive simulation-based training and clinical observation. Part 3 is performing procedures under supervised training in the clinical setting. Each part ends with a certification. The participant finishes the entire training programme by submitting 20 written reports and three video-taped procedures for final assessment.

This approach represents the principles behind proficiency-based learning. The participants are guided through the process and given significant time to complete all parts, while allowing opportunities for deliberate practice and mastery learning. In 2015, the European Society of Gastrointestinal Endoscopy (ESGE), in collaboration with the ERS and the European Society of Thoracic Surgery (ESTS), included a structured training curriculum that comprised simulation-based training, followed by supervised training on patients in the clinical environment [63]. This initiative is a revolutionary step in medical education. It will be a fulfilled vision to include other procedures in the guidelines.

A recent systematic review explored the possibilities for simulation-based training in flexible bronchoscopy and EBUS, with a special focus on optimal training programmes, assessment methods and available simulators [64]. The study concluded that residents who underwent simulation-based training gained similar, or better, technical skills compared with residents who followed standard residency training.

Complementary to EBUS-TBNA, EUS-FNA is useful for accessing the inferior mediastinum, the left paratracheal lymph nodes, the left adrenal gland, the left liver lobe

and structures in the aortopulmonary window [65]. By combining EBUS with oesophageal ultrasound, complete hilar and mediastinal staging of the patient with lung cancer can be achieved. EUS-FNA can be performed either with a conventional gastrointestinal scope (EUS) or with an EBUS scope in the oesophagus (EUS-B). For mediastinal nodal staging in patients with suspected or proven nonsmall cell lung cancer, combining EBUS-TBNA and EUS-FNA/EUS-B-FNA is preferred over either test alone [66]. EUS-FNA ranked fourth on the needs assessment performed by Nayahangan *et al.* [15]. Since this study was published, EUS-B-FNA has rapidly been gaining ground throughout Europe as an alternative to EUS-FNA. A single-scope approach (EBUS-TBNA plus EUS-B-FNA) has obvious logistical, practical and economic advantages over a dual-scope approach (EBUS-TBNA plus EUS-FNA). Unfortunately, an EUS-B-FNA simulator does not currently exist. There is a huge need for simulation-based education in combining EBUS-TBNA and EUS-B-FNA, which may inspire medical-simulation companies to collaborate to fulfil this need.

Laryngoscopy

A laryngoscopy is a risky procedure that is performed not only by pulmonologists but also by many healthcare professionals. The manoeuvring skills associated with laryngoscopy are difficult to learn. Early in their training, residents are expected to know and perform the different key aspects of the procedure, such as positioning, and timely and atraumatic insertion of the laryngoscope blade [67]. These skills are traditionally learned during clinical rotation, in which patients are at risk. There is little research on the extent to which training requirements achieve competency. Most training programmes are inadequate, despite the proliferation of different training models. The advent of new technology, especially from direct laryngoscopy to the use of video laryngoscopy, requires extensive hands-on training for residents to learn technical laryngoscopic skills in a safe environment, away from patients. Two studies to determine the required training experience needed to become competent in intubation concluded that a 90% success rate requires considerable experience after a mean of 47 or 57 laryngoscopic intubations, respectively [67, 68]. The question remains of how we define a good laryngoscopy. Assessment tools with established pass/fail criteria have yet to be developed.

Interestingly, laryngoscopy simulators have been around for more than a century. The first were developed from 1827 to 1907 by Adalbert von Tobold. The phantoms were created in the shape of a skull and used for practising indirect laryngoscopy before attempting to do the procedure on patients [69]. Today, many advanced training modalities are available. A review of the literature has explored the use and impact of simulation as an educational intervention for direct and video laryngoscopy [70]. Eleven studies explored different kinds of simulators and assessments and analysed other specificities, such as time of intubation, and success and failure rates (including number of attempts), and the Cormack and Lehane classification [71]. In conclusion, these studies suggest that trainees learn faster and commit fewer errors, especially with video laryngoscopy [70].

Conclusion

The future of interventional pulmonology depends largely on giving residents extensive training opportunities in which they can learn procedural skills in a safe environment without putting patients at risk. Establishing structured, evidenced-based training programmes is crucial and should be a top priority among educators and policy-makers.

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New training modalities, such as simulation, allow the acquisition of basic competency. Amidst all the challenges that the medical-education community is facing today, this new training environment exposes trainees to many opportunities to deliberately practise procedural skills until competency. Assessment tools with solid validity evidence should be used at every level, allowing timely feedback and ensuring optimal outcome and increased retention. High-volume, centralised, standardised training programmes at centres of excellence are recommended. Ongoing research and development must be pursued to explore different ways of training interventional pulmonologists, in conjunction with a changing medical society to enhance patient safety and quality of care.

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Chapter 6

Laryngoscopy

Andrew J. Kinshuck and Gurpreet S. Sandhu

Laryngoscopy has become a routine part of the examination of patients presenting to the ENT specialist. The development of flexible fibreoptic endoscopes has enabled laryngoscopy to be performed in the clinic in patients of all ages. It provides a visual assessment and allows dynamic evaluation of the larynx and upper airway. Laryngoscopy continues to gain popularity and is now regularly used by other specialists, including respiratory specialists, speech therapists and anaesthetists. There has been a continued growth in office-based procedures on the larynx using a variety of laryngoscopy and anaesthetic techniques. Suspension laryngoscopy allows the surgeon to perform endoscopy and surgical procedures on the entire airway, from the supraglottis to the bronchi, under general anaesthesia. Suspension laryngoscopy enables the surgeon to use both rigid and flexible endoscopes, surgical instruments, fibre lasers, cryoprobes, and insert stents. Adding the operative microscope allows binocular vision, magnification, improved illumination and use of the carbon dioxide laser through a "line-of-sight" technique.

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The larynx is a complex structure in the neck consisting of a framework of cartilages connected by ligaments, membranes and muscles. The primary functions of the larynx include protection of the airway, phonation, Valsalva and control of respiration. Examination of the larynx (laryngoscopy) is routinely performed by specialists to evaluate laryngeal structure and function. Laryngoscopy also allows procedures on the larynx and upper airway to be performed. Laryngoscopy has progressed since it was first described, and continues to develop and evolve along with advances in technology.

History of laryngoscopy

There remains debate regarding the invention of laryngoscopy. From as far back as 1743, Leveret reported visualisation of the nasopharynx with a metal spatula and removal of a laryngeal polyp [1]. However, it was not until the 19th century that further advances in laryngoscopy were made. During this pre-antibiotic era, the common airway and laryngeal

National Centre for Airway Reconstruction, Dept of Ear, Nose and Throat Surgery, Imperial College Healthcare NHS Trust, Charing Cross Hospital, London, UK.

Correspondence: Andrew Kinshuck, Dept of Ear, Nose and Throat Surgery, Imperial College Healthcare NHS Trust, Charing Cross Hospital, Fulham Palace Road, London, W6 8RF, UK. E-mail: akinshuck@gmail.com

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pathologies were the result of infective causes, including syphilis, diphtheria and tuberculosis. Previously, these could only be treated with a tracheostomy and diagnoses only made *post mortem*.

Philip Bozzini, in 1807, invented a primitive endoscope known as the "lichtleiter" or light conductor. This enabled examination of anatomical orifices, including the mouth and larynx [2]. In 1855, Manuel Garcia presented his findings on laryngoscopy to the Royal Society of London [3]. The technique of visualising the larynx relied on an angled mirror in the mouth with light provided by a head-mounted mirror. This method of indirect laryngoscopy was further developed by Johann Czermak, in Budapest, who was able to make adjustments to focus the light. In 1858, Czermak presented his work to the Vienna Imperial Society of Medicine and this helped indirect laryngoscopy become popular among laryngologists [4]. In 1865, Sir Morrell Mackenzie published a book on "The Use of the Laryngoscope in Diseases of the Throat" and indirect laryngoscopy (using laryngeal mirrors) continued to be widely used around the world until the development of the endoscope [5].

Direct laryngoscopy was first described by Horace Green, in 1855, in the USA [1]. A blade-like instrument was used; however, it was not well tolerated by patients prior to the development of anaesthesia. In 1864, Albert Tobold in Germany was able to directly visualise laryngeal papillomatosis [1]. Further work in Germany by Alfred Kirstein, in 1895, using an electric light and a tubed oesophagoscope, which he termed an "autoscope", developed direct laryngoscopy [1].

In 1909, suspension laryngoscopy was developed by Gustav Killian to allow both hands to be free to operate on the larynx [6]. In the USA, in 1904, Chevalier Jackson continued to make further advances in laryngoscopy, bronchoscopy and oesophagoscopy with improved light and suction [7].

At this period at the turn of the 20th century advances in anaesthesia had allowed intubation and enabled anaesthesiologists to make further developments to laryngoscopy. In 1913, in the USA, Henry Janeway developed a laryngoscope with an internal light source which was battery powered for tracheal intubation [8].

Fibreoptic endoscopy was developed in 1957 by Basil Hirschowitz and Larry Curtiss [9]. This was first used in examining the gastrointestinal tract. However, there were limits to the image quality. Harold Hopkins solved this problem in the 1950s by inventing the rod lens telescope with improved light and optics. He used rods of glass between the lenses in the rigid endoscope, thus preventing any loss of image quality [10]. The Hopkins rod lens system is still used today, but with the addition of a detachable digital chip camera head to provide a high-definition view with recording capabilities. These rigid endoscopes are used under general anaesthesia and suspension laryngoscopy to provide a detailed view of the airway. The Hopkins rods are available in various lengths and diameters, which allows them to be used with rigid bronchoscopy sets in the paediatric airway. The endoscopes are made with different angulations at the tip, ranging from 0° to 120°. A 70° endoscope enables a view of the anterior commissure and ventricle (the area between the true and false vocal cords), which is important when assessing vocal fold tumours.

The first fibreoptic bronchoscope was developed in the 1960s in Japan by Shigeto Ikeda [11]. The fibreoptic flexible endoscope continued to develop over the 20th century

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with the addition of working channels and suction. Further advances in flexible endoscopes, including distal chip or "chip-on-tip" systems, have virtually confined indirect laryngoscopy to the history books. Recent advances in technology have greatly improved the quality of modern flexible endoscopes. The "chip-on-tip" endoscopes provide high-definition image quality not seen previously with flexible endoscopes [12]. Digital recording allows laryngoscopy to be documented, analysed and demonstrated to patients.

Flexible nasoendoscopy

Flexible nasoendoscopy is now the main method for performing diagnostic laryngoscopy. In the ENT clinic it is used to assess the nasal cavity, pharynx and larynx. It is also used by speech and language therapists (SLTs) to perform swallow assessments. This is known as a fibreoptic endoscopic evaluation of swallowing. Unlike flexible bronchoscopes, standard nasoendoscopes have no suction or port for instrumentation. This makes them cheaper, easier to clean, portable and readily available.

The flexible nasoendoscope is passed along the floor of the nose and directed at the post-nasal space to assess the larynx. There are numerous sizes of nasoendoscopes and an ultra-thin (2.2 mm diameter) flexible nasoendoscope is available to assess the neonatal airway [13]. Nasoendoscopy is well tolerated by patients. Topical anaesthesia, decongestant or lubricant can be used, although there is no clear evidence in the literature if these provide any benefit [14].

Flexible nasoendoscopy is a safe procedure with most patients only experiencing mild discomfort. The endoscopist must be careful not to cause trauma to the nasal mucosa, which can cause epistaxis (although normally only mild). In patients with a strong gag reflex, retching and vomiting can occur, and the scope should be withdrawn to prevent further discomfort. In patients with acute airway oedema, nasoendoscopy may cause further airway compromise and should only be performed by a specialist in a safe environment.

Training in flexible nasoendoscopy is performed routinely by ENT, anaesthesiology and SLT trainees. In the authors' department the trainees first perform nasoendoscopy on a plastic model to help them become familiar with the equipment and demonstrate the anatomy. This is followed by practice on other trainees before supervised use on patients. The use of a camera and a video display helps to demonstrate the anatomy and to teach useful tips and manoeuvres to visualise anatomical structures. ENT trainees in the UK, as part of their syllabus, have to complete a work-based assessment in direct observation nasoendoscopy procedures. The Royal College of Speech and Language Therapists produced a position paper in 2008 on nasoendoscopy, which includes recommendations on achieving adequate competencies and training [15].

For detailed assessment of vocal fold movement and vibration, rigid endoscopes have traditionally been used due to the improved image. Rigid 70° or 90° rigid endoscopes are passed through the mouth and positioned just beyond the tongue base. This provides an excellent image of the vocal folds and, together with the use of stroboscopy, demonstrates the mucosal waveform of the vocal folds. Laryngeal stroboscopy creates an apparent slow-motion video by sampling successive phases of the vocal fold cycle.

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Office-based procedures in laryngology

Office-based procedures in laryngology have been performed since the first descriptions of visualising the larynx. In 1865, Mackenzie [5] described how to apply remedies to the larynx with the aid of the laryngoscope. This required a great deal of skill and cooperation from the patient to use a laryngeal mirror and curved forceps on the larynx. The development of safe general anaesthesia and the operative microscope enabled the majority of laryngeal procedures to be performed under general anaesthesia. More recently there has been a drive towards redeveloping office-based procedures in laryngology using topically applied anaesthesia. The various laryngeal procedures include injection of botulinum toxin, vocal fold medialisation, biopsies of laryngeal lesions, and laser treatment for laryngeal papillomatosis and laryngeal dysplasia [16]. Some of these procedures require a flexible endoscope with a channel to pass instruments or a laser fibre. The KTP (potassium titanyl phosphate) laser can be passed *via* the endoscope through a small channel. The KTP laser has a wavelength of 532 nm, corresponding to a greater absorption for oxyhaemoglobin. Thus, the light is well absorbed by haemoglobin and pigmented tissue. The KTP laser has been used for treating both laryngeal papillomatosis and laryngeal dysplasia in the clinic [17]. The arrival of the carbon dioxide (CO_2) laser "fibre" system has also allowed its use in the clinic setting.

In specialist voice clinics the laryngologist works closely with SLTs. The development of digital cameras attached to the endoscope allows joint assessment of laryngeal function. Patients with vocal fold immobility due to malignancy often present with a weak, breathy voice. If they are not medically fit for general anaesthesia then vocal fold augmentation or

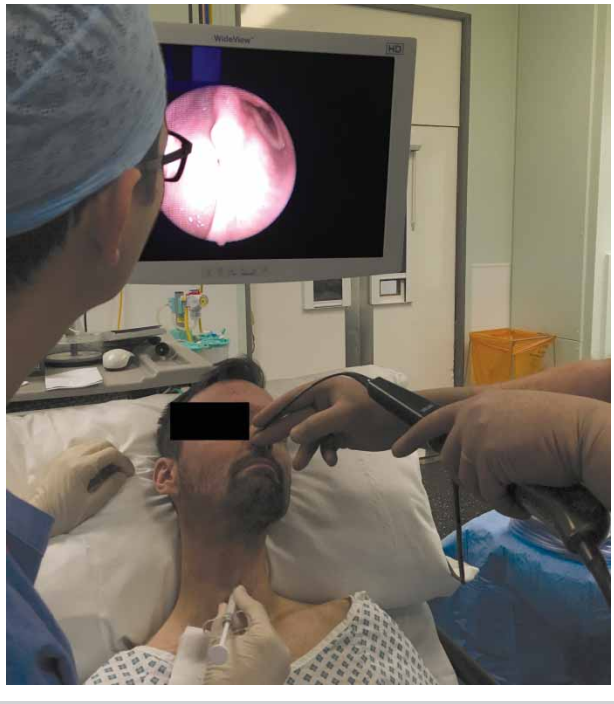

Figure 1. Vocal cord medialisation under local anaesthesia. Image taken by the authors with patient consent.

medialisation can be performed in the clinic with the assistance of the SLT (figure 1). Optimising the amount of material injected into the vocal fold will enable good vocal fold contact and ultimately improved phonation and swallowing safety [18].

Suspension laryngoscopy

Although nasoendoscopes and flexible bronchoscopes allow assessment of the airway under local anaesthetic or sedation, there are some clear advantages to performing suspension laryngoscopy under general anaesthesia. The rigid laryngoscope is essentially a metal tube with a handle. The handle allows for insertion and removal, but also the attachment of a suspension arm (figure 2). This method enables the surgeon to have a more detailed view of the airway and perform more invasive procedures that would not be tolerated under local anaesthesia.

This "shared airway surgery" requires the surgeon to work closely with the anaesthetist, and each must know the skills and limitations of the other in the event of airway obstruction. In suspension laryngoscopy, a subglottic jetting catheter or an ETT can be inserted *via* the laryngoscope to support the airway and improve ventilation. Jet ventilation anaesthesia provides a tubeless field, *i.e.* no intubation or ETT *in situ* during the procedure. This provides its own challenges to the anaesthetist, but it is vital to have this unhindered view of the larynx and airway so that assessment and procedures can be performed.

In the authors' department anaesthetists induce general anaesthesia with an intravenous bolus of propofol 3 $mg \cdot kg^{-1}$, fentanyl 1–1.5 $\mu g \cdot kg^{-1}$ and atracurium 0.5 $mg \cdot kg^{-1}$ for muscle relaxation. The vocal cords are sprayed with lidocaine at 4 mL of 4% solution through an atomiser device. Intermittent positive pressure ventilation is established using a classical laryngeal mask airway (LMA). Once ventilation is established, the patient is transferred from the anaesthetic room to the operating theatre. The LMA is only removed when the surgeon is ready to perform suspension laryngoscopy and supraglottic jet ventilation can take place. Total *i.v.* anaesthesia is maintained using an infusion of propofol and alfentanil. At the end of the operation, the laryngoscope is removed and the LMA is re-inserted to support intermittent positive pressure ventilation. At this stage, neuromuscular block is antagonised

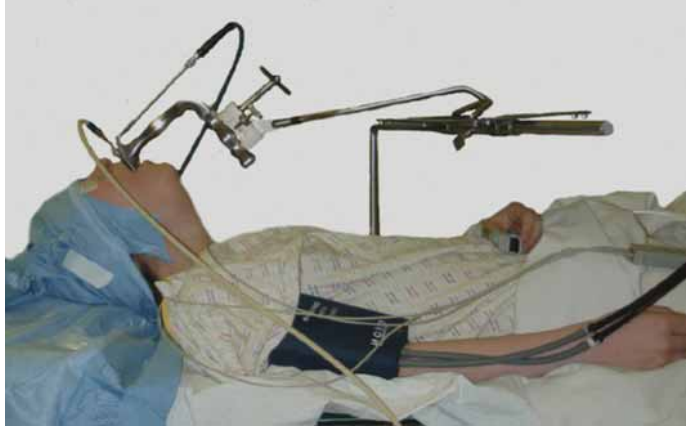

Figure 2. Suspension laryngoscopy. Reproduced from [19] with permission.

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with neostigmine and glycopyrrolate. The exception to the use of a LMA is in a patient who already has a tracheostomy in place. This can be used for intermittent positive pressure ventilation. The tracheostomy can be removed and the stoma covered with a wet swab to allow unencumbered access to the airway for surgery, while performing supraglottic jet ventilation.

Supraglottic jet ventilation delivers 100% oxygen jets, about 100 times per minute, *via* a cannula attached to the laryngoscope (figure 3), but can also be delivered using a subglottic catheter [20] or transtracheal needle [21]. The jetting can be performed using a hand-held jetting device such as the Manujet (VBM, Sulz am Neckar, Germany) or an automated machine such as the Mistral or Monsoon III (Acutronic, Baar, Switzerland) [22]. The automated systems have a "cut-out" safety system if there is an obstruction to jetting. This minimises the risk of a pneumothorax. Paediatric suspension laryngoscopy and airway surgery is performed with a spontaneously breathing child. The adult physiology does not allow for a spontaneously breathing, yet deeply sedated patient. Traditionally, jet ventilation in a young child was also contraindicated because of a much higher risk of a pneumothorax. However, there are newer jet ventilation machines that use a double-jet technique (*e.g.* TwinStream; Carl Reiner, Vienna, Austria) that can be used in patients of all ages [23]. The double-jet technique allows ventilation at two different pressure levels and different frequencies. This enables CO_2 levels to be regulated, minimising the risk of a pneumothorax, and can be used for longer periods in obese patients before desaturation [23].

The THRIVE (Transnasal Humidified Rapid Insufflation Ventilatory Exchange) technique using the OptiFlow (Fisher and Paykel Healthcare, Auckland, New Zealand) high-flow oxygen delivery system to maintain oxygenation while conducting airway procedures has recently been introduced [24]. Although this has a definite role in cases where it is difficult to access the airway for intubation, it should be used with caution if there is any kind of fire risk.

When conducting suspension laryngoscopy the patient is positioned in the supine position with a head ring in place. "Sniffing the morning air position" is a good description of the

Figure 3. Dedo-Pilling laryngoscope (Pilling, Horsham, PA, USA) (left) with a transtracheal cannula (centre) and subglottic jetting cannula (Hunsaker subglottic jet ventilation tube; Medotronic Xomed Inc., Jacksonville, FL, USA) (right). Reproduced from [19] with permission.

optimum position for visualisation of the larynx. The neck is flexed and the head is extended. Flexion of the head is achieved by using the articulated head of the operating table. There are a variety of rigid laryngoscopes available to surgeons. The authors use only two types of laryngoscope: the Dedo-Pilling laryngoscope (Pilling, Horsham, PA, USA) and the Lindholm laryngoscope (Karl Storz, Tuttlingen, Germany). The Dedo-Pilling laryngoscope tip lies beyond the epiglottis just above the vocal folds. It is used for an optimal view of the vocal folds, subglottis and trachea. The Lindholm laryngoscope tip sits in the vallecula and provides a good view of the supraglottis. Once the laryngoscope is in position it is placed in suspension using a suspension arm (*e.g.* the Lewy suspension arm) resting on a platform that is attached to the operating table. Figure 4 shows the theatre layout during suspension laryngoscopy.

Formal airway assessment can take place once the suspension laryngoscope is in place and the patient is being jet ventilated adequately. A rigid 0° Hopkins endoscope is passed through the laryngoscope so that the larynx, subglottis, trachea and bronchi are assessed.

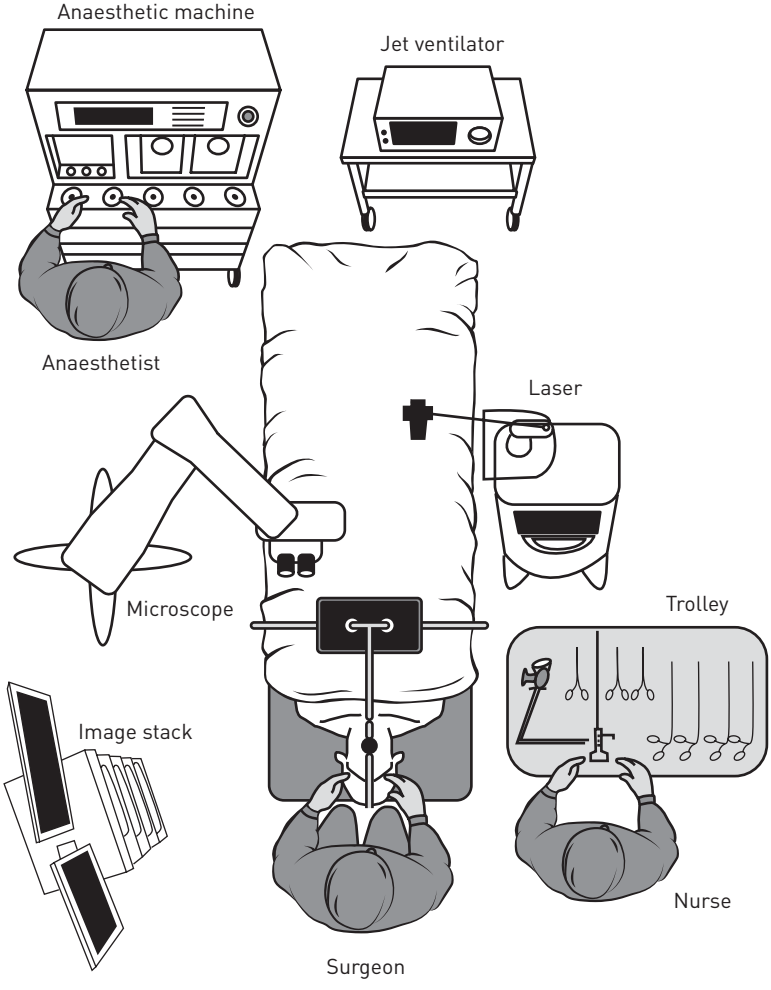

Figure 4. Layout of the operating room during suspension laryngoscopy. Reproduced and modified from [19] with permission.

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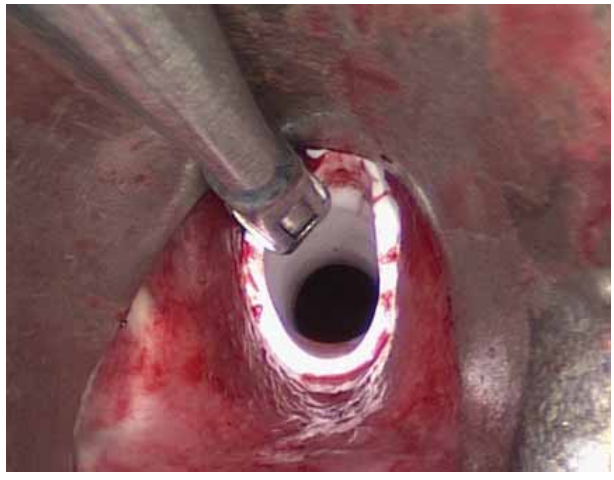

Figure 5. Silicone stent inserted into the trachea with grasping forceps. Intra-operative image taken by the authors with patient consent.

Images and videos of the airway can be recorded on an image stack. The operating microscope can then be brought into position. The working distance for the microscope is set at 400 mm to allow for a working area between the laryngoscope and the microscope. The CO_2 laser can be attached to the microscope *via* an articulating arm. The microscope has a micromanipulator attachment that allows control of the laser spot by the surgeon, and the beam is delivered by a "line-of-sight" technique to the larynx and airway. There are different power settings for the laser, and the size of the laser spot and the focus can also be altered. For an accurate incision, a small spot size is used with a high power density. The effects on the surrounding tissues will also depend on the wavelength, power and duration of the laser. To minimise thermal damage to the surrounding tissues, pulsing of the laser can be performed which still allows a high-density delivery [25]. A super-pulse setting allows high energy, delivered at up to 1000 pulses·s^{-1}, permitting tissue cooling between these pulses yet averaging the same total energy delivery. This allows for less thermal injury and less carbonisation of tissues.

A CO_2 laser fibre is also now available which allows the laser to be used where line-of-sight delivery is not possible [26]. The laser fibre system works by allowing the laser beam to bounce off the inside of a reflective metal tube with an outer sheath through which a cooling gas is passed. The laser fibre is useful for operating in the distal airway where

Figure 6. Stenting forceps with Dumon "Y"-stent.

line-of-sight surgery is not possible. It is also a useful tool where the laryngoscopy access is restricted due to anatomical reasons (*e.g.* prominent teeth, neck fixation and retrognathia).

When using any kind of laser there must be no flammable material in the airway such as an ETT, tracheostomy or stent. The jet ventilator's oxygen delivery does not need to be reduced under these circumstances, but all theatre laser safety protocols need to be followed and staff to have been trained appropriately [27].

Suspension laryngoscopy allows two hands free for surgery with the additional use of the microscope. Silicone stents (both straight and "Y"-shaped) can be delivered directly with grasping forceps without the need for special insertion devices (figures 5 and 6). In addition to lasers, balloons, cryoprobes and microdebriders, this technique can incorporate all the tools used in flexible bronchoscopy.

Bronchoscopy under suspension

Suspension laryngoscopy also allows for closer working with the interventional pulmonologist, who can at the same time use flexible endoscopes to manage lower airway problems (figure 7). Suspension laryngoscopy with jet ventilation and flexible bronchoscopy enables procedures to be performed on the distal airway without periods of apnoea [28]. This allows procedures such as dilatation and airway stent insertion to be undertaken in a more controlled manner. In these multidisciplinary theatre lists, the patient generally has a dynamic flexible bronchoscopy prior to paralysis and ventilatory support.

Future of laryngoscopy

There have been continual advances in laryngoscopy as technology improves and becomes more accessible. Current "chip-on-tip" endoscopes provide high-definition views of the larynx and are becoming readily available, replacing the more expensive fibreoptic and rigid endoscopes. The wavelength of the endoscope light can be changed, known as NBI. This imaging technique uses light of specific wavelengths to enhance the surface mucosa,

Figure 7. Flexible bronchoscopy *via* suspension laryngoscopy. Image taken by the authors with patient consent.

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Figure 8. Continued laryngeal examination during swimming. Reproduced with kind permission of J.H. Hull (Royal Brompton Hospital, London, UK), with patient consent.

helping to identify abnormal mucosa such as dysplasia and malignancy [29]. Disposable endoscopes have allowed emergency laryngoscopy to be readily available for anaesthetists and are now part of their difficult airway equipment [30]. Laryngeal telemetry is a concept that is now possible with the modern equipment currently available. Continued laryngeal examination enables examination of the larynx during exercise, *e.g.* running or swimming (figure 8), and is now the gold standard test for diagnosing exercise-induced laryngeal obstruction [31, 32].

In patients with laryngeal dysfunction a provocation laryngoscopy can be helpful in both diagnosis and treatment. Allowing the patient to view their laryngoscopy findings will improve the patient's understanding of their condition. It also allows SLTs and physiotherapists to demonstrate the benefits of different therapy techniques to the patient under laryngoscopy [33].

Conclusion

Laryngoscopy is an essential tool in examining and treating patients with laryngeal symptoms and pathology. Flexible endoscopy is well tolerated by patients, and its popularity continues to grow with other medical specialists and allied medical professions. Clinic-based procedures in laryngology have regained popularity and rely on modern laryngoscopy techniques. Suspension laryngoscopy provides an unrivalled view of the airway and allows intricate procedures to be performed, using all modalities of intervention, jointly with the pulmonologist if required. It also allows for easy access for ventilation tubes and different ventilation methods in the event of airway obstruction.

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Early cancer detection

Renelle Myers[1,2] and Stephen Lam[1,2]

Lung cancer is the leading cause of cancer deaths worldwide as the majority of patients have advanced disease at diagnosis. Detection and early treatment of pre-invasive and minimally invasive lung cancer can significantly improve the current 5-year survival of <18%. Endoscopic optical imaging (such as autofluorescence imaging), NBI and OCT provide sensitive means to rapidly scan the central airways, in order to detect early lung cancer for biopsy confirmation and delineate the extent of the tumour spread to guide treatment. However, with the worldwide shift in lung cancer cell type to adenocarcinoma and the increasingly smaller lung lesions found by screening low dose CT, it is necessary to develop miniature imaging probes and better biopsy catheters to enable biopsy under real-time imaging.

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With an estimated 1.8 million new cases and 1.6 million deaths in 2012, lung cancer is the most common cause of cancer death worldwide [1]. Clinical interventions over the last 40 years have had a minimal effect on lowering lung cancer death. The 5-year survival rate for lung cancer patients is currently <18%; this is because most are diagnosed when they become symptomatic with advanced incurable disease [2]. When stratified by stage, 70% of lung cancer patients who are diagnosed early (stage IA) survive ⩾5 years, compared to <5% of those diagnosed late (stage IV). Improvements to early detection therefore hold significant promise in reducing mortality from this devastating disease. It is important to be able to detect *in situ* and minimally invasive lung cancers because of the survival advantage when detected early. Stage 0 (carcinoma *in situ* (CIS)), or micro-invasive, disease has a survival of >90% [3, 4]. Early malignancies can be adequately treated with minimally invasive endoscopic methods such as electrocautery, PDT [5] or cryotherapy [5–9]. In spite of the improved imaging capability of video bronchoscopy, early central type lung cancers remain difficult to detect with white light bronchoscopy; this is because these lesions are usually small and relatively flat, with subtle endobronchial changes [10]. Peripheral lesions in small airways or lung parenchyma are beyond the visible range of comparatively larger size standard video bronchoscopes. Advances in photonic imaging methods and fibreoptic probes offer advanced capabilities to use visible and

[1]Dept of Integrative Oncology, British Columbia Cancer Agency, Vancouver, BC, Canada. [2]Dept of Medicine, University of British Columbia, Vancouver, BC, Canada.

Correspondence: Renelle Myers, 675 West 10 Avenue, Vancouver, British Columbia, Canada, V5Z 1L3. E-mail: renelle.myers1@bccancer.bc.ca

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near-infrared light to identify the early morphological, and biochemical changes occurring in the airways in pre-invasive and early invasive bronchial cancers. Photonic imaging is based on the physical phenomena that result when the bronchial surface is illuminated by light. Light can: 1) be reflected from the surface (specular reflection); 2) be absorbed; 3) induce autofluorescence; 4) travel in the bronchial tissue; 5) be back-scattered at the same wavelength as the incident light (elastic scattering); or 6) be scattered at a different wavelength (inelastic or Raman scattering) due to light energy modification by the vibrational state of molecules [11]. The simplest and most commonly used bronchoscopic imaging method is white light bronchoscopy (WLB). This method makes use of the specular reflection, back-scattering and absorption properties of broadband visible light from ~400 nm to 700 nm, allowing it to define the structural features of the bronchial anatomy and surface features, in order to detect abnormal tissues. NBI, often used in conjunction with high magnification video bronchoscopy, [12–14], uses narrow band blue light centred at 415 nm coupled with green light centred at 540 nm (corresponding to the maximal haemoglobin absorption peaks) to highlight the vasculature of the airways. The blue light highlights the superficial capillaries while the green light penetrates deeper to highlight the larger blood vessels in the submucosa, providing a more detailed image of the microvasculature in pre-neoplastic and neoplastic lesions corresponding to the altered angiogenesis process.

This chapter reviews the principles of photonic imaging, the clinical application of these principles and the clinical trials supporting their ability to detecting early lung cancers.

Autofluorescence imaging and NBI

AFB uses fluorescence and absorption properties to provide information about the biochemical composition and metabolic state of bronchial tissues [11]. Bronchial tissue's fluorescence properties are determined by the distribution of fluorophores, their distinct excitation and emission spectra, metabolic state and the tissue architecture. Autofluorescence also depends on the light attenuation (wavelength-dependent) concentration and distribution of non-fluorescent chromophores, such as haemoglobin [11]. Most endogenous fluorophores are either involved in the cellular metabolic processes or are associated with the tissue matrix. The most important fluorophores are structural proteins, such as collagen and elastin, and those involved in cellular metabolism, such as nicotinamide adenine dinucleotide (NADH) and flavins. Other fluorophores include the aromatic amino acids, various porphyrins and lipopigments.

When illuminated with violet or blue light (380–460 nm), normal bronchial tissues fluoresce strongly in the green (480–520 nm). When dysplasia or a neoplastic tissue is present in the bronchial epithelium, there is a progressive decrease in green autofluorescence and a proportionately less decrease in the red fluorescence intensity. These differences are caused by: the breakdown of stromal collagen cross-links; an increase in cellular metabolic activity leading to changes in NADH; flavin adenine dinucleotide coenzymes; and increased absorption of the excitation violet/blue light by haemoglobin due to angiogenesis. There are also changes in the light scattering process caused by an increase in nuclear size, cellular density and distribution of the cells associated with lung cancer development. An excitation wavelength of 405 nm produces the highest tumour to normal tissue light intensity and chromatic contrast [11, 15, 16].

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The fluorescence differences seen at 480–700 nm in normal, dyplastic and neoplastic tissues have provided a basis for the design of several autofluorescence endoscopic imaging devices. These devices are in clinical use for the localisation of early lung cancer in the bronchial tree [17]. In 1991, Palcic *et al.* [18] and Lam and co-workers [19, 20] reported using tissue autofluorescence for fluorescence diagnosis. Until then, an exogenous agent *via* injection had been required, which caused photosensitivity in the patient. When using autofluorescence alone, normal tissue appears green and abnormal areas appear reddish brown due to reduced green autofluorescence but maintenance of or an increase in red autofluorescence in dysplastic and neoplastic lesions. Commercially available AFB devices optimise the image quality through a combination of autofluorescence and reflectance imaging. Small amounts of reflected light (blue, green or near infrared) are used to form a reflectance image; this image enhances the chromatic contrast and normalises the green autofluorescence image to correct for non-uniformity caused by optical and geometrical factors, such as variable distances and angles between the endoscope tip to the bronchial surface [18, 19]. Depending on the type of reflected light used to combine with the fluorescence image, abnormal areas may appear brownish red, red, purple or magenta, while normal areas are green or light blue (table 1) [20–26]. Some devices allow white-light and fluorescence images to be displayed simultaneously [26, 27].

Several meta-analyses and multicentre studies demonstrate the ability of AFB alone, or in addition to WLB, to improve the detection rate of precancerous lesions [28, 29]. Sun *et al.* [28] evaluated 21 studies involving 3266 patients. The pool relative sensitivity on a per-lesion basis of AFB plus WLB *versus* WLB alone to detect intraepithelial neoplasia and invasive cancer was 2.04 (95% CI 1.72–2.42) and 1.15 (95% CI 1.05–1.26), respectively.

Table 1. AFB devices

Device	Bronchoscope	Excitation light nm	Fluorescence nm	Reflectance nm	Image composition	Abnormal lesion
Onco-LIFE	Fibrescope	395–445	500–720	675–720	Green fluorescence, red reflectance	Reddish brown/ red on green background
SAFE-3000	Video endoscope	408	430–700	408	Green/red fluorescence, blue reflectance	Purple on bluish green background
AFI	Video endoscope	395–445	460–490	550–610	Green fluorescence, green and red reflectance	Magenta/purple on green background
DAFE	Fibrescope	390–470	500–590	650–680	Green fluorescence, red reflectance	Red on green background
D-Light	Fibrescope	380–460	⩾480	380–460	Green/red fluorescence, blue reflectance	Purple on bluish green background
ClearVu Elite	Fibrescope	400–450	470–700	720–800	Green fluorescence, red reflectance	Reddish brown/ red on green background

Manufacturers' details are as follows. Onco-LIFE: Novadq, Richmond, BC, Canada. SAFE-3000: Pentax-Hoya Corp., Tokyo, Japan. AFI: Olympus Corp., Tokyo, Japan. DAFE: Wolf, Knittlingen, Germany. D-Light: Storz, Tuttingen, Germany. ClearVu Elite: Perceptronix Medical Inc., Vancouver, BC, Canada.

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The pool relative specificity on a per-lesion basis of AFB plus WLB *versus* WLB alone was 0.65 (95% CI 0.59–0.73). AFB plus WLB is better than WLB alone in detecting pre-invasive lesions but there is not a lot of gain for invasive cancers. The lower specificity of AFB is due to false-positive changes related to inflammation and bronchoscopic trauma. As discussed later, training may also be an issue, with different colour schemes by different device manufacturers. Bronchoscopic trauma can be minimised by cough suppression and avoiding airway wall contact, as well as reducing suction during the bronchoscopic examination.

As NBI enhances visualisation of normal blood vessels and abnormal vasculature associated with the angiogenesis process and is less susceptible to artefacts from trauma and inflammation, a randomised trial was performed comparing AFB and NBI with WLB [30]. The sensitivity of WLB was 0.18 and the specificity was 0.88. In comparison with WLB, AFB had a slightly but not significantly higher sensitivity than NBI (3.7 *versus* 3.0). NBI has a comparatively higher specificity than AFB (1.0 *versus* 0.5). Combining AFB and NBI did not increase diagnostic yield significantly. Zhang *et al.* [29] reported a meta-analysis that compared WLB, AFB and NBI. The study included 53 studies (39 WLB, 39 AFB, 17AFB and WLB, and six NBI), involving 6543 patients with 18458 biopsies. It showed a sensitivity and specificity of: 54% (95% CI 46–61%) and 79% (95% CI 73–84%), respectively, for WLB; 87% (95% CI 82–90%) and 65% (95% CI 58–72%), respectively, for AFB; and 96% (95% CI 78–99%) and 84% (95% CI 70–92%), respectively, for NBI. A meta-analysis by Iftikhar and Musani [31], involving 632 patients who underwent NBI in eight studies, showed a sensitivity of 0.80 (95% CI 0.77–0.83) and a specificity of 0.84 (95% CI 0.81–0.86). Data from studies where NBI and AFB were used together showed a pooled sensitivity and specificity of 0.86 (95% CI 0.82–0.89) and 0.75 (95% CI 0.71–0.79), respectively. NBI had a high sensitivity and specificity, with both at >80% when assessing the range of pathology from hyperplasia to invasive lesions; however, when narrowing the pathology criteria from moderately dysplasia to invasive cancer, the specificity dropped to 43% [29]. Therefore, NBI appears to perform well for cancerous lesions but no conclusion could be reached for NBI's performance when detecting precancerous lesions. Additional studies are needed.

Angiogenesis takes place relatively early in lung cancer pathogenesis [32]. NBI is able target the angiogenic features of neoplasia, improving the detection of pre-invasive lesions and differentiating these lesions from invasive carcinoma. The progressive pattern of neovascularisation correlates with the progression of invasiveness. Dotted vessels, increased vessel growth and complex networks of tortuous vessels of various sizes are observed with angiogenic squamous dysplasia. Dotted vessels and small spiral or cork-screw type tumour vessels are observed with CIS. In micro-invasive or invasive lung cancer, prominent spiral or cork-screw type tumour vessels of various sizes and grades are visible [12, 33].

Photonic imaging is also used by head and neck surgeons to examine vocal cord abnormalities and help guide biopsies. The addition of both AFB and NBI has a higher sensitivity and specificity than WLB alone in predicting malignant and premalignant lesions based on the vascular pattern surrounding the lesion. For bronchoscopists it can guide referral for concerning vocal cord lesions, as biopsies can often lead to dysphonia [34–36].

Recognition of abnormal vascular patterns for biopsy using NBI requires training. Development of an image-based program to teach NBI and other image-enhanced endoscopic technologies to identify areas for biopsy and for competency assessment is an

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important step in the realisation of the clinical benefits of new technologies (figure 1) [37]. The lack of standardisation by AFB manufacturers using different technology platforms (such as autofluorescence with green autofluorescence alone, green and red autofluorescence or a combination of autofluorescence and reflectance imaging (table 1)) makes developing training and competency testing tools that are similar to NBI very challenging. This may be a significant factor contributing to the low specificity of AFB. When using an objective measure by quantifying the red to green fluorescence ratio (R/G) of the target lesion during the bronchoscopic procedure, at a sensitivity of 85% to detect moderate/severe dysplasia and CIS, the specificity of AFB was found to be 80%. The specificity further improved to 88% by combining the R/G ratios with the visual score [38]. A higher false-positive rate was also

a)

Chose the type of pathology for this area	What is your confidence with this analysis?	Optional comments
Normal mucosal vessel	1) Very unsure	
Normal submucosal vessel	2) Pretty unsure	
Abnormal mucosal end-on vessels	3) Pretty sure	
Abnormal mucosal dilated vessels	4) Definitely sure	
Abnormal mucosal convoluted vessels		
Abnormal submucosal vessel		

b)

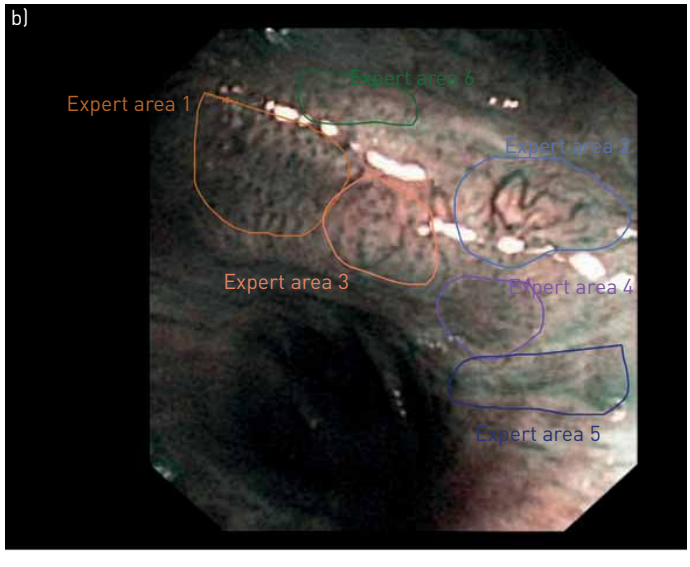

Figure 1. Example of dotted (end-on) blood vessels and spiral (convoluted) blood vessels visualised by NBI. a) The areas were marked by experts for a quiz used in training. The trainee must choose the type of pathology from the list and state their degree of confidence (options 1–4) for each area. There is also an area for comments. In this example, the areas in b are as follows. Expert area 1: abnormal mucosal end-on vessels; expert area 2: abnormal mucosal convoluted vessels; expert areas 3 and 4: abnormal mucosal end-on vessels; expert area 5: normal submucosal vessels; expert area 6: abnormal end-on vessels. Reproduced with the kind permission of Dr David Fielding (Royal Brisbane and Women's Hospital, Brisbane, Australia) and Dr Cédric Dumas (Ecole des Mines de Nantes, Nantes, France).

found in a multicentre trial by EDELL *et al.* [21], in which bronchoscopists were unaware of the R/G ratios when making the visual classification of the bronchial mucosal changes. Quantitative imaging decreases intra- and inter-observer variation.

The issue of training and competency assessment also applies to WLB. New technologies like AFB and NBI force bronchoscopists to look much more carefully at the mucosa for the subtle changes indicative of early bronchial cancer (*e.g.* loss of mucosal sheen, mucosal irregularity, loss of longitudinal or circular folds and thickening of subcarina) that pioneers in bronchoscopy had meticulously described in the past (table 2) [39].

Clinical use of AFB and NBI

Current evidence supports the use of AFB and NBI in the following clinical situations.

1) In patients with severe atypia or malignant cells in their sputum cytology and a negative chest radiograph or CT scan. In comparison with WLB alone, the use of AFB and NBI improves localisation of early central bronchial cancers [40–42].

2) To define the bronchial resection margin pre-operatively for central bronchial cancers [43, 44].

3) In order to determine the extent of tumour involvement prior to endobronchial therapy with curative intent in patients with CIS/micro-invasive cancer [44, 45].

4) For the detection of synchronous lung cancer in patients with central squamous cell carcinoma (SCC) [46, 47].

5) In surveillance of patients with high-grade dysplasia and CIS for progression to invasive cancer [48, 49].

Changes in the epidemiology of both central and peripheral airway tumours

As AFB is highly sensitive in the detection of early lung cancer in the central airways, and CT can detect early lesions in the lung parenchyma, it was hypothesised that the addition of AFB to a screening chest CT can improve the detection rate of early lung cancer. This was investigated by TREMBLAY *et al.* [50] as part of the Pan-Canadian Early Detection of Lung Cancer Study, a multicentre Canadian trial. The multicentre trial performed a screening AFB

Table 2. The endoscopic findings of early lung cancer

Carcinoma *in situ*	**Submucosal invasion**	**Peribronchial extension**
Loss of luster	Loss of longitudinal striations	Vascular engorgement
Fine mucosal irregularity	Loss of circular folds	External compression
Mucosal thickening	Indistinct bronchial cartilage	
Pale mucosa		
Redness		
Nodular or polypoid lesion		

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Table 3. Size of lung cancers diagnosed in the National Lung Screening Trial

Nodule size	CT		
	Baseline	Year 1	Year 2
4–6 mm	7%	7%	7%
7–10 mm	13%	27%	28%
11–20 mm	41%	44%	41%
21–30 mm	22%	12%	11%
>30 mm	17%	5%	10%

in addition to a low-dose CT scan in the first 1300 participants from seven centres who had ⩾2% lung cancer risk over 6 years. Dysplasia, CIS or invasive cancer was detected in 5.3% of the participants. Only one typical carcinoid tumour and one CIS lesion were detected by AFB alone, with a rate of 0.15% (95% CI 0.0%-0.6%) for CT scan occult cancer. Smoking duration (OR 1.05, 95% CI 1.02–1.07) and FEV_1 % pred (OR 0.99, 95% CI, 0.98–0.99) were the only independent risk factors for finding dysplasia or CIS on AFB [50]. The study points to an important shift in the lung cancer cell type and location of tumours in the trachea-bronchial tree in recent years, such that most of the lung tumours are now beyond the range of a standard 4–6-mm flexible bronchoscope. With the exception of men in France, Spain and the Netherlands, peripherally located adenocarcinomas have now overtaken SCC as the predominant lung cancer cell type worldwide [51]. Even the location of SCC has shifted to smaller airways. With the implementation of lung cancer screening programmes using low-dose CT in the USA, Canada and other countries, the size of potentially malignant lung nodules that require a biopsy for diagnosis is also becoming smaller. For example, in the National Lung Screening Trial, 60% of the lung cancers found at baseline screening CT were ⩽20 mm, and up to 78% of the cancers in subsequent screenings were ⩽20 mm (table 3) [52, 53]. Because of the small size of these tumours, in a lung cancer screening setting, only 20–34% of screening-detected lung cancers are currently diagnosed by endoscopic methods and the diagnostic yield of bronchoscopic biopsies is modest (table 4) [52–54]. In the real world setting, even with advanced bronchoscopic methods such as navigation bronchoscopy and radial ultrasound, the diagnostic yield of peripheral lung lesions is <60% [55, 56]. Better methods and smaller devices are needed in endoscopic detection and in the diagnosis of peripheral lung cancer, especially early lung cancer ⩽20 mm. The addition of AFB and NBI to

Table 4. Mode of diagnosis and malignancy diagnostic rate of bronchoscopy, CT-guided lung biopsy and surgical resection

Modality	NSLT [52, 53]		PanCan [54]	
	Diagnostic method	Yield	Diagnostic method	Yield
Bronchoscopy	34%	55.8%	20%	55.6%
CT FNA/core	19%	66.5%	38%	81.1%
Surgery	47%	73.9%	42%	77.6%

NSLT: National Lung Screening Trial; PanCan: Pan-Canadian Early Detection of Lung Cancer Study; FNA: fine-needle aspiration.

low-dose CT scans during lung cancer screening is not recommended as there are too few CT scan occult cancers found to justify the procedure.

Optical coherence tomography

OCT is an imaging method that provides near-histologic resolution for visualising cellular and extracellular structures at and below the tissue surface [57–60]. It is similar to ultrasound, but uses near-infrared light rather than sound. The light that is back-scattered or reflected by the tissue is used to generate a one-dimensional tissue profile using optical interferometry. Two-dimensional images or three-dimensional volumetric images can be displayed by scanning the light beam over the tissue. In bronchoscopic application, the imaging procedure is performed using fibreoptic probes inserted down the instrument channel to airways of interest. The probes are miniaturised to enable imaging of airways down to the terminal bronchiole. The axial and lateral resolutions of OCT range ~5–30 μm and the imaging depth is 2–3 mm, depending on the imaging conditions. This combination of resolution and imaging depth is ideal for examining changes in the epithelium of central and peripheral airways. Unlike ultrasound, light does not require a liquid coupling medium. There are no associated risks from the weak near-infrared light sources that are used for OCT [57–61].

In time-domain OCT, a depth-resolved line profile of tissue is obtained by measuring the auto-correlation function using a low-coherence-time light source and an interferometer comprised of a variable-length reflective reference arm and a sample arm where the tissue is illuminated [59]. A signal is generated when the path length of light scattered from a particular tissue depth matches that from the reference arm. In frequency-domain OCT, the spectral density function is measured to obtain a depth-resolved optical scattering of the tissue through Fourier transformation. The spectral density function can be measured with interferometers using either a broadband light source and a spectrometer or a wavelength-swept light source and a square-law detector. This approach has been shown to provide orders of magnitude enhancement in detection sensitivity compared with time-domain OCT [62–66]. In resected lung specimens, OCT findings were found to correlate precisely with histopathology [61, 67–70]. Cartilage usually appears as a darker, signal-poor region due to its low scattering properties. OCT measurements of mean luminal diameter, inner luminal area, airway wall area and airway wall thickness percentage prior to surgical resection were found to correlate significantly with the histology, down to the 9th generation bronchi in the resected specimens [71]. A recent advance in OCT imaging is co-registered autofluorescence OCT (AF-OCT) [72, 73]. AF-OCT makes use of the same optical principles as AFB in the central airways. AF-OCT overcomes the limitation of AFB because the OCT imaging probes are much smaller than flexible video bronchoscopes, allowing access to small peripheral airways beyond bronchoscopic view (figure 2). AF-OCT allows rapid scanning of airway vasculature, which is less prone to motion artefacts compared with other approaches, such as Doppler-OCT (figure 3) [73].

Clinical studies have been performed that suggest OCT can be used to discern invasive cancer from CIS or dysplasia [70, 75]. Normal/hyperplasia is characterised by one or two cell layers above a highly scattering basement membrane and upper submucosa. The thickness of the epithelial layer increases as the epithelium changes from normal/hyperplasia to metaplasia, various grades of dysplasia and CIS. The basement membrane is still intact in CIS but becomes discontinuous or is no longer visible in invasive cancer [75].

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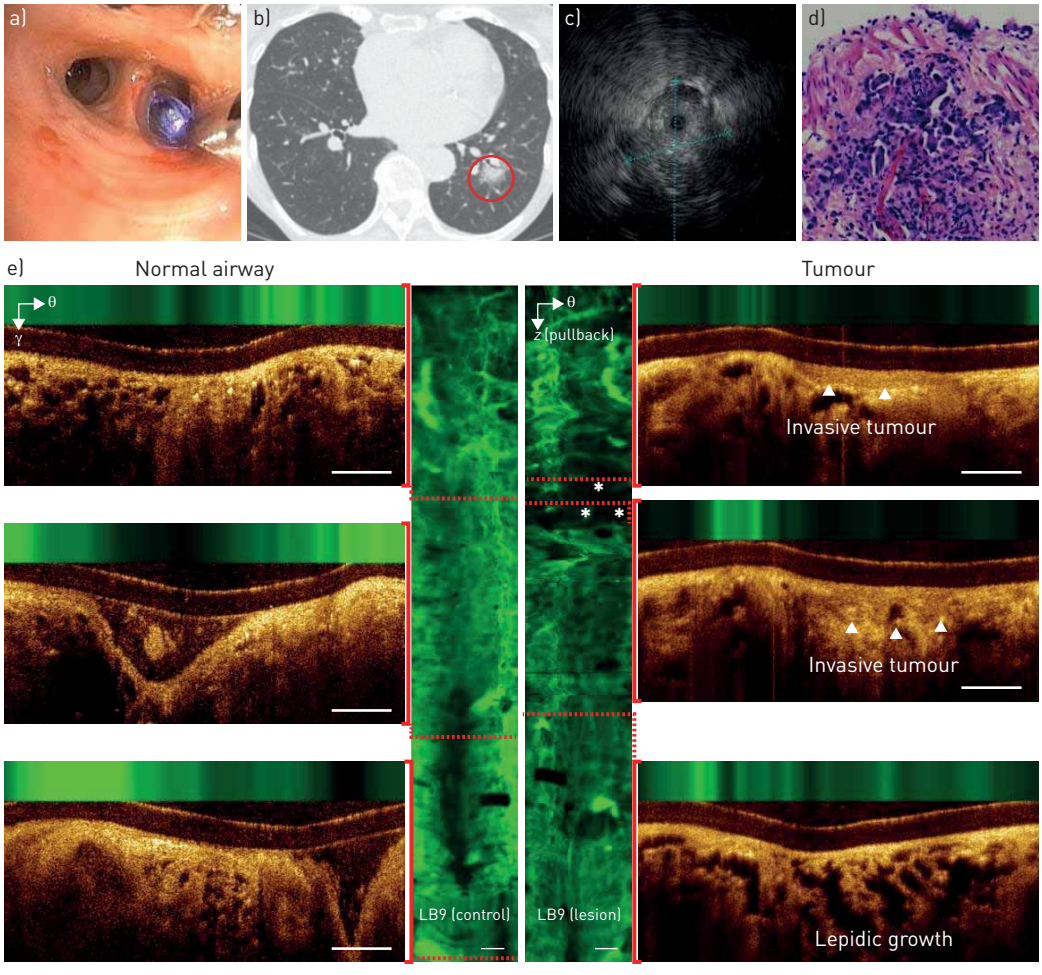

Figure 2. Example of an *in vivo* autofluorescence OCT (AF-OCT) image from a patient with a peripheral lung adenocarcinoma. a) Insertion of the AF-OCT probe into an airway. b) The CT image of the tumour in the left lower lobe. c) The radial ultrasound image of the tumour. d) The histopathology of the biopsied tumour. e) A normal airway and its corresponding AF image (green) is shown on the lower left. The invasive tumour (arrowheads) with the lepidic growth pattern is shown on the lower right. The corresponding AF image showed loss of autofluorescence in the tumour area (asterisks). Scale bars=1 mm. Reproduced and modified from [74] with permission.

The OCT features of SCC differ to adenocarcinoma [61, 67]. In centrally located bronchial cancers that are not visible with CT, it is often difficult to differentiate between CIS and invasive carcinoma using WLB, AFB or NBI, although there are qualitative NBI features (such as convoluted vessels) that tend to suggest submucosal tumour invasion [33]. EBUS has been used to determine the depth of tumour invasion into the bronchial wall [76]. The ability to diagnose the depth of tumour invasion can guide therapy. The relative accuracy of OCT *versus* balloon probe EBUS to determine the depth of tumour invasion into the bronchial wall needs be compared. However, the significant drop in the prevalence of centrally located SCC makes studies of this kind difficult.

OCT is a promising method to guide diagnosis of peripheral lung nodules. Normal lung parenchyma can be identified by the presence of signal-void alveolar spaces that appears as

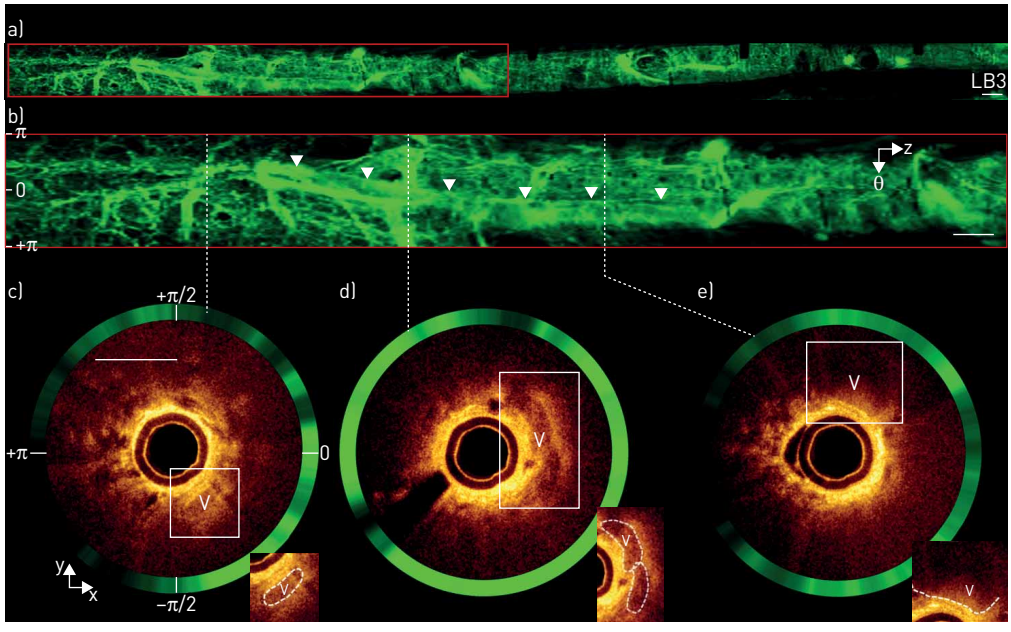

Figure 3. *In vivo* autofluorescence OCT (AF-OCT). a) *In vivo* AF image obtained from a 50-mm pullback of an airway. b) Magnified AF region enclosed by red box in a. c, d, e) OCT cross-sectional images corresponding to the dashed lines highlighting large vessels (v). Inserts show vessel segmentation. Arrowheads indicate a large blood vessel. Scale bars=1 mm. Reproduced and modified from [73] with permission.

a honeycomb-like structure. Pulmonary nodules are identified by replacement of the alveoli with solid tissue [74, 77–79]. Adenocarcinomas with lepidic growth patterns are recognised by their thickened alveolar walls (figure 2) [74]. After OCT-interpretation training sessions, clinicians can diagnose common primary lung cancers (adenocarcinoma, SCC and poorly differentiated carcinoma) with an average accuracy of 82.6% (range 73.7– 94.7%) [78]. Although OCT cannot replace the pathologist in the diagnosis of lung carcinoma, it may be useful for confirming the nature of the lesion before taking a biopsy. As OCT probes can be miniaturised, they can be inserted into biopsy needles/catheters to guide biopsy in real-time without removing the imaging probe from a guide sheath and re-inserting the biopsy forceps or needle, which creates the possibility of displacement or migration to a different airway [80]. Randomised clinical trials are required to assess the clinical utility of OCT or AF-OCT to localise abnormal lesions and guide biopsy in comparison with other methods. Radial EBUS (R-EBUS) is commonly used to confirm the location of target lesions before taking a biopsy [55, 56, 81]. The use of confocal micro-endoscopy has been investigated in the characterisation peripheral lung lesions [82, 83]. The potential advantages of OCT/AF-OCT are: probes can be as small as 0.45 mm; the resolution is significantly higher than R-EBUS; and several centimetres of airway can be scanned rapidly without the use of contrast agents. In comparison, confocal micro-endoscopy is a point monitoring method that requires the use of contrast agents [82, 83]. Besides OCT, there are emerging technologies that guide precision biopsy of peripheral lung nodules, such as a miniature 0.8-mm wide-field multispectral endoscopic imaging, which enables reflectance and fluorescence imaging [84] with a resolution superior to reflectance imaging alone using a 1-mm optical fibre [85]. These newer bronchoscopic technologies need to be evaluated in future studies.

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Conclusion

AFB and NBI are sensitive methods of detecting early lung cancer in the central airways and delineating the extent of tumour spread in order to guide treatment. OCT and AF-OCT provide high-resolution structural and functional information on airway and lung tissue, which cannot be otherwise obtained by imaging modalities such as CT or magnetic resonance imaging. To realise the clinical benefits of these new endoscopic imaging technologies, it is important that image-based programs are used to teach endoscopists how to apply these technologies and identify areas for biopsy, and for competency assessment. With the worldwide shift in lung cancer cell type to adenocarcinoma and increasingly smaller lung lesions found using low-dose CT screening, development of miniature imaging probes, more precise navigation devices and better biopsy catheters to enable biopsy under real-time imaging are needed.

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Chapter 8

Biopsy techniques

Samuel V. Kemp

Fibreoptic bronchoscopy is the predominant method for obtaining diagnostic tissue in a wide range of respiratory diseases. There are many ways to obtain such tissue, and the choice of which technique to use is determined by the location of the lesion, experience of the bronchoscopist and availability of facilities. A basic set of abilities is essential for the independent bronchoscopist, comprising of histology and cytology collection methods, *i.e.* endobronchial biopsy and TBB (histology), bronchial brushing, bronchial washing and BAL (cytology), and TBNA (histology and cytology). With this simple set of skills, it is possible to successfully target central and peripheral lesions as well as masses and lymph nodes outside of the airways, and mastery of these techniques is encouraged.

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The term "biopsy" is derived from the Greek words *bios* (life) and *opsis* (sight), and was first used in 1879 by Ernest Besnier [1], a French Dermatologist also credited with the term "lupus pernio" [2]. It is defined as "An examination of tissue removed from a living body to discover the presence, cause, or extent of a disease" [3] and is therefore not limited to forceps biopsy for the purposes of histological examination. Tissue can be obtained at bronchoscopy for the histological and cytological diagnosis of both benign and malignant disease, and can be very important in the diagnosis of infection when the appropriate microbiological samples are taken. This chapter covers the basic- and intermediate-level techniques for obtaining tissue *via* the bronchoscope, with more advanced techniques discussed elsewhere in this *Monograph* [4].

General considerations

There are a number of general considerations when one is considering sample collection at bronchoscopy. Why do you want samples: are you suspicious of malignancy, infection, parenchymal disease? How are you hoping to process those samples: histology, cytology, microbiology? Then consider where in the lung the pathology in question is: peripheral or central; in the airways, parenchyma or nodes? What comorbidities does the patient have,

Dept of Respiratory Medicine, Royal Brompton Hospital, London, UK.

Correspondence: Samuel V. Kemp, Dept of Respiratory Medicine, Royal Brompton Hospital, Fulham Road, London, SW3 6NP, UK. E-mail: s.kemp@rbht.nhs.uk

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are they on anticoagulants or antiplatelets and can they cope with the complications of sampling (*e.g.* pneumothorax after TBB)?

Training and assessment of competence in bronchoscopy is covered in more depth elsewhere in this *Monograph* [5], but every bronchoscopic sampling technique, however apparently simple, will present challenges and a learning curve, and each bronchoscopist will progress along that curve at a different rate [6]. Therefore, it is essential that tuition and supervision are provided during the learning phase for each and every technique, and that records are kept to demonstrate the maintenance of competence.

In this chapter, sampling techniques have been split into: 1) basic techniques: endobronchial biopsy, bronchial brushings and bronchial washings (*i.e.* those that are most commonly used and easiest to learn) and 2) intermediate techniques: TBB, BAL and TBNA (generally variations on basic techniques that require more practice and skill, but should still be part of the basic armoury of any independent bronchoscopist).

Most of the yield and sensitivity data for bronchial sampling techniques have been collected in the context of malignant airways disease (also see Myers and Lam [7]) and although this is the focus of most of the evidence presented here, benign disease is discussed where appropriate, especially for intermediate techniques. Also discussed where relevant is how to combine techniques to ensure the highest possible yields.

Basic techniques

Endobronchial biopsy

The predominant aim of bronchial biopsy is to obtain a small piece of tissue that contains all the relevant structures and cells for appropriate histological analysis. However, in cases where there is the suspicion that endobronchial abnormalities result from infection (*e.g.* tuberculosis and fungal disease), biopsy specimens can also be sent for tissue culture. The indication for bronchial biopsy is usually to sample abnormal tissue visualised in the airways to confirm or refute the diagnosis of suspected malignancy (primary or secondary), but is also useful in the diagnosis of benign airway pathology, such as conditions of an infiltrative or inflammatory nature (*e.g.* sarcoidosis, amyloidosis and tracheobronchopathia osteochondroplastica). Biopsy can also be used to confirm the presence of normal tissue, such as at previous resection sites or when monitoring areas of previous dysplasia or carcinoma *in situ*.

The vast majority of endobronchial biopsies, however, are for the diagnosis of suspected malignancy and endobronchial biopsy is the most reliable technique for obtaining a diagnosis in cases where a lesion is visible at bronchoscopy. Location, lesion accessibility, operator experience and tumour type are all factors in determining yield. The overall yield quoted for forceps biopsy in the literature is predominantly within the range of 74–85% [8–14], although that from exophytic tumours in the central airways has been documented at >90% [15–17]. Yield can be increased further with the addition of brushings and washings for cytological examination [10, 18–20].

Once a visible lesion has been identified, the bronchoscopist passes the forceps through the working channel of the bronchoscope. The forceps are opened and then advanced onto (or

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into) the lesion and closed when sufficient tissue is felt to be within the jaws of the forceps. The forceps are removed from the working channel and the sample placed in the desired transport medium for transfer to the laboratory for processing. Guidelines suggest that at least five biopsies are taken from visible tumours, such that enough tissue is retrieved to ensure diagnostic material is obtained, and that further molecular and genetic testing can be performed as appropriate [21]. Ideally a subepithelial area of at least 0.3–0.5 mm^2 is required; it may be necessary to take more biopsies if the mass appears necrotic.

Greater than 50% of lung cancers involve the central airways [22], with >80% of some tumour subtypes visible at bronchoscopy [14]. However, there has been a shift in histological subtypes of lung cancer over the last 40 years or so, with a greater proportion of adenocarcinomas and a decreasing proportion of squamous and small cell lung cancers, at least partly due to changing smoking habits (figure 1) [23]. Adenocarcinomas have a greater predilection for the peripheral lung, and squamous and small cell cancers for the central airways, which has led to a greater number of lesions invisible to the standard bronchoscope. For these tumours, the yield is lower and more advanced techniques need to be employed, some of which are discussed later in this chapter and elsewhere in this *Monograph* [4].

Several types of forceps are available (figure 2). Forceps with a central spike can assist with anchoring to a smooth, hard, tumour where other forceps may simply slide off as they are closed. However, the choice of forceps is usually down to operator preference and there is no good evidence that yield or performance is affected by cup design. Some forceps are equipped with a swing-jaw mechanism, which can allow for tangential biopsies to be taken.

Biopsies are immediately fixed in formalin in the bronchoscopy suite and embedded in paraffin wax blocks on arrival at the laboratory. Sections are then cut onto glass slides and stained with haematoxylin/eosin, although other targeted stains can also be used in certain situations (*e.g.* Masson's trichrome for the collagenous connective tissue of pulmonary fibrosis). Additional sections can then be cut for immunohistochemistry and molecular testing as appropriate.

Complications from simple forceps biopsy of visible lesions are rare. Statistics for bleeding rates are difficult to determine, as the definition of what constitutes a "significant" bleed is variable, and accurately measuring blood loss can be impossible owing to the admixture of secretions, saline and other instilled liquids, but clinically significant bleeding following endobronchial biopsy is seen in <0.5% of cases [24]. Bleeding requiring intervention is usually the preserve of therapeutic rather than diagnostic procedures. Several patient factors have been associated with an increased risk of bleeding at bronchoscopy, including renal failure [25] and the use of anticoagulant or antiplatelet medication [26], and these should be taken into account when deciding whether to undertake a biopsy. Thrombocytopenia has been associated with bleeding following BAL [22], but there are no robust statistics available for the risk following endobronchial biopsy.

Bronchial brushings

Bronchial brushings involve the collection of cells and material from the airway epithelium, tumour or other abnormality using a catheter-based flexible bush. The technique is simple and relatively cheap, but only provides cytology and therefore cannot give information about invasion. Covered brushes can also be used to obtain microbiology samples, predominantly for fungi or viruses. More recently, brushings have been utilised for the

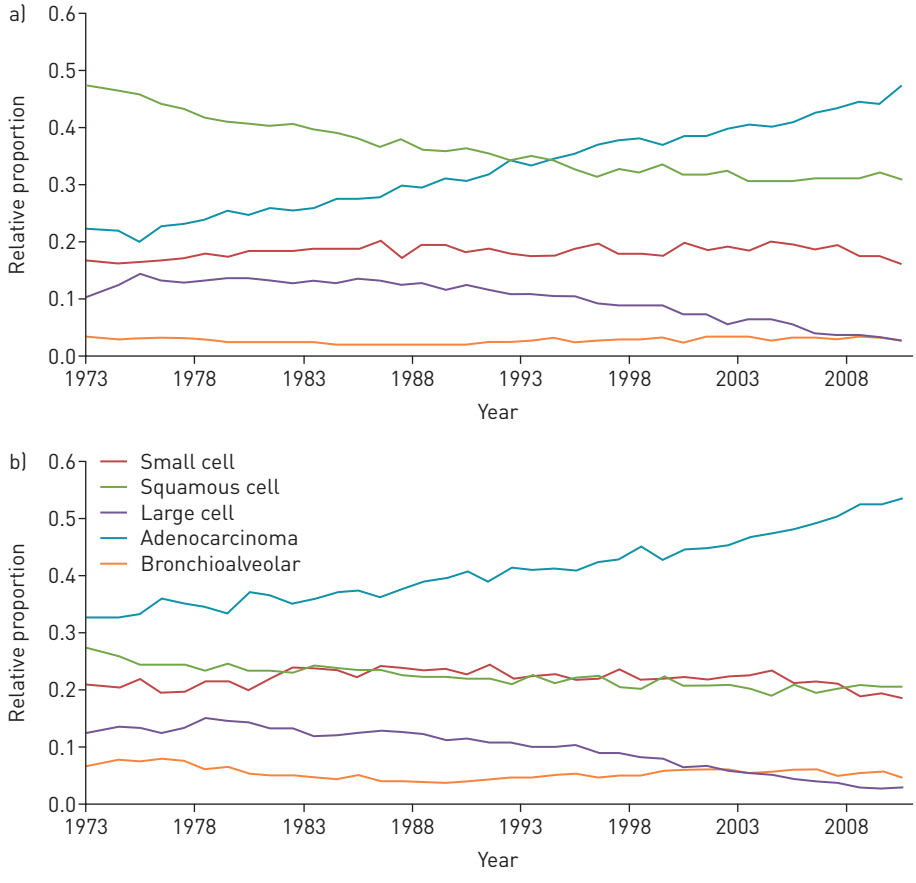

Figure 1. Changes in relative incidences of lung cancer cell types 1973–2010: a) male and b) female (all races). Reproduced and modified from [23] with permission.

assessment of the microbiome and microenvironment of the airways in health and disease [27–30]. The lesion in question is identified either under direct vision or at fluoroscopy and the brush passed through the working channel to make contact with the lesion. The brush is then agitated against the lesion. Processing of the brush sample varies between institutes, and close liaison is required between the bronchoscopy team and the pathologists to ensure optimum sample processing. At the author's institute, specimens are first cytospun onto slides and stained with Papanicolaou stain for reporting. If immunocytochemistry is needed, formalin is added to fix the cells, which are then centrifuged and agar added to make a pellet that is processed as a histology specimen to make paraffin wax blocks and slides.

Reported sensitivities for bronchial brushings vary greatly depending on location and tumour type. Diagnostic yields of 44–82% have been reported for endoscopically visible tumours [14, 31–34]. Samples from the main bronchi and bronchus intermedius outperform those from lobar airways, and when a tumour is not visible at bronchoscopy, yields are as low as 19–40% [14].

Although common sense dictates that when there is visible tumour within the airway, bronchial brushings are unlikely to add much to forceps biopsy, which provides a far greater amount of information for the pathologist and crucially provides information about

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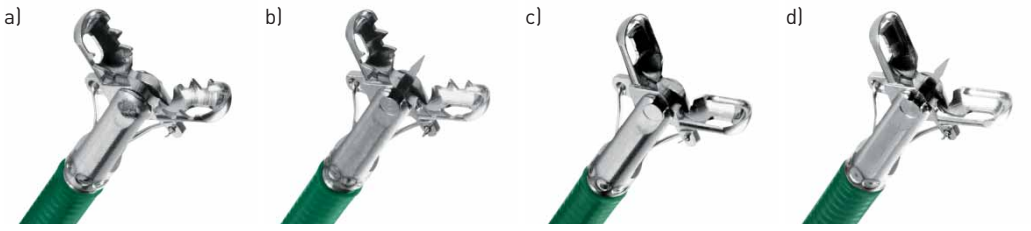

Figure 2. Examples of different biopsy forceps: a) alligator cup forceps, b) alligator cup forceps with spike, c) oval cup forceps and d) oval cup forceps with spike. Reproduced with kind permission of Olympus (Southend-on-Sea, UK).

invasion, there is evidence of increased yields over biopsy alone [14, 35]. As sampling relies on the adherence of material to the bristles of the brush, yields can be affected by other material present in the airway, *e.g.* blood and mucus, and the order in which samples are taken does appears to be important, with pre-biopsy brushings providing higher yields that post-biopsy brushings in one study [36]. In contrast to endobronchial biopsy, brushings may perform better when faced with a necrotic tumour and at least one study has shown brushings to outperform biopsies in the diagnosis of small cell lung cancer as there is no crush artefact to obscure cell morphology [37].

Bronchial washings

Bronchial washings are used to clear the airways of debris and secretions, and where indicated are intended to gather cells and microorganisms washed from the airway walls to be analysed for the presence of disease states. Aliquots of 10–20 mL of 0.9% saline are instilled into the airways and suctioned into a specimen collection pot. Washings can be particularly useful in the diagnosis of infectious states and are the test of choice for the detection of nontuberculous mycobacteria. Washings for the diagnosis of *Pneumocystis jirovecii* pneumonia (PJP) first came to prominence in the early years of HIV/AIDS in the USA, and have even been shown to outperform tissue biopsy and bronchial brushings [38, 39].

The reported yield of bronchial washings for the diagnosis of cancer varies greatly, and can be dependent on the location and type of tumour, with a range of 14–63% [14, 31, 40–43], although yields can be increased by preparing cell blocks [44, 45]. However, while guidelines continue to recommend them [21], the utility of bronchial washings in cases where the tumour is bronchoscopically visible is questionable if biopsies and brushings have also been obtained, and several studies have shown washings not to be cost-effective or significantly increase yield [11, 40, 46, 47]. Unlike with bronchial brushings, the order in which samples are obtained does not appear to alter yield [20], except perhaps in submucosal lesions where post-biopsy washings perform best, probably owing to the exposure of cancer cells with the removal of overlying tissue [48].

Intermediate techniques

Transbronchial biopsy

TBLB is performed when the target lesion is in the peripheral airways and not visible at bronchoscopy. The bronchoscope is first wedged in the (sub)segmental bronchus of interest

and forceps are passed through the working channel of the bronchoscope. The forceps are advanced beyond view until resistance is encountered and then withdrawn by 1–2 cm. The jaws of the forceps are then opened, the forceps advanced and the jaws closed to obtain the biopsy sample. Some operators advocate the coordination of forceps advancement and closure with the patient's respiration, where the forceps are opened and advanced in inspiration and the biopsy taken at end-expiration. The sample is placed into formalin (histology) or saline (microbiology) and processed in the same manner as for endobronchial biopsy.

As with BAL, TBLB performs best in the diagnosis of diffuse lung diseases, including ILD, infection and malignancy [49–51]. In solitary lesions, yield is heavily influenced by lesion size and also distance from the hilum, with very poor yields for lesions <2 cm in diameter in the outer third of the lung [7, 49, 52–53]. When targeting a discrete or focal lesion, the use of fluoroscopic guidance has been shown to significantly improve the diagnostic yield [54, 55], although it appears not to do so in diffuse disease [55, 56]. The use of fluoroscopic guidance is, however, being superseded by modern navigation techniques in the investigation of discrete pulmonary lesions and these are described in detail elsewhere in this *Monograph* [57].

Although BAL and CT together can be diagnostic in some cases of ILD, TBB is still sought in many cases for histological confirmation where the multidisciplinary team is not confident about the underlying process(es). In a review of 164 TBLB cases, Hanson *et al.* [58] reported diagnostic accuracies of 62%, 64% and 67% in infectious, interstitial and malignant lung diseases, and another early report by Smith *et al.* [59] of TBLB *via* the flexible bronchoscope reported diagnostic material in 34 out of 40 patients (85%). Yields for sarcoidosis are variable, ranging from 50% to 91% [56, 60–63]. TBLB is also used in the surveillance of rejection in lung and heart–lung transplant patients [64, 65], and has been shown to be useful in the diagnosis of peripheral lung amyloidosis [66].

The usefulness of TBLB in the diagnosis of usual interstitial pneumonia or idiopathic pulmonary fibrosis has been hotly debated, particularly in the era of high-resolution cross-sectional imaging [67, 68], and is probably most useful for excluding other interstitial processes [69]. However, especially in early disease or where other confounding factors exist, such as the presence of rheumatological disease, it is still desirable to obtain diagnostic tissue. Although some studies have suggested that TBLB may have a role to play in the diagnosis of usual interstitial pneumonia [70, 71], surgical lung biopsy is often recommended by guidelines [72–74]. Nonetheless, recent advances in the examination of pathological specimens, such as machine learning and genetic analysis [75], have the potential to increase the sensitivity of TBLB in this setting, and the advent of transbronchial cryobiopsy may allow surgical biopsy to be avoided in many cases [76, 77]. Transbronchial cryobiopsy is discussed in detail elsewhere in this *Monograph* [78].

The sensitivity of TBLB reported in the setting of suspected malignancy varies greatly, ranging from 17% to 80% [14, 16, 17, 79–82], and depends on the population studied, whether primary or secondary disease and on lesion size (as discussed earlier). TBLB is, however, the investigation of choice when considering lymphangitis carcinomatosis, with yields as high as 100%, albeit in small series [51, 83]. There is also recent evidence that TBLB is helpful for rebiopsy in relapsed nonsmall cell carcinoma for the purposes of mutational analysis [84].

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There appears to be little or no difference in the size or quality of biopsies obtained with different types of biopsy forceps [85–87] and although larger forceps appear to obtain larger specimens, this does not necessarily translate into significantly higher diagnostic yields [88, 89].

Owing to the inherent inaccuracies of the technique, guidelines recommend taking four to six samples in diffuse lung disease and seven or eight samples in focal lung disease to maximise the chances of obtaining diagnostic material [21], although there is a balance to be struck between the need for diagnostic tissue and the risk of complications.

Complications are more common with TBB than endobronchial biopsy, although they are rarely serious. Where reported, pneumothorax and clinically significant bleeding are the two main significant complications, occurring in 1–10% and up to 9%, respectively [49–51, 55, 56, 58, 63, 90]. Pleuritic pain during the procedure can be a feature and is important as it suggests the forceps have been advanced too far: the only pain-sensitive structure encountered is the parietal pleura, supplied by the intercostal and phrenic nerves (the visceral pleura is innervated by the autonomic nervous system and therefore has no sensory innervation). Other adverse events are rare, but include mediastinal and subcutaneous emphysema [91, 92]. Although death is very rare, it has been reported [93, 94], occurring in ~0.2% of cases [90].

While there is a risk of pneumothorax, and a chest radiograph is often requested after the procedure, there is little or no evidence that routine imaging is required. One study at the University of Virginia (Charlottesville, VA, USA) did not find a single case of unsuspected pneumothorax in over 300 patients across nearly 6 years [95], suggesting that imaging should only be requested if there is clinical concern. The study only included patients undergoing TBLB with fluoroscopic guidance, but, perhaps surprisingly, there does not appear to be any difference in pneumothorax rates between procedures performed with and without fluoroscopy [55, 56, 96].

More than with any of the other techniques described in this chapter, attention to the patient's coagulation status is vitally important. Peripheral lung biopsies very often contain vascular structures and while rare, catastrophic haemorrhage has been reported [90]. Each institution will have its own safety protocols in this regard, but the following seem practical and reasonable: international normalised ratio <1.5; low-molecular-weight heparin discontinued for at least 24 h; clopidogrel and other platelet ADP receptor blockers discontinued for 5–7 days. The duration of action of the novel oral anticoagulants (*e.g.* rivaroxaban and dabigatran) varies and advice on the duration of cessation should be sought where appropriate.

Owing to the potential increased risks with TBBs over other bronchoscopic biopsy techniques, there are a number of relative and absolute contraindications which largely relate to the ability of the patient to cope with either a pneumothorax or significant haemorrhage. Absolute contraindications include medical instability, severe hypoxia, life-threatening arrhythmia, massive haemoptysis and uncorrectable bleeding diathesis. Caution should be exercised if there is thrombocytopenia $<50\,000\ \mu L^{-1}$, pulmonary hypertension and uraemia, where there is a danger of serious haemorrhage even with normal coagulation. Desmopressin and cryoprecipitate can be effective in controlling haemorrhage in such situations [97, 98].

Bronchoalveolar lavage

BAL is a technique designed to sample the peripheral rather than central airways, and although used in the diagnosis of peripheral lung cancers, has a greater role to play in nonmalignant disease. BAL has been used for almost 100 years as a means of irrigating the lungs [99, 100], but began to be used more widely for the diagnosis of respiratory disease in the 1970s and 1980s. First, the bronchoscope is passed as distal as possible towards the target area of lung and "wedged" into an airway to provide as good a seal as possible. Aliquots of 0.9% saline are then instilled *via* the working channel of the bronchoscope and aspirated. In general, 30–60 mL is instilled at a time, with a total of between 100 and 300 mL being used dependent on institutional protocols and indication. Return is variable, and depends on the underlying condition(s) and the location of the lavage. The resultant aspirate contains cells, proteins, organisms and other material from the airways and epithelium. The American Thoracic Society clinical practice guidelines on the clinical utility of BAL in ILDs provides a comprehensive overview of the history and application of BAL [101].

When used for nonmalignant disease, BAL is important in determining the nature of a variety of pulmonary diseases and aims to sample the epithelial lining fluid (ELF). ELF provides information about the immunological, inflammatory and infectious processes taking place at the alveolar level, and is perhaps most often used in the investigation of ILDs and for the diagnosis of infection in the immunocompromised (*e.g.* chemotherapy and immunosuppressant drugs, haematological malignancies, and HIV). Approximately 1 mL of ELF is recovered for each 100 mL of saline instilled.

BAL fluid is usually sent for a differential cell count, which can give important guidance as to the nature of the underlying interstitial process when used in conjunction with the clinical history and radiology. Table 1 provides an overview of the diseases associated with various differential cell counts. Microbiology samples can be sent for standard bacterial and mycobacterial cultures, but also for PJP, viral studies and to determine levels of proteins associated with various atypical infections, such as galactomannan for invasive aspergillosis [102, 103] and β-glucan for PJP [104–106].

While BAL does have a potential role in the diagnosis of peripheral lung malignancies, the sensitivity and availability of CT-guided lung biopsy has relegated it to an infrequently used technique. Nonetheless, there is evidence of its usefulness in diagnosing both primary and secondary malignancies, although evidence is not as readily available as for bronchial washings and results have been somewhat variable. Sensitivity for primary lung malignancy ranges from 19% to 69%, although agreement with final cell typing is not universal [14, 81, 82, 107–111]. Success appears to be higher with adenocarcinoma, in particular with lepidic-predominant and invasive mucinous adenocarcinomas (both formerly under the umbrella of bronchoalveolar cell carcinoma) [112], and molecular analysis of BAL fluid may provide supplementary information on the likelihood of malignancy [113, 114].

The first report of its use for secondary malignancy was in 1985 in a case of lymphangitic spread of an adenocarcinoma of unknown primary [115] and a later small series detected lymphangitic spread in five out of five patients [116]. Studies have also shown its utility in the investigation of breast cancer, with one study identifying metastatic disease in 35% of pre-chemotherapy breast cancer patients [110]. A second series identified pulmonary metastatic disease in the BAL of 10 out of 14 post-treatment patients (71%) with metastatic invasive ductal carcinoma and was even able to provide information on prognosis by

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evaluation of lymphocyte counts in the lavage fluid [117]. Several series have demonstrated that BAL can be a useful adjunct in the diagnosis of a variety of haematological malignancies, including Hodgkin's lymphoma [110, 118, 119], acute myeloid leukaemia [120], non-Hodgkin's lymphoma [121] and primary pulmonary lymphoma [122].

BAL is generally a very safe procedure, with no complications in the majority of patients. Transient fever is seen in ~2.5% of cases [123], and temporary falls in lung function [124] and partial pressure of oxygen [125, 126] have been reported, although these are rarely clinically significant. Bleeding occurs in <1% [123]. Although infiltrates may be seen on chest radiology, there is no requirement for routine post-procedure imaging and unlike with TBB, pneumothorax is extremely rare.

Transbronchial needle aspiration

TBNA is a method of collecting cytological specimens by passing a needle down the bronchoscope and inserting it through the airway wall into a lesion of interest. It is used for lesions throughout the endobronchial tree, as a method of sampling mediastinal nodes and masses, and for the sampling of peripheral parenchymal masses. SCHIEPPATI [127] produced the first description of mediastinal lymph node sampling using a transbronchial needle to puncture the subcarinal space in 1949. In 1978, WANG *et al.* [128] adapted the technique using an oesophageal varices needle *via* the rigid bronchoscope to sample right paratracheal masses seen on chest radiographs, postulating even then that the technique could be adapted for use down the flexible bronchoscope to allow diagnosis and staging of lung cancer in a single procedure. A larger series demonstrated the technique's safety and usefulness as an alternative to invasive surgical staging [129].

The technique was adapted for the flexible bronchoscope, with the first series reported in 1983 showing a sensitivity for cancer of 62.5% with no complications [130]. TBNA has probably been an underused technique owing to the blind nature of the procedure and (unfounded) concerns about potential damage to mediastinal vascular structures. The now

Table 1. Differential diagnosis by BAL cell type

Cell type	Normal	Examples of disease states associated with elevated levels
Alveolar macrophages	>80%	
Lymphocytes	<15%	Sarcoidosis; drug reactions; hypersensitivity pneumonitis; organising pneumonia; tuberculosis; viral pneumonia; HIV infection; lymphoma; alveolar proteinosis
Neutrophils	<3%	Infection; idiopathic pulmonary fibrosis; acute respiratory distress syndrome; granulomatosis with polyangiitis; pneumoconiosis
Eosinophils	<2%	5–20%: drug reactions; infection (*e.g.* fungal, parasitic) >20%: allergic bronchopulmonary aspergillosis; eosinophilic pneumonias; hypereosinophilic syndrome; eosinophilic granulomatosis with polyangiitis

Haemosiderin-laden macrophages are highly sensitive and specific for alveolar haemorrhage.

Periodic acid–Schiff-positive material indicates pulmonary alveolar proteinosis.

widespread use of EBUS-guided TBNA (EBUS-TBNA; discussed in more detail elsewhere in this *Monograph* [131]) is testament to this and although conventional TBNA has been replaced by EBUS-TBNA for the investigation of mediastinal nodal disease in many centres, it still plays an important role where the cost of setting up EBUS-TBNA is prohibitive, and in the sampling of airway and peripheral lesions.

The flexible needle is contained within a sheath, often metal, and also comes with a round-tipped stylet so as to present a blunt forward end while manipulating the needle within the working channel, in order to protect the bronchoscope from damage to the working channel. The needle should be advanced down the working channel with the bronchoscope in the neutral position to further protect the scope from puncture. Once the needle is beyond the end of the working channel, the stylet is withdrawn slightly to reveal the bevel of the needle and inserted into the lesion in question. With lymph node aspiration, the needle should be inserted as perpendicular to the airway as possible to prevent shearing of the airway wall and inadequate sample collection. The stylet is withdrawn, suction is applied *via* a syringe at the proximal end of the needle apparatus and the needle is agitated within the lesion to collect the sample. Any negative pressure should be removed prior to withdrawing the needle to prevent contamination from bronchial mucosa and airway secretions. Samples are then expelled from the needle into the appropriate collection media for processing.

TBNA has been most widely used in the context of (nonsmall cell) lung cancer, enabling both diagnosis and mediastinal staging in one procedure *via* the flexible bronchoscope, and allowing for a reduction in more invasive procedures such as mediastinoscopy and "open and shut" thoracotomies. A number of different needles are available, ranging in size from 19 gauge histology needles to 22 gauge cytology needles. Yields appear to be significantly better with larger needles [132, 133]. TBNA is capable of sampling nodal stations adjacent to the major airways, *i.e.* the upper and lower paratracheal nodes (stations 2 and 4), retrotracheal nodes (station 3P), subcarinal nodes (station 7), hilar nodes (station 10), and interlobar nodes (station 11) (figure 3) [134]. Paraoesophageal nodes (station 8) can also occasionally be sampled. It is critically important when sampling multiple nodes that nodes with the highest N staging are sampled first, *i.e.* N3/N2/N1, and that all nodes are sampled before approaching or sampling any endobronchial disease to avoid potential upstaging by sample cross-contamination. A thorough step-by-step approach to the anatomy and practice of TBNA can be found in dedicated texts [135], and is beyond the scope of this chapter.

Reported sensitivities vary greatly, with a range of 14–93% [132, 136–142], likely due to a combination of operator experience, size of needle used, lymph node size and location, and prevalence of nodal disease in the population studied [143]. One study even suggested that experienced operators may have similar sensitivities for diagnosis and staging using conventional TBNA as for EBUS-TBNA, although the study was unique in that the operator in question had 30 years experience of the technique *via* the flexible bronchoscope [144]. Specificity approaches 100%, although exact figures are not available for most studies as they do not surgically confirm all positive results. The pooled specificity from methodologically sound studies has been reported as 99% [145]. An overwhelming majority of the literature is concerned with the diagnosis and staging of nonsmall cell carcinoma. Where small cell lung cancer has been specifically studied, TBNA performs well, although numbers are small [37].

The use of rapid onsite evaluation (ROSE) of cytology specimens obtained by TBNA has been reported to improve sensitivity, reduce the need for additional procedures and reduce

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complication rates [146–150], although some studies have suffered from selection bias and selective rather than blanket use may be a better approach [151]. A recent study has demonstrated that, when combined with ROSE, conventional TBNA may even perform as well as EBUS-TBNA, but with lower sedation requirement and shorter procedure time, although the study was limited by the small number of subjects [152].

TBNA is used predominantly for the diagnosis and staging of malignancy, although it is also useful for the detection of benign disease, especially sarcoidosis, and infection. Diagnostic yield for sarcoidosis in a meta-analysis by AGARWAL *et al.* [153] ranged from 6% to 90%, with a pooled accuracy of 61.6%. Interestingly, prospective studies demonstrated a significantly higher sensitivity than retrospective studies (71.4% *versus* 52.8%). Predictors of success in sarcoidosis appear to be limited to the number of nodes sampled [143] and size of needle used [153].

WANG *et al.* [154] reported the first use of needle aspiration of bronchoscopically invisible peripheral nodules in 1984, obtaining diagnostic malignant tissue in 11 out of 20 patients, with TBNA being the only positive sample in seven. Since then, TBNA has been used as an alternative or complimentary technique to TBLB in the investigation of peripheral lesions, with sensitivities ranging from 47% to 70% [80, 82, 111, 154, 155]. The AQuIRE registry [111], which collated clinical procedure details across multiple investigators and sites, and therefore is likely to most closely resemble "usual practice", reported a sensitivity of 47.4% and TBNA was diagnostic in ~10% of cases where TBLB was negative, and was the only positive test in ~6% of cases where all of TBLB, TBNA, brushings and BAL were performed.

TBNA can also be used for endoscopically visible lesions, where more correctly the term endobronchial needle aspiration (EBNA) is used, but for the purposes of this chapter both

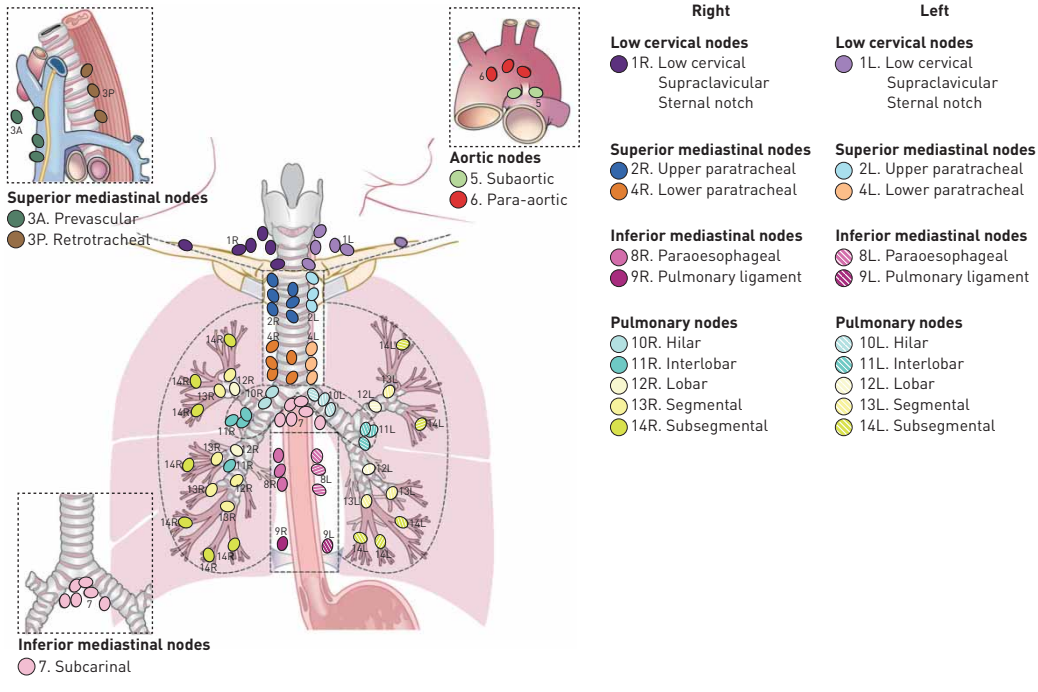

Figure 3. Intrathoracic lymph node map. Reproduced and modified from [134] with permission.

are considered to be the same procedure. Reported yields vary dramatically, ranging from 23% to 90% [156–161], and it may increase diagnostic yields even where conventional diagnostic techniques are also used [162, 163], although the already high yield of endobronchial biopsies makes statistical significance difficult to achieve. Lesions that appear predominantly or wholly submucosal at bronchoscopy can often produce negative endobronchial biopsy specimens and EBNA has been shown to significantly increase the sensitivity of bronchoscopy in these situations, as the needle is able to penetrate the overlying normal mucosa and collect cytology specimens from the underlying tumour [157, 163].

TBNA is a very safe procedure, with a pooled reported major complication rate of <0.3% [144], and although bacteraemia [164], pericarditis [165], haemomediastinum [166], pneumomediastinum [136, 167] and pneumothorax [130, 168] have been reported, long-term sequelae are rare. Fatal episodes of bacterial pericarditis [169] and cerebral infarction [170] associated with EBUS-TBNA of mediastinal nodes have been reported, but death from TBNA has not appeared in the literature.

Conclusion

Flexible bronchoscopy has become the primary intervention in the diagnosis and staging of lung cancer, and has a critical role to play in many cases of diffuse infiltrative lung disease and infection, with good sensitivity and specificity in most settings. Multiple complimentary techniques have been developed for the acquisition of diagnostic material since Shigeto Ikeda first wielded a flexible bronchoscope in the mid-1960s, and innovations and improvements, many of which are discussed throughout this *Monograph* [4], continue to improve its diagnostic capability. Most of the techniques described in this chapter can be performed competently with only a modicum of training and all independent bronchoscopists should be encouraged to attain expertise in these methods.

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Minimally invasive endosonographic techniques: combined EBUS and EUS

Pravachan V.C. Hegde[1] and Moishe Liberman[2]

Minimally invasive endosonographic techniques (combined EBUS/EUS/EUS-B) provide a much broader ability to biopsy lymph nodes compared with conventional mediastinoscopy in the staging of nonsmall cell lung cancer (NSCLC). When compared with traditional mediastinoscopy, the ability of combined EBUS/EUS/EUS-B to sample multiple stations and distant metastases, including structures below the diaphragm, with high sensitivities and negative predictive values makes endosonography a new gold standard in the initial staging of NSCLC when performed by an experienced operator. The two techniques (EBUS and EUS) should not be considered competitive; they are complementary. The physician should choose the best approach depending on the available resources, expertise and biopsy target location of interest. In addition, endosonographic fine-needle aspiration has become the first procedural test in cases where the clinical and imaging findings suggest an infectious and granulomatous lesion accessible by these techniques.

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Minimally invasive endosonographic techniques include both EBUS- and EUS-guided fine-needle aspiration (FNA). These are minimally invasive ultrasound-guided FNA techniques either through the endobronchial route (EBUS) or endo-oesophageal route (EUS). They are predominantly used in the diagnosis and staging of lung cancers. In addition, they are also used in diagnosing mediastinal adenopathy, infection and granulomatous lesions of the thoracic cavity accessible by these techniques. These techniques have replaced invasive surgical techniques in the evaluation of the mediastinum in many centres. In addition, combined EBUS/EUS/EUS-B is superior to standard mediastinoscopy in the initial staging of lung cancer because it allows for biopsy of lymph nodes and metastases not attainable with mediastinoscopy. In comparison with conventional

[1]Advanced Interventional Thoracic Endoscopy/Interventional Pulmonology, Division of Pulmonary Critical Care Medicine, University of California San Francisco-Fresno, Fresno, CA, USA. [2]Division of Thoracic Surgery, Dept of Surgery, CHUM Endoscopic Tracheobronchial Center (CETOC), Centre Hospitalier de l'Universite de Montreal, University of Montreal, Montreal, QC, Canada.

Correspondence: Pravachan V.C. Hegde, Advanced Interventional Thoracic Endoscopy/Interventional Pulmonology, Division of Pulmonary Critical Care Medicine, University of California San Francisco-Fresno, 2335 East Kashian Lane, Suite 260, Fresno, CA 93701, USA. E-mail: pv.pulm@gmail.com

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mediastinoscopy, endosonographic techniques are less invasive and are carried out as an outpatient day case under conscious sedation, with less morbidity, considerable cost savings and are also well tolerated by patients. The ability of the combined EBUS/EUS/EUS-B techniques to sample multiple lymph node stations and distant metastases, including structures below the diaphragm, makes the use of such techniques the preferred test in the initial staging of lung cancer. Current European Society of Gastrointestinal Endoscopy (ESGE)/European Respiratory Society (ERS)/European Society of Thoracic Surgeons (ESTS) guidelines recommend a combination of EBUS/EUS over either test alone in the mediastinal staging of lung cancer [1]. Current American College of Chest Physicians (ACCP) lung cancer guidelines recommend EBUS-FNA, EUS-FNA or the combination of EBUS/EUS-FNA over surgical staging as the initial test for the staging of the mediastinum in nonsmall cell lung cancer (NSCLC) [2].

Accurate staging of the mediastinum is extremely important in determining the treatment plan in NSCLC. Testing with minimally invasive or noninvasive tests can prevent surgery in patients with advanced, benign or medically treatable diseases. Noninvasive radiological tests, including CT and PET-CT scans, are very valuable in procedure planning, but these techniques cannot provide tissue diagnosis. Therefore, it is vital to prove positivity or negativity of lymph node stations by obtaining a definitive tissue diagnosis in certain subgroups of patients.

In this chapter, we discuss the utility of combined EBUS/EUS/EUS-B in daily practice and highlight some technical aspects of the procedure. The traditional gold standard test in mediastinal staging has been cervical mediastinoscopy. We also discuss why mediastinoscopy may no longer be the gold standard for invasive mediastinal staging and why it is time to put an end to the era of a traditional gold standard procedure.

Combined endosonographic techniques are superior to conventional mediastinoscopy and should be the new gold standard in the initial staging in NSCLC. Our aim in this chapter is to discuss the current role of endosonographic techniques for the evaluation of mediastinal adenopathy and staging of lung cancer. A special emphasis will be on staging of NSCLC as it is the most common indication for using endosonographic techniques in daily practice. In addition, endosonographic FNA has become the first procedural test in cases where the clinical and imaging findings suggest an infectious and granulomatous lesion accessible by these techniques.

Endosonographic ultrasound (combined EBUS/EUS/EUS-B)

What are EBUS, EUS and EUS-B?

EBUS-FNA and EUS-FNA are minimally invasive ultrasound-guided FNA techniques. When a linear EBUS ultrasound scope is used to sample tissue through the transoesophageal route, the terminology EUS-B-FNA is used.

Indications and contraindications

The most common indication in daily practice is diagnosis and staging of lung cancer. In addition, they are also used in diagnosing mediastinal adenopathy, infection and granulomatous lesions of the thoracic cavity.

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Contraindications include patient-related clinical conditions such as unstable angina, refractory hypoxia, haemodynamic instability, bleeding diathesis and coagulopathy. Other operator-dependent contraindications include inadequate expertise, facilities and equipment to handle complications.

Brief technical aspects and protocol of systematic FNA

A detailed description of the endosonographic anatomy and procedural technique is beyond the scope of this chapter. Here, we briefly describe some basic technical aspects.

The convex probe EBUS scope is a flexible scope with a field of vision between 50° and 70° and image parallel to the shaft of the scope. The depth of the image is between 3 and 5 cm. The linear EUS scope has a wider range of imaging compared with the EBUS scope. It provides a 180° view and can obtain images to a depth of 8 cm. EUS can also be performed using a convex probe EBUS scope (EUS-B-FNA). In order to produce good quality images, the transducer must oppose the tracheal or oesophageal wall with the lever pushed down and continuous suction applied throughout while performing needle aspiration. It is recommended to start with assessing the contralateral hilum/mediastinal nodes (N3), followed by N2 mediastinal nodes and then finally ipsilateral hilar nodes (N1) (in appropriate cases). The order of the examinations depends mainly on the side and location of the tumour [3]. The International Association for the Study of Lung Cancer (IASLC) 2009 map of the mediastinal and hilar lymph nodes is shown in Chapter 8 of this *Monograph* [4].

The classical approach described by Jenssen *et al.* [5] is to start by learning the six basic landmarks for EBUS and EUS, and to practice finding them in sequence order. The six EBUS landmarks described in sequence order are: stations 4L, 7, 10L, 10R, azygous vein and 4R. Similar EUS landmarks in sequence order are: liver, aorta, left adrenal gland, stations 7, 4L and 4R.

Lymph node puncture is achieved with a quick forward movement advancing the needle. We prefer to hold the needle with the thumb downward. The thumb controls the needle advancing into the lymph node. In and out movements are performed with the needle inside the lymph node. It is very important to see the needle moving inside the lymph node and not to move the lymph node with the needle. Two samples are taken without suction to avoid blood on the slides. The third sample is collected with negative pressure suction for cell block, histology and molecular analysis. This is just an example of how to approach a node. There is no evidence for the use of suction, no suction or a slow-pull method.

Balloons filled with saline can be used to overcome poor contact between the ultrasound probe and the bronchial wall, and to assist in obtaining a clear ultrasound image. Although a saline-filled balloon can enhance image acquisition, it is unclear if this translates into a better diagnostic yield. Balloons are made of latex and thus cannot be used in patients with latex allergies. Latex-free balloons are available for linear EUS scopes. From a practical perspective, balloons are commonly used for the slightly challenging angle of the left paratracheal lymph node (4L) and hilar stations (10R and 10L). There are no studies comparing the use of a balloon *versus* no balloon and diagnostic yield with endosonography.

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Needle size and number of aspirations

There is no difference in specimen adequacy or yield between 21G and 22G needles in EBUS-TBNA; however, 21G needles are associated with fewer needle passes only if rapid onsite evaluation (ROSE) is available [6]. Better characterisation of benign disease (83% *versus* 60%) and NSCLC histology subtyping (88% *versus* 65%) has been shown with 21G needles [7]. Studies evaluating the role of EUS in solid lesions adjacent to the gastrointestinal tract showed no difference in diagnostic yield between EUS-FNAs *versus* fine-needle biopsy needles [8]. The newer 19G EBUS needles have shown promising results with a greater degree of flexion, safety and diagnostic yield [9]. Prospective randomised controlled trials have shown no benefit in applying suction to needle aspiration. There is no difference in diagnostic yield or adequacy of the specimen [10]. There is insufficient data in studies comparing with and without suction in obtaining molecular markers in NSCLC. Optimal results can be obtained with three passes per lymph node station in EBUS-TBNA for mediastinal staging of potentially operable NSCLC. The increased yield plateaus after three passes [11].

Lymph node characteristics

The lymph node characteristics that are suggestive but not diagnostic of malignancy include round and heterogeneous nodes with a distinct margin and a coagulation necrosis sign [12]. A heterogeneous sign is more predictive of malignancy compared with other signs [13]. However, no lymph node characteristics can exclude or prove malignancy. These signs may be potentially useful if there are multiple lymph nodes in a single station and lymph node size is below the commonly used cut-off of 5 mm [14]. Colour Doppler sonography based on the bronchial artery in-flow sign is a fast, reproducible and effective tool that could help in targeting suspected malignant lymph nodes during EBUS-TBNA. The sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of the bronchial artery flow sign using colour Doppler were found to be 93%, 64%, 84%, 60% and 81%, respectively, in a prospective study by Nosotti *et al.* [15].

In addition, endosonographic elastography is potentially capable of further differentiating between benign and malignant lymph nodes. Elastography is a noninvasive method in which the relative stiffness of tissues is imaged as a colour map or measured as shear wave velocity. Two techniques are commonly used: shear wave elastography and strain elastography. Most inflammatory processes do not change the elastographic architecture of lymph nodes, whereas metastases cause diffuse hard infiltration of the lymph node. Normal and inflammatory lymph nodes reveal a significantly harder cortex than the medulla and the hilum. Early metastatic infiltration shows a circumscribed localised stiffer neoplastic infiltration. At a later stage, there is diffuse stiff infiltration of the lymph node. A meta-analysis showed a pooled sensitivity of 88% and specificity of 85% with EUS-guided elastography for the discrimination of malignant *versus* benign lymph nodes [16]. In their prospective study of 56 patients, Sun *et al.* [17] reported EBUS elastography had a sensitivity of 91% and a negative predictive value of 82% for detecting metastases in lymph nodes.

Role of rapid onsite cytology, slides and cell blocks

Lymph node sampling should yield abundant lymphocytes in order to be considered as an adequate sample [18]. ROSE has not shown any benefit in diagnostic yield [19, 20].

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However, if available, it results in fewer needle passes and number of slides prepared during the procedure [21]. ROSE may help to improve technique and reduce the number of procedures. A meta-analysis indicated that ROSE does not increase the diagnostic yield and there is no difference in specimen preparation (slide *versus* core *versus* cell block). The adequacy of specimen preparation depends mainly on the available expertise [22].

There is evidence from a single randomised trial that ROSE may be helpful in the diagnosis of central lung tumours when conventional FNA is used. In a prospective randomised trial of 125 patients by Mondoni *et al.* [23], conventional FNA guided by ROSE had a significantly higher sensitivity (96% *versus* 76%) compared with FNA alone. Training pulmonologists in basic onsite cytological evaluation may help reduce costs and also help make a diagnosis without involving a cytopathologist during the procedure. A prospective study of conventional TBNA in 84 patients with mediastinal adenopathy evaluated the role of the pulmonologist to assess the adequacy of cytological smears onsite. The accuracy of onsite assessment performed by a pulmonologist was not statistically different from that provided by a cytopathologist. There was 81% agreement between the two observers [24]. However, the final cytological diagnosis and report must always be the responsibility of the pathologist. It should be kept in mind that these two studies were performed in patients undergoing conventional TBNA and not endosonography-guided FNA.

In a single-centre retrospective study, cytology slides and core tissue preparations demonstrated high and similar diagnostic performance when comparing cytology slides *versus* cell blocks. Cytology slides combined with core tissue or cell blocks showed the highest performance; however, these combination methods were more resource-consuming. Diagnostic yield and accuracy were: cytology slides 81% and 80%, cell block 48% and 33%, core tissue 87% and 99%, cytology slides plus core tissue 80% and 100%, and cytology slides plus cell block 86% and 100%, respectively [25].

Diagnostic yield in lung cancer staging and special considerations

The most common indication for using endosonography in daily practice is staging of NSCLC. CT and PET-CT scans have improved the radiological staging of lung cancer; however, these techniques cannot provide tissue diagnosis and are associated with high false-positive and -negative rates, and low sensitivities and specificities [2, 26–35]. Stage dictates therapy and prognosis in lung cancer. The IASLC 2009 map mentioned earlier can be used to locate mediastinal and hilar lymph nodes. Staging helps to identify N2/N3 lymph nodes and distant metastases, which can prevent futile surgery and identify patients for neoadjuvant treatment. Staging is also important in order to identify N1 lymph node metastases in candidates with poor lung function before planning SBRT or sublobar resection. The ESGE/ERS/ESTS and ACCP guidelines recommend staging in all central tumours, peripheral tumours >3 cm, CT scan demonstrating lymph nodes >1 cm, N1 lymph node involvement on PET-CT and PET with standardised uptake values in the primary tumour of <2. Patients with peripheral tumour size <3 cm with no lymph node involvement on CT/PET-CT do not require invasive mediastinal staging [1, 2]. The eighth edition of the IASLC tumour (T), node (N) and metastasis (M) staging system is shown in table 1 [36].

Mediastinal staging can either be performed minimally invasively with EBUS, EUS or the combination of both, or invasively with standard cervical mediastinoscopy, transcervical extended cervical lymphadenectomy (TEMLA) and VATS. Testing with minimally invasive

Table 1. Proposed tumour (T), node (N) and metastasis (M) descriptors for the eighth edition of the TNM classification for lung cancer

T: Primary tumour	
Tx	Primary tumour cannot be assessed or tumour proven by presence of malignant cells in sputum or bronchial washings but not visualised by imaging or bronchoscopy
T0	No evidence of primary tumour
Tis	Carcinoma *in situ*
T1	Tumour ⩽3 cm in greatest dimension surrounded by lung or visceral pleura without bronchoscopic evidence of invasion more proximal than the lobar bronchus (*i.e.* not in the main bronchus)[#]
T1a(mi)	*Minimally invasive adenocarcinoma*[¶]
T1a	*Tumour ⩽1 cm in greatest dimension*[#]
T1b	*Tumour >1 cm but ⩽2 cm in greatest dimension*[#]
T1c	*Tumour >2 cm but ⩽3 cm in greatest dimension*[#]
T2	Tumour >3 cm *but ⩽5 cm* or tumour with any of the following features[+]: *involves main bronchus regardless of distance from the carina but without involvement of the carina*; invades visceral pleura; *associated with atelectasis or obstructive pneumonitis that extends to the hilar region, involving part or all of the lung*
T2a	*Tumour >3 cm but ⩽4 cm in greatest dimension*
T2b	*Tumour >4 cm but ⩽5 cm in greatest dimension*
T3	*Tumour >5 cm but ⩽7 cm in greatest dimension* or associated with separate tumour nodule(s) in the same lobe as the primary tumour or directly invades any of the following structures: chest wall (including the parietal pleura and superior sulcus tumours), phrenic nerve, parietal pericardium
T4	*Tumour >7 cm in greatest dimension* or associated with separate tumour nodule(s) in a different ipsilateral lobe than that of the primary tumour or invades any of the following structures: *diaphragm*, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body and carina
N: Regional lymph node involvement	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary modes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene or supraclavicular lymph node(s)
M: Distant metastasis	
M0	No distant metastasis
M1	Distant metastasis present
M1a	Separate tumour nodule(s) in contralateral lobe; tumour with pleural or pericardial nodule(s) or malignant pleural or pericardial effusion[§]
M1b	*Single extrathoracic metastasis*[f]
M1c	*Multiple extrathoracic metastases in one or more organs*

Changes to the seventh edition are shown in italic. [#]: the uncommon superficial spreading tumour of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified as T1a. [¶]: solitary adenocarcinoma, ⩽3 cm with a predominately lepidic pattern and ⩽5 mm invasion in any one focus. [+]: T2 tumours with these features are classified as T2a if ⩽4 cm in greatest dimension or if size cannot be determined and T2b if >4 cm but ⩽5 cm in greatest dimension. [§]: most pleural (pericardial) effusions with lung cancer are due to tumour. In a few patients, however, multiple microscopic examinations of pleural (pericardial) fluid are negative for tumour and the fluid is nonbloody and not an exudate. When these elements and clinical judgement dictate that the effusion is not related to the tumour, the effusion should be excluded as a staging descriptor. [f]: This includes involvement of a single distant (nonregional) lymph node. Reproduced and modified from [36] with permission.

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techniques can prevent surgery and pulmonary resection in patients with advanced stage lung cancer.

Why combined EBUS/EUS/EUS-B?

Standard mediastinoscopy allows access to stations 2R, 2L, 4R, 4L and 7, and the hilum (table 2). Access to the posterior and inferior mediastinum is limited. The lymph node stations accessible by EBUS include stations 1, 2, 4, 7, 10, 11 and 12. Stations 8 and 9 cannot be accessed with EBUS. The aortopulmonary window and para-aortic lymph nodes (stations 5 and 6) cannot be accessed with EBUS in most cases without transvascular puncture. In addition, smaller station 4L lymph nodes are occasionally difficult to access easily using EBUS. There is a 1:30 chance of inferior mediastinal nodal involvement without involvement of upper mediastinal nodes in patients with NSCLC [38].

EUS is helpful in accessing the lymph nodes in the inferior mediastinal stations 8 and 9, coeliac axis, left lobe of the liver, and bilateral adrenal glands (table 2). EUS can also access stations 2, 3p, 4L, 5, 6 and 7. Station 4R can be reached if the lymph node is large enough. Smaller station 4L lymph nodes are easily accessible by EUS/EUS-B compared with EBUS. In a study of 138 patients who underwent combined EBUS/EUS, EUS better identified malignant disease in lymph node stations 5, 6 and 7 [39]. Access to stations 2R and 4R is limited due to the intervening trachea. Interestingly, Hwangbo *et al.* [40] reported that the lymph nodes detected by EUS-B and missed by EBUS were not located in the inferior mediastinum, but at stations 4L and 5. In their study EUS was performed using a convex EBUS scope. The increased sensitivity of the combined technique may not be due to the ability to evaluate inferior mediastinum, but rather due to better visualisation of stations 4L and 7 and the ability to access the aortopulmonary window lymph nodes [40].

Adding EUS to EBUS allows for complete staging of the mediastinum and greater evaluation of lymph nodes and structures below the diaphragm. It allows for greater evaluation of lymph nodes compared with either of the techniques alone. A recently reported

Table 2. Lymph node stations accessible by different techniques

Nodal basin	EBUS	EUS	CM	AM	VATS
1: Highest mediastinal	✓				
2: Upper paratracheal	✓	✓	✓		✓
3: Pre-vascular retrotracheal	✓	✓			✓
4: Lower paratracheal	✓	✓	✓		✓
5: Subaortic (AP window)		✓		✓	✓
6: Para-aortic		✓[#]		✓	✓
7: Subcarinal	✓	✓	✓		✓
8: Paraoesophageal		✓			✓
9: Pulmonary ligament		✓			✓
10: Hilar	✓		✓		✓
11: Interlobar	✓				✓

Red ticks indicate preferred initial technique. CM: cervical mediastinoscopy; AM: anterior mediastinotomy; AP: aortopulmonary. [#]: used only in centres with experience and expertise in this technique (figure 1). Reproduced and modified from [37] with permission.

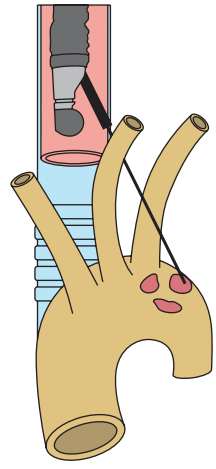

Figure 1. Station 6 access with EUS, a new technique. Reproduced and modified from [37] with permission.

meta-analysis of 13 studies showed that adding EUS/EUS-B to EBUS increased sensitivity by 12% and addition of EBUS to EUS/EUS-B increased sensitivity by 22%. The mean sensitivity of a combined approach was 86% with a negative predictive value of 92% [41]. There was no statistically significant difference in the yield when comparing the use of the EBUS *versus* EUS scope in the transoesophageal route for sampling of lymph nodes [42]. However, the EUS scope has a better range of imaging, and also allows for evaluating adrenal (both right and left), liver and coeliac axis metastases. Using a single EUS-B scope in patients with adrenal involvement allows both mediastinal nodal and adrenal evaluation with a single procedure. This staging strategy reduces patient discomfort, risk and costs. There was no difference in the yield between EUS-B *versus* conventional EUS in sampling left adrenal metastases [43]. A conventional EUS scope may be more helpful if the right adrenal gland is involved. Identifying the left adrenal gland is easier compared with the right adrenal gland; the right adrenal gland cannot be reached with the EUS-B technique. The two techniques (EBUS and EUS/EUS-B) are complementary and can potentially replace surgical staging in patients with NSCLC.

A prospective trial of 166 patients comparing combined EBUS/EUS and mediastinoscopy with final pathology results of lymph node sampling at pulmonary resection showed that EBUS/EUS was diagnostic for N2/N3/M1 disease in 14% of patients in whom standard mediastinoscopy findings were negative, thereby preventing futile thoracotomy and invasive video-assisted thoracoscopic procedures [44]. The sensitivity, specificity, negative predictive value and diagnostic accuracy of combined EBUS/EUS were 91%, 100%, 96% and 97%, respectively (tables 3 and 4) [44].

Standard mediastinoscopy can access the paratracheal and subcarinal lymph node stations, but not the paraoesophageal, inferior pulmonary ligament, aortopulmonary window and para-aortic lymph nodes [31, 32, 34, 35]. The lower aspect of the subcarinal station is sometimes inaccessible *via* standard mediastinoscopy. These stations can be reached by more invasive surgical techniques such as TEMLA and VATS. Most of the N2 nodes missed by mediastinoscopy tend to be in those stations [45, 46]. Annema *et al.* [47] performed a multicentre randomised control trial comparing surgical staging with a combined EBUS/EUS procedure. They showed that combining endosonography with

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Table 3. Endosonography *versus* standard cervical mediastinoscopy

	Sensitivity %	Negative predictive value %	Accuracy %
EBUS	72	88	91
EUS	62	85	88
EBUS/EUS	91	96	97

Information from [44].

surgical staging resulted in improved sensitivity (94%) compared with endosonography alone (85%). The mediastinal lymph node staging strategy was also more cost-effective compared with surgical staging alone (table 5) [47]. In addition, combined EBUS/EUS followed by surgical staging if negative is more effective and less costly than surgical staging alone in N2/N3 lymph node disease [48]. Transoesophageal lung biopsy using EUS can be performed during the same procedure and is safe in patients with central tumours close to the oesophagus [49]. In addition, EBUS/EUS has a lower mean cost compared with surgical staging [50–52]. In experienced hands, mediastinal staging can be performed under moderate sedation without decreasing the diagnostic yield [53].

Identifying which patients should undergo subsequent surgical staging after a negative endosonography is a matter of ongoing discussion. In patients with suspicious lymph nodes on either CT or PET it is recommended that negative endosonography should be surgically verified. In contrast, there is evidence that patients with centrally located tumours or suspected hilar involvement do not benefit from additional surgical staging [54]. This is still very controversial and further studies are required to confirm this patient population.

We think that combined EBUS/EUS is the new gold standard in the initial mediastinal staging of NSCLC when performed by an experienced operator. Further studies are needed to confirm that mediastinoscopy under certain circumstances can be omitted.

Sensitivity, specificity and accuracy in lung cancer staging

Recent meta-analyses and multiple studies have shown a pooled sensitivity of EBUS-TBNA in the range of 88% to 93%. The negative predictive value is ~91% [2, 55–62]. ACCP guidelines recommend EBUS-TBNA as the best initial test in suspected N2/N3 disease, and note that clinically suspicious nodes with a negative result should undergo surgical sampling and the choice of first test should be based on the experience of the operator [2].

Table 4. Mediastinal staging *versus* surgery

	Negative predictive value %	Accuracy %
EBUS	90	90
EUS	90	89
EBUS/EUS	92	91
Standard cervical mediastinoscopy	89	89

Information from [44].

Table 5. Diagnostic performance: detecting mediastinal nodal metastases by surgical staging *versus* endosonography followed by surgical staging

Nodal invasion N2/N3	Surgical staging [#]	Endosonography and surgical staging [¶]	p-value
Sensitivity	41/52 (79) (95% CI 66–88)	62/66 (94) (95% CI 85–98)	0.02
Negative predictive value	66/77 (86) (95% CI 76–92)	57/61 (93) (95% CI 84–97)	0.18

Data are presented as n/N (%), unless otherwise stated. [#]: N=118; [¶]: N=123. Information from [47].

The sensitivity, specificity, positive predictive value and negative predictive value of EUS-FNA for cancers of the mediastinum have been found to be 88%, 100%, 100% and 80%, respectively [63–70]. Two recent meta-analyses report pooled sensitivities of EUS-FNA in nodal staging of NSCLC of 83% and 89% [2, 69]. Meta-analytic data show an increase in sensitivity for mediastinal nodal staging in patients with proven or suspected lung cancer by combining EBUS-TBNA and EUS/EUS-B-FNA. The average increase in sensitivity was 21% compared with the oesophageal approach alone and 13% compared with EBUS-TBNA alone [1]. EUS-B-FNA improves sensitivity when added to EBUS (EUS-B 89%, EBUS 92% and EBUS/EUS-B 96%) [71]. Another similar trial of 150 patients with NSCLC who underwent EBUS and EUS in the same procedure using the bronchoscope (EUS-B) rather than an EUS endoscope showed that the combined procedure increased the sensitivity to 92% from 82% [40]. A study comparing the tolerance, efficacy and safety of EBUS-TBNA *versus* transoesophageal EUS-guided FNA with an EBUS scope for the first pathological diagnosis of lesions accessible by both procedures showed that EUS has the advantage of comparable tolerance with fewer doses of anaesthetics and sedatives, shorter procedure time, higher operator satisfaction, and fewer oxygen desaturations during the procedure [72]. As noted earlier, the meta-analysis of 13 studies by Korevaar *et al.* [41] showed that adding EUS/EUS-B to EBUS increased sensitivity by 12% and addition of EBUS to EUS/EUS-B increased sensitivity by 22%, and the mean sensitivity of a combined approach was found to be 86% with a negative predictive value of 92%.

The sensitivity of mediastinoscopy has been reported to be 79–93% with a false-negative rate of 8–11% [45, 46, 73]. Endosonographic techniques have a comparable diagnostic yield.

The previously mentioned multicentre randomised control trial performed by Annema *et al.* [47] comparing surgical staging with a combined EBUS/EUS procedure showed that combining endosonography with surgical staging resulted in improved sensitivity (94%) *versus* endosonography alone (85%) and that the mediastinal lymph node staging strategy was also more cost-effective *versus* surgical staging alone (table 5). ESGE/ERS/ESTS guidelines recommend a combination of EBUS/EUS/EUS-B over either test alone in the mediastinal staging of lung cancer [1]. It is recommended that negative endosonography should be surgically confirmed in patients with suspicious lymph nodes on either CT or PET.

Endosonographic staging in a radiologically normal mediastinum

Few studies have evaluated the role of endoscopic staging in a radiologically normal mediastinum (lymph node <1 cm and no activity on PET) by EBUS-TBNA in NSCLC. The

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sensitivity, specificity, negative predictive value and accuracy of EBUS-TBNA in radiologically normal mediastinum were reported to be around 93%, 100%, 87% and 88%, respectively [74–78]. Herth *et al.* [76] published the first EBUS-TBNA staging study on 100 patients with normal lymph nodes (<1 cm) on CT. Identifiable lymph nodes at stations 2, 4, 7, 10 and 11 underwent FNAs. All patients underwent later surgical staging. EBUS detected 19 out of 20 occult metastases missed by CT. In another similar report by the same group in 97 patients with PET and CT negative mediastinum (no activity on PET and no lymph node >1 cm), Herth *et al.* [74] were able to detect eight out of nine occult lymph node metastases by EBUS-TBNA. Shingyoji *et al.* [77] published their experience of 113 patients with radiologically normal mediastinum who underwent pre-operative EBUS staging. Of the 113 patients, 20 (17.6%) had N2 disease and only seven of those 20 patients with occult disease were diagnosed using EBUS-TBNA [77]. Recently, Ong *et al.* [78] described their experience with EBUS-TBNA in 220 patients with radiologically normal mediastinum who underwent pre-operative EBUS staging. 49 (22%) patients were found to have occult metastases. 18 (8%) out of the 49 occult disease diagnoses were detected by EBUS [78]. In addition, Ong *et al.* [78] reported that when excluding the patients with metastases outside the reach of EBUS, the overall false-negative rate of EBUS-TBNA was lower. They noticed a significant number of patients with occult disease in lymph nodes that were not accessible by EBUS. The sensitivity of EUS-FNA alone for detecting occult metastases in radiologically normal mediastinum is 58% [69].

A prospective trial combined EBUS and EUS-B with a single echoendoscope for NSCLC staging in radiologically normal mediastinum with clinical N1 disease [79]. The overall sensitivity, accuracy and negative predictive value were 67%, 81% and 73%, respectively. All patients with negative results underwent mediastinoscopy. By adding mediastinoscopy to this cohort, the sensitivity and negative predictive value improved to 73% and 91%, respectively. However, this study had several limitations. Only 25% of patients underwent combined EBUS/EUS-B; 75% underwent a single EBUS procedure. The decision to add EUS-B was left to the discretion of the operator. Lobe-specific mediastinal nodal staging was done in this study, and this may be the reason for the low sensitivity and negative predictive value. Systematic nodal mapping of all nodes accessible by both EBUS and EUS may have yielded better results [79].

In a study by Szlubowski *et al.* [80], 120 patients with radiologically normal mediastinum underwent combined EBUS/EUS followed by TEMLA for negative results. Of the 99 patients who underwent TEMLA, metastases were diagnosed in nine patients (8% of the total cohort). The negative predictive value of combined EBUS/EUS in this patient population was 91%. The results demonstrated that in a radiologically normal mediastinum, if the results of the biopsy done for staging of NSCLC are negative by EBUS/EUS, surgical exploration of the mediastinum can be omitted [80]. The data is still controversial in this patient population. In view of these data, if there is clinical suspicion of mediastinal involvement after negative endosonography (*e.g.* clinical N1 disease, central tumours, tumours >3 cm), subsequent surgical staging may be indicated before radical surgery is attempted. Further studies are required to validate any recommendations.

Endosonography in restaging the mediastinum

Selected studies have addressed the issue of restaging the mediastinum by endosonography. To downstage disease, stage III NSCLC patients may be submitted to neoadjuvant

chemoradiotherapy. It is of utmost importance to identify the responders as they are able to benefit from subsequent surgery. HERTH *et al.* [81] published the first EBUS-TBNA restaging study in lung cancer with an overall sensitivity of 67% and negative predictive value of 78%. In a restaging study by SZLUBOWSKI *et al.* [82], 61 patients underwent EBUS-TBNA. All patients with negative results underwent TEMLA. Metastases were diagnosed in only 15% of patients in whom EBUS-TBNA was negative. In a more recent study by SZLUBOWSKI *et al.* [83], 106 patients underwent a combined EBUS/EUS-B restaging procedure. Patients with negative endosonography underwent TEMLA. Metastases were diagnosed in 17% of patients in whom endosonography was negative. The mean number of lymph node stations biopsied by TEMLA was much higher compared with endosonographic techniques (TEMLA 27.4 *versus* endosonography 2.7). In addition, gaining skills in endosonographic biopsy techniques in restaging is more time-consuming and operator-dependent than in initial staging due to post-inflammatory adhesions and fibrosis. It is very difficult even for an experienced operator to distinguish suspected regions of metastases and fibrosis [83].

A very recent retrospective multicentre study analysed 44 patients who had undergone pre-operative mediastinal restaging by EBUS-TBNA. All patients with negative results underwent a subsequent surgical staging procedure. EBUS-TBNA restaging had a sensitivity and negative predictive value of 82% and 88%, respectively [84]. The sensitivity of EUS-FNA alone for restaging after chemoradiation is ~44% with a false-negative rate of 58% [85]. The sensitivity compared with the nontreated patient is decreased due to necrosis and fibrosis of the lymph nodes following chemoradiation. Therefore, a negative endosonographic restaging result should always be confirmed by surgical techniques. In view of these data, the ESGE/ERS/ESTS guidelines suggest that initial restaging may be performed by EBUS-TBNA and/or EUS-B-FNA for detection of persistent nodal disease but, if negative, subsequent surgical staging is indicated before radical surgery is attempted (grade C recommendation) [1].

Planning stereotactic body radiation therapy

EBUS-TBNA is helpful in diagnosing N1 disease prior to initiation of SBRT in medically inoperable patients. In a retrospective review of 50 patients who underwent mediastinal nodal sampling by EBUS prior to fiducial placement for SBRT, SARWATE *et al.* [86] reported a downward stage shift in 10% of patients who were initially thought to have stage II and III disease and were considered for SBRT. In addition, 16% patients who did not have radiographic evidence of metastases were upstaged as they were found to have mediastinal lymph node metastases and were not candidates for SBRT [86]. Another very recent retrospective study of EBUS-TBNA prior to SBRT reported upstaging by 3% in patients who were thought to have clinical N0 disease and downstaging from clinical N1 to N0 in 50% of patients. The patients who were downstaged became eligible for SBRT [87]. In another retrospective report by NAKAJIMA *et al.* [88], 49 patients with either clinical N1/N2/N3 based on PET-CT underwent EBUS-TBNA prior to undergoing SBRT. EBUS-TBNA downstaged 43 patients to N0 disease, thereby making them eligible for SBRT. 40 out of 43 patients remained disease-free at 6–46 months of follow-up [88]. It is very important to rule out N1 disease prior to initiation of SBRT as a positive EBUS will change patient management.

Role of endosonography in the era of molecular markers

With the advent of tumour markers and the ability to characterise different types of NSCLC, the availability of suitable tissue samples has become an important issue and

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studies evaluating the role of EBUS have shown promising results [89–95]. The adequacy rate of EBUS-TBNA for molecular analysis depends on many factors: small sample size, tumour necrosis, sampling of nodal micrometastasis and contamination of the samples with blood or bronchial cells [96]. Several studies demonstrated that molecular analysis can be routinely performed on the majority of samples obtained by EBUS/EUS, with success rates ranging from 89% to 98% [92, 97, 98]. A recently emerging approach in the management of NSCLC is to manipulate the immune checkpoint controlled by programmed death ligand receptor 1 (PD-L1). As PD-L1 expression is evaluated by immunohistochemistry, acquisition of sufficient tissue is the key first step in PD-L1 testing. PD-L1 expression might be heterogeneous and therefore small biopsies might not be suitable for the assessment of PD-L1 expression. The utility of EBUS-TBNA for assessment of PD-L1 is currently being investigated in terms of tumour cell numbers and validation of PD-L1 assays. Sakakibara *et al.* [99] compared EBUS-TBNA samples to TBB specimens to evaluate the usefulness of EBUS-TBNA for evaluation of PD-L1 expression. They also looked at the correlation of PD-L1 positivity between EBUS-TBNA samples and the corresponding surgical specimens. EBUS-TBNA, TBB, corresponding surgical specimens and corresponding lymph node metastases had mostly similar outcomes in terms of PD-L1 positivity. EBUS-TBNA was found to be a more robust method than TBB in terms of the number and intactness of collected tumour cells [99]. Further studies are needed to validate the utility of endosonography in this setting.

Endosonography in lymphoma, granulomatosis and mediastinal cysts

The sensitivity of EBUS to diagnose lymphoma is ~57–61% [100–104]. The value of EBUS-TBNA in the diagnosis of lymphoma still remains controversial. EBUS-TBNA can be the first diagnostic modality in lymphoma diagnosis. However, for suspected new cases, especially for Hodgkin's lymphoma, the diagnostic yield of EBUS-TBNA is low and negative results cannot exclude lymphoma. Further interventions such as mediastinoscopy should be performed for patients with a high suspicion of disease following negative or nondiagnostic endosonography [100–104]. The sensitivity of EUS-FNA for the diagnosis of lymphoma is ~55–74% [105, 106]. The sensitivity is better (88%) for recurrent disease [107]. Further surgical biopsy is warranted in high-risk patients.

Endosonography has an excellent yield when assessing granulomas in patients with sarcoidosis. The imaging findings in sarcoidosis are generally of a symmetrically distributed cluster of lymph nodes around large vessels. The lymph node architecture is typically not destroyed and a hilum can be visualised. The sensitivity and accuracy of endosonography are superior compared with simple mucosal biopsies without and with a blind transbronchial puncture. Pooled sensitivity and specificity of EBUS-TBNA in the diagnosis of sarcoidosis were found to be 84% and 100%, respectively [108]. The diagnostic accuracy of combined endosonography (EBUS/EUS) is much higher (80%) compared with conventional bronchoscopic biopsies (53%) in patients with sarcoidosis [109].

The sensitivity, specificity and accuracy of EBUS-TBNA in diagnosing hilar and mediastinal lymph node tuberculosis are 70%, 97.2% and 89.9%, respectively, using cytological/pathological demonstration of caseating granulomatous biopsy [110]. In 102 cases with acid-fast staining and *Mycobacterium tuberculosis* PCR, the following results were demonstrated: 63.7% accuracy, 90.9% sensitivity and 66.7% specificity [110]. EBUS-TBNA has a higher yield than conventional TBNA for the diagnosis of histoplasmosis [111]. In a

study of 43 HIV-positive patients with mediastinal lymphadenopathy, the combined yield of BAL with TBB was 69.8%, the yield of BAL with EBUS-TBNA was 86% and that of TBB with EBUS-TBNA was 88.4%. The most common diagnoses were of tuberculosis, with a higher diagnostic accuracy using EBUS-TBNA than BAL [112].

The role of FNA cytology in diagnosing infections has expanded due to the increase in the number of immunocompromised patients and the increasing role of endosonographic FNA where infection is a major cause of illness. Endosonographic FNA has become the first procedural test in cases where the clinical and imaging findings suggest an infectious lesion accessible by these techniques. Extreme caution should be taken in aspirating mediastinal cysts as a transbronchial or transoesophageal route can infect the cyst. Duplication and foregut cysts have typical characteristics on echoendoscopy (multilayered wall structure, anechoic material) and therefore, if uncomplicated, can be diagnosed without the need and risk of biopsy.

Complications

The complications related to endosonographic needle aspiration include mediastinitis, sepsis, airway oedema, abscess, oesophageal perforation, pneumothorax and mediastinal haematoma. These complications are rare, with a reported mortality rate of 0.04% [113–118]. The complication rate of endosonographic techniques is significantly lower compared with surgical biopsy techniques. In comparison, the complication rate of conventional mediastinoscopy is significantly higher compared with EBUS/EUS. The complication rate is ~2%, including recurrent laryngeal nerve injury, haemorrhage and tracheal injury. Mortality has been reported to occur in 0.08% and is typically related to major vascular injury [46].

Training and competency

A systematic training in mediastinal endosonography should ideally be based on knowledge of anatomy, performance on simulators and supervised performance on patients. The diagnostic yield is highly operator-dependent and the learning curve shows substantial variation between individual operators. The traditional model of supervised training on real patients is not optimal, as trainee participation increases procedure time, amount of sedation used and shows a trend towards increased complication rates [119]. Simulation-based training might shorten the learning curve and can ensure basic competence before unsupervised performance. The classical approach is to start by learning the six landmarks for EBUS and EUS (as described earlier) and to practice finding them in sequence order, and then to perform supervised procedures on patients [120, 121].

The American Thoracic Society, ERS and ACCP recommend 40 procedures for initial competence and 20 procedures per year to maintain competency. The yield and the skill of the operator continue to improve after performing approximately 140 procedures [122–126]. Inadequate training may lead to increased healthcare costs as procedures are often repeated due to inadequate specimens.

Trained interventional pulmonologists are more likely to perform adequate staging compared with general pulmonologists with minimal procedural experience. This is

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expected as increased procedural volume correlates to evidence-based standard of care [127]. General aspects of training of interventional pulmonologists are discussed elsewhere in this *Monograph* [128].

Future of endosonography

An *ex vivo* human lung study showed that the newer thin convex probe EBUS had a greater reach and a higher success rate than standard convex probe EBUS, and could assess selectively almost all segmental bronchi. This will allow for more precise assessment of N1 nodes and, possibly, intrapulmonary lesions normally inaccessible to conventional convex probe EBUS [129]. This may prove to be very useful in the future, especially prior to making decisions on sublobar resections. There may also be therapeutic utility of endosonography in intratumoral injection of chemotherapeutic agents at locations accessible by these techniques [130, 131].

Conclusion

Combined endosonographic techniques (EBUS/EUS/EUS-B) have replaced conventional mediastinoscopy as the best initial test in staging NSCLC. When compared with traditional mediastinoscopy, the use of EBUS/EUS/EUS-B to sample multiple stations and distant metastases, including structures below the diaphragm, with higher sensitivities and negative predictive values makes it a new gold standard in the initial staging of NSCLC when performed by an experienced operator.

EBUS and EUS/EUS-B should complement each other and not be considered as competitors. The physician should choose the best minimally invasive approach depending on the available resources and expertise. It is recommended that negative endosonography should be surgically confirmed in patients with suspicious lymph nodes on either CT or PET.

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Bronchoscopic cryotherapy and cryobiopsy

Rajesh Thomas[1,2] and Martin J. Phillips[1,2]

Bronchoscopic cryotherapy is one of several complementary modalities that can be used for the management of malignant and benign endobronchial diseases. Cryotherapy can safely restore airway patency and improve symptoms in patients with central airways obstruction from exophytic tumours. It is also used in the treatment of granulation tissue and benign strictures, and to remove inhaled foreign bodies or impacted biological matter. Bronchoscopic cryobiopsy in endobronchial tumours and ILD improves diagnostic yield, and provides large amounts of well-preserved, high-quality tissue. However, the risk of severe bleeding following cryobiopsy is a major concern, and knowledge gaps remain about the ideal technique and patient selection. Future research must characterise the risks *versus* benefits of cryobiopsy compared with surgical lung biopsy and its role in the evaluation of diffuse parenchymal lung diseases. Research into novel applications of cryotherapy is underway and has the potential to transform the practice of interventional pulmonology.

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Cryotherapy is the use of extreme cold to freeze and so sample, damage or destroy human tissue. Bronchoscopic cryotherapy for thoracic diseases was initially used in the 1970s to treat inoperable endobronchial tumours. Since that time, applications have greatly expanded from being a bronchoscopic therapeutic debulking tool (by cryoablation) to include other forms of airway recanalisation treatments (*e.g.* cryorecanalisation and cryoextraction techniques) and diagnostic techniques (cryobiopsy).

Cryoapplications for thoracic diseases are known by various terms in the literature, including cryotherapy, cryoablation, cryorecanalisation, cryodebridement, cryocautery, cryosurgery, cryoextraction and cryobiopsy. The following terminology will be used in this chapter to describe the different cryotechniques. 1) Cryoablation: application of alternating freezing and thawing cycles to induce delayed cellular necrosis and tissue destruction. 2) Cryorecanalisation: debulking of an exophytic tumour by repeated cryoadhesive freezing and removal, leading to immediate re-establishment of airway patency. 3) Cryoextraction:

[1]Dept of Respiratory Medicine, Sir Charles Gairdner Hospital, Perth, Australia. [2]School of Medicine, University of Western Australia, Perth, Australia.

Correspondence: Rajesh Thomas, School of Medicine, Harry Perkins Building, Queen Elizabeth II Medical Centre, Perth, WA 6009, Australia. E-mail: rajesh.thomas@health.wa.gov.au

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removal by adhesive freezing of an inhaled foreign body, blood clot or impacted biological tissue (*e.g.* a mucus plug in the airway). 4) Cryobiopsy: sampling of bronchial, lung or pleural tissue by a cryoadhesion technique for histopathological evaluation.

Bronchoscopic cryotherapy is one of several modalities that can be used for the management of endobronchial conditions, both malignant and benign. Such therapies include laser photocoagulation, electrocautery, APC, mechanical debridement, airway stenting, PDT, radiotherapy (both brachytherapy and external beam) and chemotherapy. Each modality has its own properties and role to play, and many of these techniques and therapeutic procedures are discussed in more detail throughout this *Monograph* [1].

Here, we review the literature on bronchoscopic cryotherapy and cryobiopsy for thoracic diseases, and discuss their roles, principles, indications, techniques, outcomes and safety. Key gaps in knowledge, which may guide future research, are highlighted.

Literature search

MEDLINE, Excerpta Medica and the Cochrane Database of Systematic Reviews were interrogated using the following search terms: "cryotherapy", "cryoablation", "cryorecanalisation", "cryodebridement", "cryocautery", "cryosurgery", "cryoextraction", and "cryobiopsy"; and "bronchoscopy", "thoracoscopy", "endobronchial tumour", "lung cancer", "endobronchial biopsy", "transbronchial biopsy", "lung biopsy" and "pleural biopsy". References and their citation lists were scrutinised.

History

In 1850, James Arnott invented a device using salt and crushed ice solution to treat breast and skin cancer by freezing (−24°C) [2, 3]. Improvements in cryotechnology using liquefied gas over the next century led to further advances in medical cryoapplications, including cryotherapy [4–6]. Cryotherapy was initially used in the treatment of skin cancers; later, closed-tip and specially shaped applicators called cryoprobes were employed for the delivery of cryotherapy to cancers in other anatomical areas [7, 8].

A rigid cryoprobe applicator for endobronchial cryotherapy was successfully used in the 1960s [8]. The Mayo group pioneered the bronchoscopic cryoablation technique to treat bronchogenic tumours [9–15]. Early work in animals showed that the cryoablation process caused a localised and reproducible mucosal ulceration that evolved within 6 h and healed by 2 weeks [13, 16]. Cryonecrosis and subsequent repair of the frozen tracheal cartilage lagged the mucosal changes, but also normalised by 4 weeks. In 1975, Sanderson *et al.* [15] reported the first case of bronchoscopic cryotherapy by cryoablation in a patient with endobronchial cancer. During the following decades, many American and European centres adopted this method of endobronchial cryotherapy to debulk tumours in the central airways and relieve endobronchial strictures, and demonstrated its effectiveness and safety [17–22].

The introduction of a nonrigid cryoprobe with interchangeable tips allowed cryotherapy to be extended to tumours in the upper lobe bronchi [20]. The subsequent development of a fully flexible cryoprobe that could be used along with a flexible bronchoscope provided more

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versatility [23]. This, combined with improvements in the tensile strength and freezing power of the flexible cryoprobe, enabled a more rapid debulking of endobronchial tumours by the cryorecanalisation method [24–26] and transformed thoracic cryopractice. More recently, spray cryotherapy (SCT), a technique that utilises non-contact-mode flash-freeze from vapourised liquid nitrogen, has been approved for bronchoscopic treatment of airways pathology [27–30].

Today, bronchoscopic cryotherapy is supported by major thoracic societies as an accepted treatment modality for inoperable airway malignancy [31, 32].

Cryobiology

Contact cryotherapy with a cryoprobe acts by cryoablation, a slow-freeze process that causes cell necrosis and tissue destruction through immediate and delayed effects [33, 34]. Immediate intracellular and extracellular ice crystallisation damages vital intracellular organelles such as mitochondria and endoplasmic reticulum, while efflux of intracellular fluid causes cellular dehydration and shrinkage, resulting in direct cell injury [7]. Delayed effects result from vasoconstriction, endothelial injury and microvascular thrombosis, causing tissue ischaemia that leads to selective cellular necrosis and cell death [33]. This ischaemic effect also extends beyond the immediate area of probe contact to cause surrounding tissue infarction.

SCT acts by a flash-freeze mechanism whereby liquid nitrogen applied directly onto the tissue vapourises (−196°C), causing intracellular ice formation and cell death. This method may have an advantage in promoting tissue regeneration as the extracellular matrix is preserved during the process [27, 35].

Sensitivity to cryotherapy is mainly determined by tissue water content and vascularity. Highly vascular tissues such as tumour, granulation tissue, mucous membranes and endothelium are very cryosensitive; fat, collagen, connective tissue and cartilage are cryoresistant and less susceptible to the cryoadhesive effect [33, 36, 37]. The differential effects of cryotherapy on different layers of the tracheobronchial tissue may allow mucosal healing without formation of strictures and bronchial cartilage or wall damage.

The extent of tissue damage is greater with more rapid freezing and slower thawing, a higher number and duration of freeze–thaw cycles, a lower applied temperature, a larger probe size, and a larger tissue contact area with the probe [33, 38–42]. A rapid fall in temperature to below −40°C results in >90% cell destruction [12, 43].

Equipment

Current bronchoscopic cryotechniques utilise the Joule–Thomson principle, in which rapid freezing is caused by the sudden expansion of certain gases, such as nitrous oxide (−89.5°C) and carbon dioxide (−78.5°C), moving from a high-pressure to a low-pressure region. The original cryotherapy techniques used liquid nitrogen (−196°C) based on its property of having an extremely low boiling point.

The cryoequipment is simple to set up, and consists of a cylinder containing a freezing gas (cryogen) stored under high pressure, a console (cryomachine) that controls the flow of

cryogen and a catheter with a cryoprobe at one end to freeze target tissue by direct contact. The bronchoscopist uses a foot pedal to activate and regulate the flow of the cryogen through the catheter from the cylinder to the cryoprobe. The cryogen rapidly freezes the tip of the cryoprobe as it exits a higher pressure region within the catheter to a lower pressure region outside the probe (figure 1). The theoretical lowest temperature for the gas is achieved only inside the probe immediately as it exits the catheter; the actual freezing temperature achieved on the outside of the probe is usually slightly higher. Spontaneous defrosting occurs once the flow of the cryogen is ceased following deactivation.

Endobronchial cryoprobes are of different types (rigid, semirigid and flexible), and have probe tips of various shapes (straight and angled) and diameters (1.1–2.4 mm flexible and 2.4–5.5 mm rigid probes). The larger rigid cryoprobe can treat more tissue in a shorter period as it has an additional mechanism for active thawing that allows a shorter freeze–thaw cycle. Thawing is spontaneous and, therefore, slower with a flexible probe; however, the slower thawing process has the advantage of causing more tissue necrosis.

Rigid cryoprobes can only be used with a rigid bronchoscope. A rigid probe with straight forceps is used to treat lesions in the central airways and lower lobes, while forceps with an angled tip are needed for lesions in the upper lobe bronchi [17]. A flexible cryoprobe is easier to use as it can be inserted through the working channel of a flexible bronchoscope; a flexible cryoprobe can also access the distal bronchi and peripheral lung parenchyma, in addition to the central airways [23].

General considerations

Debulking an endobronchial tumour to relieve central airways obstruction is primarily a palliative procedure, and is performed in patients with inoperable disease to improve distressing or life-threatening symptoms and quality of life. An interventional pulmonologist has many bronchoscopic modalities to choose from, including cryotherapy, to achieve optimal palliation. Cryotherapy can be used alone or, on occasion, together with other methods such as laser, electrocautery, APC, mechanical debridement, PDT and brachytherapy. These are complementary techniques that act through different effects on

Figure 1. Flexible cryocatheter with an ice ball formed on the tip of the probe after freezing.

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tissue so that often a multimodality approach may be required to optimise patient outcomes [1].

The optimal choice of bronchoscopic treatment depends on the availability of treatment equipment, expertise of the bronchoscopy team, site (central *versus* peripheral) and type (intraluminal *versus* extraluminal) of airways obstruction, extent of disease, and performance status of the patient. A patient with a short endoluminal lesion and patent distal airway is appropriate for bronchoscopic tumour debulking. In the case of critical airway obstruction, urgent recanalisation is necessary and best achieved by cryorecanalisation, laser, APC or mechanical debridement. Cryoablation, brachytherapy and PDT are unsuitable because their effects are delayed.

As with any bronchoscopic intervention, patient selection and assessment for cryotherapy are crucial, and should be individualised. This involves a complete clinical examination, assessment of performance status, CT evaluation, pulmonary function testing, evaluation of fitness for anaesthesia and assessment of bleeding risk. Anticoagulant and/or antiplatelet drugs, particularly clopidogrel, are ceased preoperatively.

Cryoprocedures can be performed under general anaesthesia or intravenous sedation. High-risk procedures such as bronchoscopic cryorecanalisation and cryobiopsy are best performed under general anaesthesia with a rigid bronchoscope or endotracheal tube in place as this allows better ventilation and adequate control of the airway in case of complications, particularly severe bleeding. A combined approach using a flexible bronchoscope introduced through a rigid bronchoscope or endotracheal tube during cryoadhesive procedures provides both the flexibility to reach less accessible regions in the tracheobronchial tree and the ability to rapidly withdraw the flexible bronchoscope, cryoprobe and attached frozen tissue, and re-introduce the scope.

Therapeutic cryoapplications

Cryotherapy: cryoablation and cryorecanalisation

Cryoablation

Bronchoscopic cryoablation was the original cryotherapy method used to debulk central airway tumours. Cryoablation causes freeze injury to effect cellular necrosis, tissue devitalisation and tumour destruction.

Technique

The endobronchial tumour is exposed to multiple freeze–thaw cycles during the bronchoscopic cryoablation procedure. The distal tip of the flexible bronchoscope is held just above the target area when using a flexible cryoprobe; the tip of the probe is pushed 5–10 mm beyond the bronchoscope to touch the lesion perpendicularly, tangentially or within and then activated under direct visualisation. Activation while the probe tip is still inside the working channel of, or too close to, the bronchoscope can cause damage to the scope and cryoprobe from ice crystal formation.

Each freeze–thaw cycle lasts for 1–3 min and is repeated up to three times at each region depending on the size and depth of the lesion [17, 18, 20, 23, 44]; this process is then performed sequentially in an adjoining region until the entire tumour is treated. Freezing

variably damages the surrounding tissue depending on the size and freezing power of the probe, the probe–tissue contact area and the tissue type [37]. Additional treatments, spaced 2–4 weeks apart, may be necessary.

Blood and slough are often seen following cryoablation of large necrotic tumours. This is removed either in between the cryoapplications by cryoextraction with the cryoprobe and/or with forceps, or continuously using a suction catheter deployed through a rigid bronchoscope. The remaining frozen tissue undergoes delayed necrosis, and is sloughed off and expectorated over the following days. A clean-up bronchoscopy may be necessary within 5–14 days to debride and remove devitalised tissue and airway secretions [23].

SCT also has similar disadvantages of delayed treatment response and the need for follow-up bronchoscopy [28, 35, 45]; it is therefore not recommended for cryoablation of tumours causing critical airway obstruction. Of concern, the early studies of SCT also showed high rates of severe complications related to barotrauma and hypoxaemia [28]. Further research to refine the technique and establish the safety and efficacy of SCT is needed.

Cryorecanalisation

Cryorecanalisation is a more recent bronchoscopic technique. It utilises the power of cryoadherence, instead of repeated freeze–thaw injury, to forcefully shear off tissue such as tumour, adherent on the frozen tip of the cryoprobe. During the cryorecanalisation process, the endobronchial tumour is debulked piecemeal by repeating the process of cryoadherence and tissue removal many times. This allows a more rapid clearance of an obstructed airway in a single bronchoscopic session and is a major advantage compared with the slower cryoablation method [24, 26].

Technique

Hetzel *et al.* [24] first described the cryorecanalisation technique using a flexible catheter cryoprobe. The tip of the cryoprobe is guided through the working channel of the flexible bronchoscope, placed tangential, perpendicular or within the tumour and frozen for up to 20 s. The depth and extent of the ice front can be controlled under direct vision to ensure that only the diseased area, not healthy tissue, is frozen. After adequate freezing, both the cryoprobe and bronchoscope are firmly pulled back together to tear the adhered tissue away from the bronchial wall. The tumour breaks off easily from the bronchial wall when traction is applied as the ice formation is inhomogeneous in the transition area between the tumour and normal bronchial wall.

As the frozen tissue attached to the probe is larger than the working channel of the flexible bronchoscope, the scope, cryoprobe and adhered tumour are removed en bloc; the tissue is then removed by immersion and thawing in saline. This process is repeated multiple times to rapidly remove tumour pieces and recanalise the airway (figure 2).

Outcomes

Cumulative data show that complete or partial restoration of airway patency occurs in 59–90% of cases after bronchoscopic cryoablation [17, 20, 21, 23] and in >80% of cases after cryorecanalisation [24–26]. Cryotherapy improved dyspnoea (37–86% of cases), haemoptysis (67–100%), performance scale (63%), oxygenation (66–71%), radiology (59%) and pulmonary function (in 28% of cases with mean improvements in FEV1 and forced vital capacity of 0.12 and 0.2 L, respectively) [17, 18, 20, 21, 23, 44]. Further interpretation

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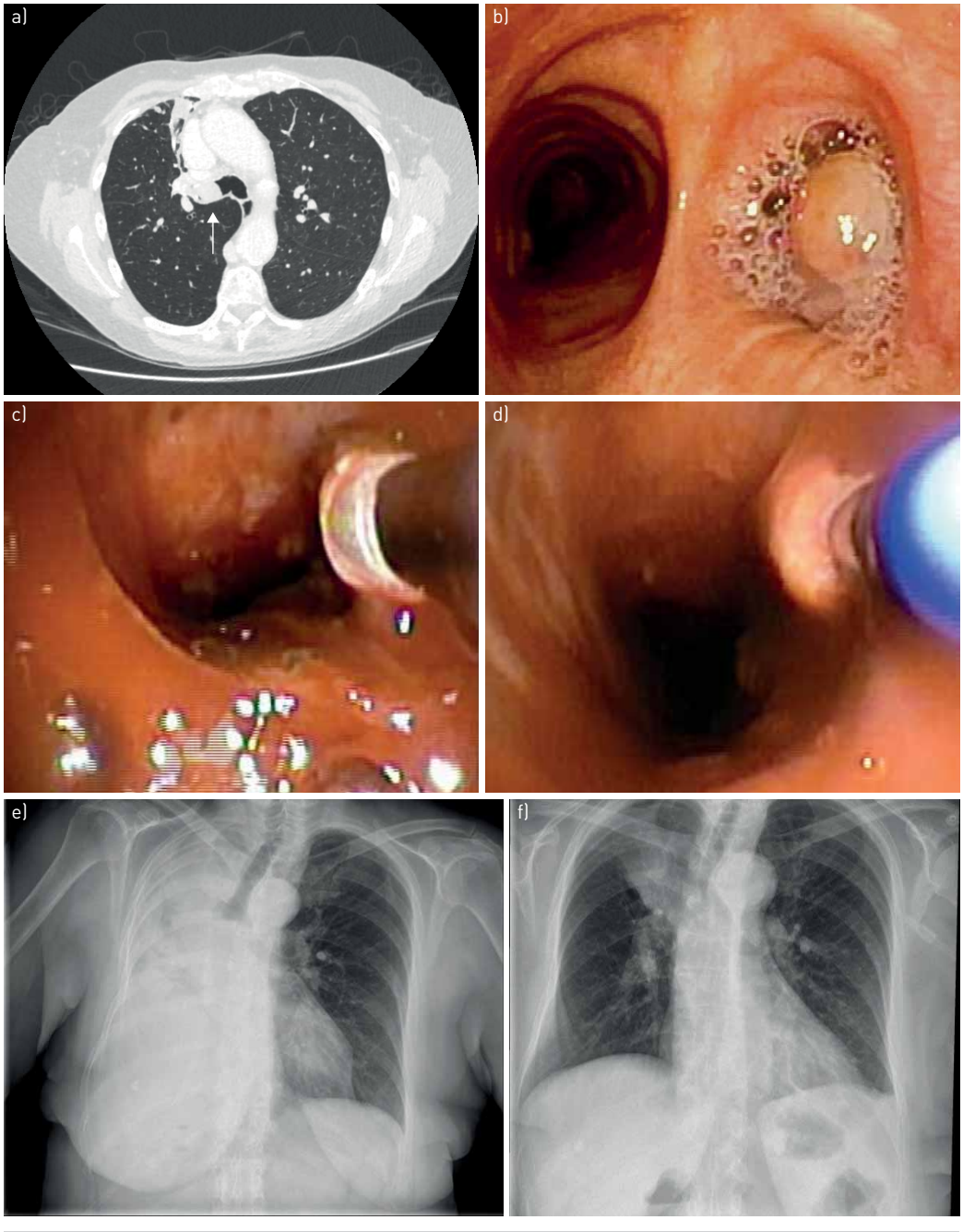

Figure 2. a) CT (axial view) of thorax showing a tumour (arrow) arising from the right upper lobe and completely obstructing the right main bronchus. b) Bronchoscopic view of the tumour completely obstructing the right main bronchus. c) Piecemeal removal of tumour adherent to the cryoprobe. d) Re-establishment of patency of the right main bronchus following cryorecanalisation procedure. e) Pre- and f) post-cryorecanalisation chest radiographs showing re-expansion of collapsed right middle and lower lobes. The right upper lobe tumour and collapse persist.

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of this data is not possible given that most reports were of uncontrolled cohort studies with variable outcome measures, definitions of success and heterogeneous populations.

Treatment success of bronchoscopic cryotherapy is determined by the location and type of the tumour, and the type and number of cryotherapy procedures. Cryotherapy is very effective in the treatment of endobronchial exophytic tumours, although cryotherapy may need to be repeated in the case of large tumours. A higher success rate is seen with cryorecanalisation and repeated treatments [46]. Submucosal or extrinsic tumours are best treated by airway dilatation and/or placement of an airway stent [47, 48].

Complications

The safety profile of cryoablation treatment is comparable to, or better than, other interventional bronchoscopic modalities; however, this has to be balanced against the relatively limited and delayed therapeutic effects. Most complications are minor (e.g. airway oedema, bronchospasm and fever) that could be managed with conservative measures [49]. However, mucosal oedema, necrotic debris, blood and secretions following cryotherapy can worsen critical airway obstruction and cause respiratory distress [25]. This is not unique to cryoablation and could occur regardless of the bronchoscopic intervention chosen as these procedures are inherently high risk due to the nature of advanced cancer, extent of airway obstruction and impairment of cardiopulmonary reserve.

Bleeding is the major complication associated with cryorecanalisation [24–26]. Mild bleeding (requiring cold saline or topical epinephrine) and moderate bleeding (requiring APC or a bronchial blocker) following recanalisation were seen in 4% and 8% cases, respectively, in one series (n=225) [26]. Severe bleeding causing haemodynamic instability did not occur in this series; however, it is advisable to avoid cryorecanalisation in highly vascular tumours. Prophylactically devitalising vascular tumours using APC or electrocautery further reduces the risk of bleeding [25].

Cryotherapy versus *other bronchoscopic therapeutic interventions*

Bronchoscopic cryotherapy has many advantages and few limitations compared with common bronchoscopic modalities, yet remains underutilised [50]. It is easy to learn and perform; international guidelines recommend 10 supervised procedures is sufficient to establish competency [51]. The procedure is well tolerated by the patient and most patients can be discharged home on the same day.

The initial establishment costs and recurring expenses for cryotherapy are significantly lower than other modalities. The cost of consumables is minimised as the cryoprobe catheter can be reused after sterilisation. The main operational expense is for the cryogen that needs replacement depending on usage. The cryotherapy equipment is portable, and can be set up quickly and easily. In comparison, treatment with laser therapy is expensive due to the high initial cost of a laser unit, and the recurring cost for maintenance of the laser unit and the disposable catheters. Optical protection and specialised safety training for the bronchoscopy team are also necessary when using laser therapy.

Bronchoscopic cryotherapy also has safety advantages. The risk of cryonecrosis and accidental airway injury or bronchial wall perforation are low as bronchial cartilage and fibrous tissue are cryoresistant. Unlike with other bronchoscopic interventions, with cryotherapy there is little risk of collateral damage to covered metallic stents, radiation exposure, electrical injury or endoluminal fire when using high-flow oxygen.

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Cryotherapy in early superficial bronchogenic carcinoma

There is no consensus on the ideal treatment method of early superficial bronchogenic carcinoma (ESBC). Limited data exist regarding surgical resection and bronchoscopic methods, including cryotherapy, laser therapy, electrocautery and PDT. Results from one cryoablation study involving 35 patients with 41 ESBC lesions showed complete response lasting >1 year in 91% of treated patients and up to 50% survival at 4 years [52]. This is comparable to the results of PDT without the severe or prolonged cutaneous photosensitisation associated with PDT [53–55]. Future studies comparing cryotherapy with surgery and other bronchoscopic treatments for ESBC are needed.

Cryotherapy in benign airway disease

Bronchoscopic cryotherapy is an excellent treatment modality for removal of cryosensitive benign endobronchial tumours such as hamartoma (figure 3) [56]. Endobronchial lipomas, despite the relative cryoresistance of fat, are also treatable by cryotherapy [57, 58]. Bertoletti *et al.* [56] performed bronchoscopic excision of carcinoid tumours and cryoablation of the implantation base in 18 patients. Tumour recurrence was seen in one patient only after 7 years; none developed bronchial stenosis or long-term complications.

Granulation tissue is also highly cryoresponsive. Endobronchial granulation tissue and benign strictures that develop after lung transplantation, tracheostomy, placement of airway stents and endobronchial tuberculosis have been treated successfully by bronchoscopic cryotherapy [19, 23, 59–61]. Cryotherapy is not effective in severely fibrotic benign strictures as dense collagen is cryoresistant.

SCT is a potential new bronchoscopic treatment for glottic and subglottic narrowing. Krimsky *et al.* [62] treated three females with four cycles of 5 s SCT, and recorded restoration of airway patency and laryngeal function without complications. Larger studies are needed to confirm its benefits and safety as SCT has been associated with major intra-operative complications [28, 45].

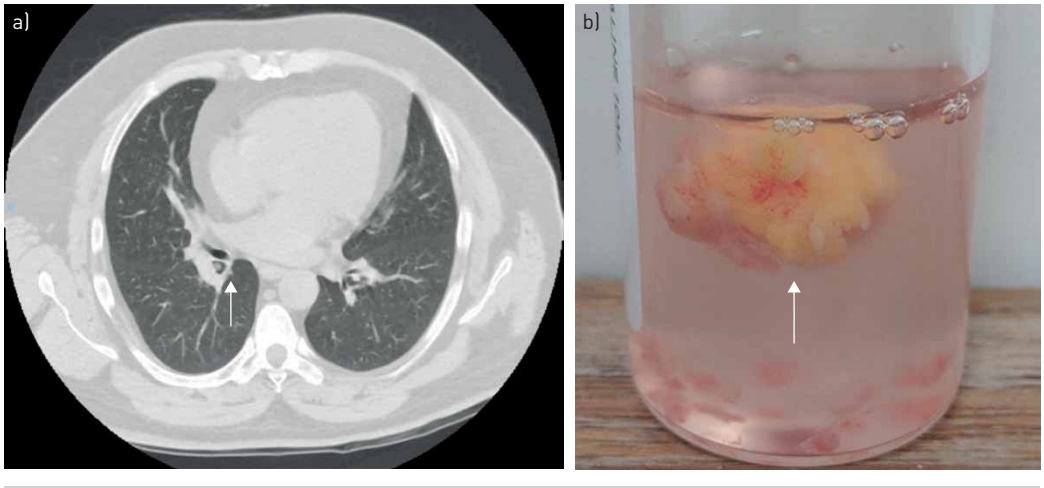

Figure 3. a) CT (axial view) of thorax showing a tumour (arrow) occluding the right lower lobe bronchus. b) Macroscopic appearance of the tumour (arrow) removed by cryorecanalisation. Histopathological examination confirmed a hamartoma. Reproduced with kind permission of Phan Nguyen (The Royal Adelaide Hospital, Adelaide, Australia).

Cryoextraction of foreign bodies, blood clots and biological matter

A variety of inhaled organic foreign bodies such as food material (figure 4) and pills have been removed from the airway using a cryoadherence and extraction process [63–68]. Cryoextraction is also effective in removing impacted blood clots (figure 5a–d), mucus plugs (figure 5e), necrotic slough and other biological matter, such as teeth and bones [69, 70]. These objects have a high water content and firmly adhere to the cryoprobe on freezing, and are then removed en bloc with the probe and bronchoscope. Foreign bodies with a lower water content, *e.g.* metal coins, are poorly cryoadherent and less amenable to removal by freezing. General procedures for foreign body removal are discussed elsewhere in this *Monograph* [71].

Diagnostic cryoapplications

A modified cryoadherence technique for tissue biopsy is a novel diagnostic tool in the evaluation of thoracic diseases. Endobronchial and transbronchial lung cryobiopsy during bronchoscopy and thoracoscopic pleural cryobiopsy are described in the literature.

Cryobiopsy provides large amounts of well-preserved, high-quality tissue that shows little mechanical damage despite the cryoinsult [72–78]. The specimens have preserved architectural integrity without the tear and burn artefacts seen with conventional forceps biopsy and electrocautery, respectively. The haemostatic effect of freezing helps to reduce artefact formation. Comprehensive immunohistochemistry and molecular studies can be reliably performed on cryobiopsy specimens, vital for planning of targeted therapy in thoracic cancers [77].

Endobronchial cryobiopsy

Technique

The technique to perform endobronchial cryobiopsy is similar to the cryorecanalisation technique described earlier. The bronchoscope, cryoprobe and adhered biopsy tissue are removed en bloc after freezing the tumour under direct visualisation. The tissue attached to the tip of the cryoprobe is spontaneously thawed in normal saline at room temperature and once detached is transferred into a formalin preservative for further processing.

Outcomes

Endobronchial cryobiopsy has a higher diagnostic yield and provides larger specimens than forceps biopsy (figure 6). The reported diagnostic yield of endobronchial tumours by cryobiopsy is 89–95% compared with 66–85% by flexible forceps biopsy [73, 76, 79]. The cryobiopsy specimens are significantly larger (10.4 *versus* 5.2 mm^2) and have more artefact-free tissue area [77, 79]. Two cryobiopsy specimens are sufficient to provide the maximal diagnostic yield (94%) while minimising the risk of bleeding [80].

Complications

The rate of severe bleeding (0.3% of cases) after endobronchial cryobiopsy is comparable to that seen after flexible forceps biopsy [79].

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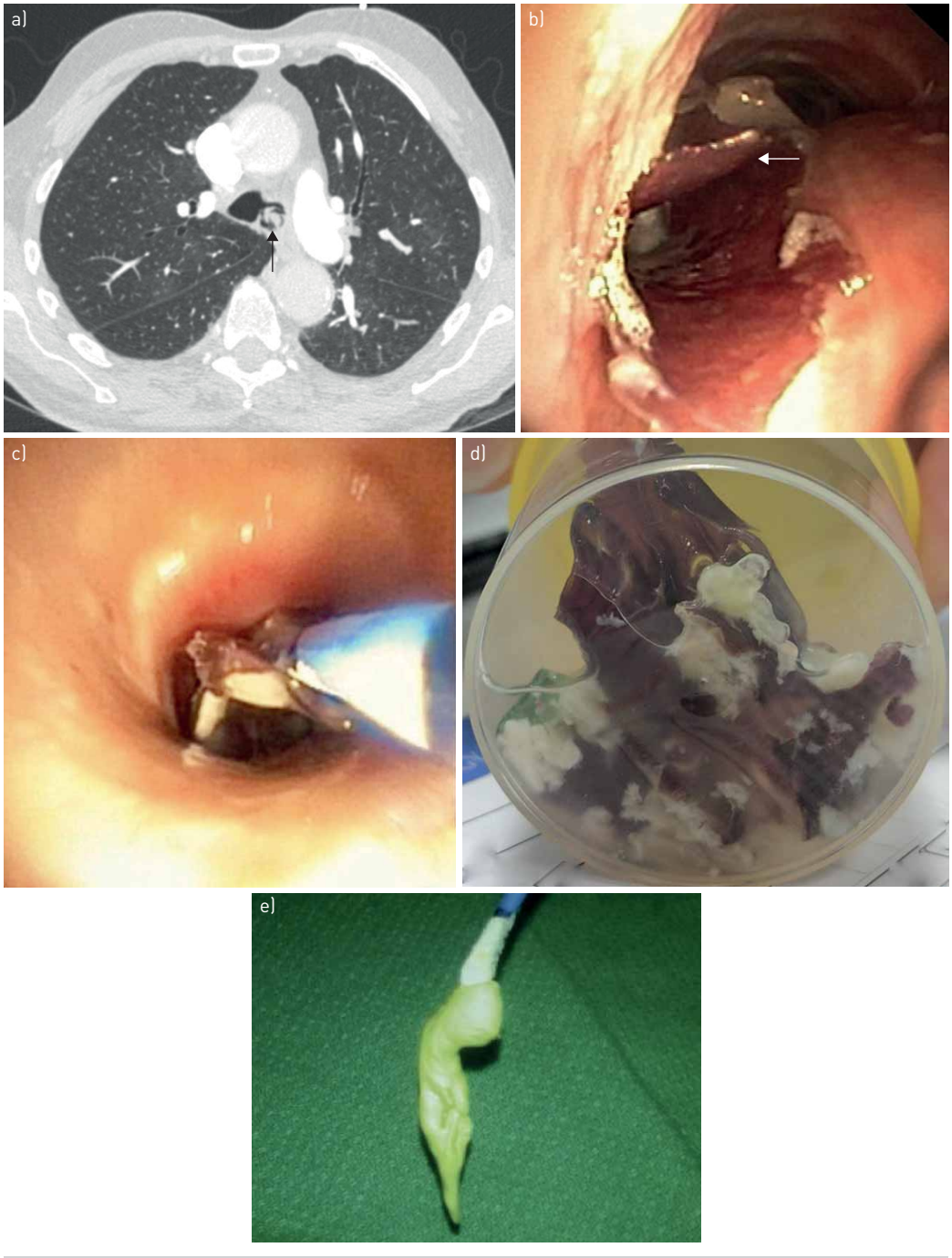

Figure 4. a) CT (axial view) of thorax showing aspirated veal parmigiana within the left main bronchus (arrow). b) Bronchoscopic view of the foreign body in the left main bronchus (arrow). c) Bronchoscopic removal of the foreign body by the cryoextraction process. d) Macroscopic view of the extracted piece of veal parmigiana. e) Aspirated chewing gum that was removed by bronchoscopic cryoextraction in a different patient. a–d) Reproduced with kind permission of Phan Nguyen (The Royal Adelaide Hospital, Adelaide, Australia); e) reproduced with kind permission of Jonathan Williamson (Macquarie University Hospital, Sydney, Australia).

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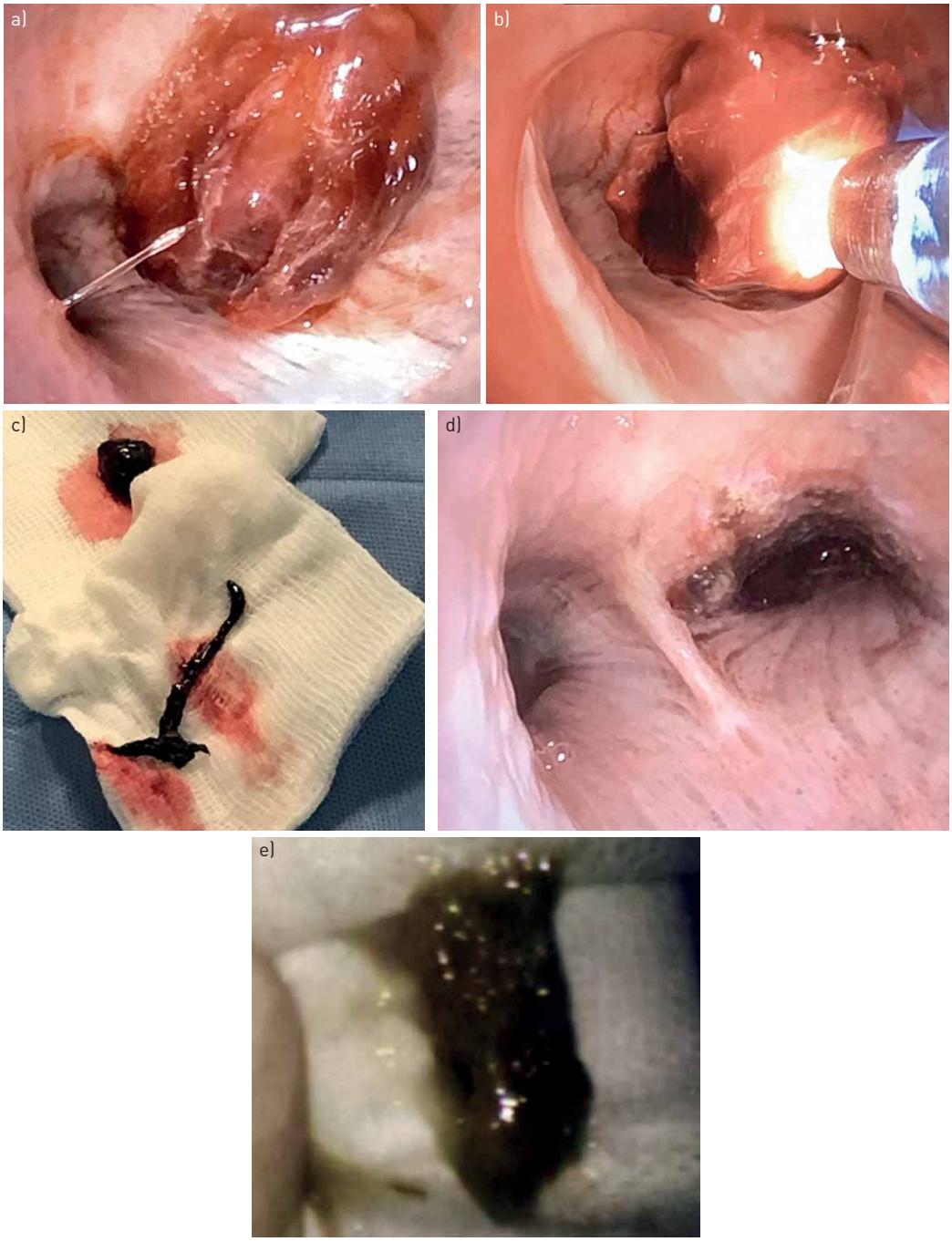

Figure 5. a) Bronchoscopic view of a large blood clot completely obstructing the right main bronchus. b) Bronchoscopic cryoextraction of the blood clot. c) Macroscopic view of the extracted blood clots. d) Establishment of patency of the right main bronchus following removal of blood clot with evidence of underlying mucosal infiltration and residual bronchogenic carcinoma. e) Macroscopic view of an impacted mucus plug removed from within a metallic stent by cryoextraction. a–d) Reproduced with kind permission of Matt Salamonsen (Fiona Stanley Hospital, Perth, Australia); e) reproduced with kind permission of Jonathan Williamson (Macquarie University Hospital, Sydney, Australia).

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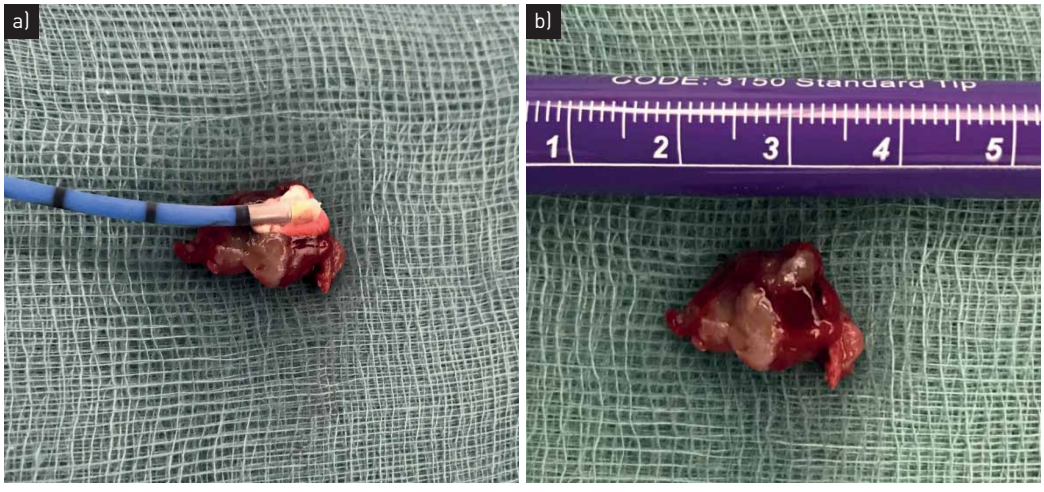

Figure 6. a) Tumour tissue adherent to the tip of the cryoprobe following endobronchial cryobiopsy. b) Demonstrating the large size of an endobronchial cryobiopsy specimen.

Cryo-transbronchial lung biopsy

Cryo-TBLB is a promising, less invasive alternative to surgical lung biopsy to diagnose idiopathic pulmonary fibrosis (IPF) and other diffuse parenchymal lung diseases. As with endobronchial cryobiopsy, cryo-TBLB utilises the cryoadhesive effect to obtain larger samples of high-quality lung tissue without the crush artefacts seen with TBLB using flexible forceps [81].

Technique

Cryo-TBLB is performed using a flexible bronchoscope placed immediately above the bronchial opening of the target lung segment. The flexible cryoprobe is guided through the working channel of the bronchoscope and pushed towards the periphery of the appropriate lung segment under fluoroscopic guidance. On activation, the cryoprobe tip freezes the surrounding lung tissue. The adhered lung is torn off as the scope and probe are forcefully pulled back, and removed en bloc.

The ideal freeze time for cryo-TBLB is not known. A study on anesthetised sheep involving 49 cryo-TBLBs with a 1.9 mm cryoprobe showed a strong correlation between increased freeze time and the number of serious complications [82]. An initial freezing time of 3 s appeared optimal, yielding the largest biopsy size while minimising the rate of bleeding and pneumothorax. Findings in animal experiments must, however, be extrapolated with caution to humans with fibrotic lungs.

Outcomes

A number of studies have demonstrated the feasibility of cryo-TBLB in the evaluation of IPF [83, 84], diffuse parenchymal lung diseases [74, 85–90] and lung transplant rejection [75, 78, 91]. Cryo-TBLB specimens have a higher diagnostic yield than standard TBLB in fibrotic ILD (51% *versus* 29%) [89] as the cryobiopsy specimens are significantly larger (15.11 *versus* 5.8 mm^2) and provide more contiguous lung to help delineate the spatial and temporal heterogeneity characteristic of usual interstitial pneumonia (UIP) [74].

Cryo-TBLB can support a confident diagnosis in many subtypes of ILD; its reported diagnostic yield ranged between 74% and 98% (83% pooled estimate) when histopathological assessment alone was used [85, 88–90], and between 51% and 98% (79% pooled estimate) when the cryo-TBLB finding was discussed in a multidisciplinary setting [85, 87–89, 92].

There is growing evidence that cryobiopsy can reliably distinguish subtypes of fibrotic ILD, including IPF (the most challenging interstitial pattern to characterise). In a prospective study (n=69) of cryo-TBLB in fibrotic ILD, UIP was diagnosed on histopathology alone in 77% cases; there was very good interobserver agreement between pathologists for the UIP pattern (κ=0.83) [83]. In a retrospective study (n=32), cryo-TBLB diagnosed the type of ILD and avoided surgical lung biopsy in two-thirds of the cohort [87].

There is no direct comparison study of cryo-TBLB with the currently recommended practice of surgical lung biopsy in a multidisciplinary setting. Only one study has compared outcomes of cryo-TBLB *versus* surgical lung biopsy reviewed in a multidisciplinary setting in fibrotic ILD (n=117, 58 cryo-TBLB and 59 surgical lung biopsy). In this study, Tomassetti *et al.* [84] found that the pathologists' confidence level in diagnosing UIP was significantly lower for cryo-TBLB compared with surgical lung biopsy (52% *versus* 85%, respectively) when clinical and radiological information were unavailable. The interobserver agreement for the UIP pattern was also lower with cryo-TBLB (κ=0.59 *versus* 0.86).

The difference in the pathologists' confidence was, however, not reflected in the diagnostic confidence of multidisciplinary teams; in both groups, the number of cases diagnosed as IPF following multidisciplinary discussion after biopsy information was added doubled (69%) compared with that diagnosed by clinico-radiological criteria alone [84]. However, the study did not provide diagnostic accuracy data as it did not directly compare cryo-TBLB and surgical lung biopsy in the same patient.

The diagnostic accuracy of cryo-TBLB in fibrotic ILD compared with surgical lung biopsy may be lower because cryobiopsy specimens are smaller, often from one lobe only and possibly less representative than surgical biopsy specimens. A randomised controlled trial directly comparing the diagnostic accuracy of cryo-TBLB *versus* surgical lung biopsy in a multidisciplinary setting in IPF is currently recruiting subjects (Australian New Zealand Clinical Trials Registry: identifier ACTRN12615000718549). Other clinical trials comparing cryo-TBLB with surgical and forceps biopsies in ILD are also underway (ClinicalTrials.gov: identifiers NCT02763540, NCT01714518 and NCT01972685).

Complications

Bleeding and pneumothorax are major complications associated with cryo-TBLB; exacerbations of ILD can also occur [83]. The rates of moderate/severe bleeding (in 0–78% cases) and pneumothorax (0–26% of cases) are comparable to those seen with standard TBLB, but lower than for surgical lung biopsy [74, 83, 85–90, 93].

Regardless of this, cryo-TBLB must be considered a high-risk procedure that could result in catastrophic or fatal bleeding because there is an inherent loss of control of the airways during cryo-TBLB that is not seen with the other methods. The immediate danger with severe bleeding following cryo-TBLB is that the flexible bronchoscope needs to be taken out of the bronchial tree for several seconds for the frozen biopsy tissue to be thawed. During this period, the airway is extremely vulnerable as the scope cannot be used to wedge the

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bronchus to tamponade any bleeding. For this reason, it must be emphasised again that cryobiopsy should not be attempted before prior intubation with a rigid bronchoscope or endotracheal tube as re-introduction of the flexible bronchoscope or subsequent intubation of the airway can be extremely difficult or impossible in the event of severe bleeding.

Prophylactic use of a bronchial blocker or a Fogarty balloon during a cryo-TBLB procedure may be useful to control bleeding after cryobiopsy. A noninflated Fogarty balloon is initially positioned in the lobar bronchus before cryobiopsy and inflated immediately after the bronchoscope is withdrawn post-biopsy. The inflated balloon is left in place, and deflated only after the bronchoscope is re-inserted and bleeding has been ruled out or controlled. The balloon tamponades the affected bronchus and prevents spillage of blood into other areas.

Fluoroscopic guidance during cryobiopsy may be useful to reduce bleeding and pneumothorax rates as it helps place the cryoprobe perpendicular to and within 1–2 cm of the pleura, thereby avoiding the larger central pulmonary vessels and the parietal pleura.

The high variability in the reported yield and complication rates likely reflects the heterogeneity in cryo-TBLB practice, including technique (*e.g.* duration of freezing, probe size and its positioning), number of biopsies obtained, use (or not) of fluoroscopic guidance, targeted site of biopsy (*e.g.* the risk of pneumothorax is higher with a UIP pattern and the extent of lower lobe fibrosis [90]), inconsistent definition and reporting of outcomes and adverse events, differences in the study population, and (in)experience of the bronchoscopist [94, 95].

More evidence for the diagnostic accuracy of cryo-TBLB compared with surgical lung biopsy in a multidisciplinary setting and further characterisation of its risks *versus* benefits, particularly in IPF, are necessary before its routine use can be recommended.

Pleural cryobiopsy

Thoracoscopic pleural cryobiopsy may have a role in selected cases, although its routine use is unnecessary. The diagnostic yield of pleural cryobiopsy is noninferior to flexible forceps pleural biopsy, but may be inferior to pleural biopsy by rigid forceps [72, 96–99]. The first study on the use of rigid cryobiopsy of the pleura for undiagnosed pleural effusions (n=18) showed a 100% diagnostic yield and no significant complication [100]. Thomas *et al.* [72] reported a diagnostic yield of 90% in 22 patients with an undiagnosed pleural effusion who underwent flexi-rigid thoracoscopy and pleural biopsy using a flexible cryoprobe. This was similar to the yield of pleural biopsy by flexible forceps; however, the cryobiopsy tissue specimens were significantly larger, deeper and qualitatively better with less crush artefacts.

The main advantage of pleural cryobiopsy is in patients with thickened pleura, such as in mesothelioma and fibrothorax, who undergo flexi-rigid thoracoscopy [72, 101]. Cryobiopsy provides deeper tissue necessary to demonstrate invasion of atypical mesothelial cells into the deeper structures, the hallmark of mesothelioma. Pleural cryobiopsy is technically easy to perform and can shorten the procedural time in cases with thickened fibrotic pleura by reducing the number of passes with flexible forceps needed to reliably obtain adequate pleural tissue. A second entry port for rigid forceps biopsy during flexi-rigid thoracoscopy is also not required [72].

Pleural cryobiopsy during thoracoscopy is safe. Post-biopsy bleeding is mild and similar to conventional pleural biopsy [72, 96–99]. No major complications or deaths have been reported. The technique is discussed in more detail elsewhere in this *Monograph* in the overall context of local anaesthetic thoracoscopy [102].

Knowledge gap and future directions

The scope of bronchoscopic cryotechniques has expanded greatly in recent years; however, knowledge gaps remain about the optimal technique, risks *versus* benefits and patient selection. Previous research mainly consisted of small cohort studies that, because of the heterogeneity in patient groups, study protocols and end-points, make comparisons difficult. At the same time, large, multicentre randomised studies are challenging to perform in this patient group characterised by severe breathlessness, hypoxaemia and cardiorespiratory diseases.

Defining the risks of severe complications with cryobiopsy, particularly bleeding, and its diagnostic yield and accuracy, particularly in IPF, must be a priority. Ideally, randomised controlled studies that compare cryobiopsy with surgical lung biopsy and employ meaningful end-points in a multidisciplinary setting are necessary. The benefits of bronchoscopic manoeuvres to reduce bleeding risks during cryobiopsy, *e.g.* use of endobronchial balloon blocker, topical tranexamic acid or norepinephrine and fluoroscopic guidance, should be evaluated systematically. Standardisation of bronchoscopic cryobiopsy technique, training and accreditation must also be rigorously examined.

Technological improvements and miniaturisation of cryoequipment are likely to generate novel cryoapplications in thoracic disease in the future. New types of cryoapplicators are already in various stages of development. A 1.1 mm thin cryoprobe that can be used to perform TBLB through a 2.6 mm guide sheath was successfully used in *ex vivo* animal lung and porcine models [103, 104]. The new mini-cryoprobe with the adherent frozen tissue specimen can be removed through the working channel of the flexible bronchoscope; the scope itself remains in the bronchial tree throughout to tamponade any bleeding.

A previous pilot study had demonstrated the feasibility of bronchoscopic cryobiopsy of peripheral lung nodules [105]; it is now the subject of a randomised controlled study comparing it with CT-guided lung biopsy (ClinicalTrials.gov: identifier NCT02395939). A mini-cryoprobe has additional advantages as it allows the use of a radial ultrasound probe combined with the guide sheath to reliably access and biopsy the peripheral nodule. An early cryoneedle prototype for EBUS-guided transbronchial lymph node biopsy is also currently undergoing testing in animal models [106].

A cryoneedle that can deliver cryotherapy using a transthoracic approach is commercially available, although more robust data about its efficacy and place in cancer treatment is awaited [107]. The role of probe contact and flash cryotherapy to treat uncommon diseases such as benign subglottic stenosis is being actively explored. New data on the synergistic effects of combining cryotherapy with chemotherapy or radiotherapy in animal models might open up therapeutic options for concurrent lung cancer treatment [108–112].

These are major advancements that could open up exciting therapeutic and diagnostic possibilities once their safety and efficacy are confirmed in humans.

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Conclusion

Bronchoscopic cryobiopsy and cryotherapy have an established role in the diagnosis and treatment of thoracic diseases. Cryoablation and cryorecanalisation are effective and safe treatments for airways obstruction caused by exophytic tumours. Cryobiopsy is a useful diagnostic tool for endobronchial and transbronchial lung biopsies, and yields large amounts of high-quality tissue; however, there are concerns about the risk of severe post-biopsy bleeding. Future research must characterise risks *versus* benefits of cryobiopsy if it is to be recommended for routine use. Development of newer cryoapplications has the potential to transform bronchoscopy practice.

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Chapter 11

Navigational bronchoscopy in solitary pulmonary nodules

Ralf Eberhardt[1] and Joris van der Horst[2]

Suspicious peripheral pulmonary nodules need to be clarified histologically. Depending on the probability of malignancy and the patient's comorbidities, the lesion can be resected surgically or a nonsurgical biopsy is necessary. The challenge in diagnosing a peripheral parenchymal nodule by bronchoscopy is to detect the nodule endoscopically, especially if it is not visible on fluoroscopy. Apart from TBB under fluoroscopic guidance, various navigation techniques such as radial EBUS, virtual bronchoscopy and electromagnetic navigation bronchoscopy are available to increase the diagnostic yield. Further developments are necessary in order to make bronchoscopic treatment of small malignant peripheral lesions possible, ideally in a one-step diagnostic and therapeutic procedure.

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Lung cancer is one of the most common cancers in both men and women worldwide. Prognosis is strongly dependent on the stage of disease at presentation. Although the risk factors are well known, the majority of patients are diagnosed at an advanced stage of disease, making cure with currently available techniques unlikely. In contrast, patients with an early tumour stage can be treated curatively with surgical resection or radiotherapy and they will have improved survival [1].

The desire for early detection of lung cancer has led to the idea of lung cancer screening. Initial attempts to screen for lung cancer with sputum analysis and/or radiographs of the thorax did not show a survival benefit for participants; however, more recent lung cancer screening trials utilising low-dose CT have been more promising. The 2010 National Lung Screening Trial (NLST), completed after enrolling more than 53 000 subjects, was for the first time able to show a decrease in lung cancer mortality [2]. In screening trials using chest radiographs, pulmonary nodules were noted in only 0.2% of patients, whereas 27.3% of patients undergoing the NLST had at least one nodule with a diameter of >4 mm detected on their CT, with the majority of these considered benign [2, 3]. Several other

[1]Pneumology and Critical Care Medicine, Thoraxklinik, University of Heidelberg, Translational Lung Research Center Heidelberg (TLRCH) and Member of the German Center for Lung Research (DZL), Heidelberg, Germany. [2]Respiratory Dept, Glasgow Royal Infirmary, University of Glasgow, Glasgow, UK.

Correspondence: Ralf Eberhardt, Pneumologie und Beatmungsmedizin, Thoraxklinik am Universitätsklinikum Heidelberg, Röntgenstrasse 1, 69126 Heidelberg, Germany. E-mail: ralf.eberhardt@med.uni-heidelberg.de

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screening trials performed to date also detected a high number of pulmonary nodules [4, 5]. Furthermore, the generally increased use of thorax CT for other medical indications has led to a substantial increase in the number of incidental findings, including nodules (figure 1).

A solitary pulmonary nodule (SPN) is defined radiologically as an intraparenchymal lung lesion that is <3 cm in diameter and is not associated with atelectasis or adenopathy [6]. After radiological detection of a SPN the significant challenges are the classification of the nodule as benign or malignant and, more particularly, the diagnosis of a specific disease. The probability of malignancy of an incidentally detected pulmonary nodule in a CT scan depends on its size or diameter. Even in a high-risk group of heavy smokers the estimated risk of attaining a diagnosis of lung cancer is <1% when a pulmonary nodule with a diameter of <6 mm is found [5]. However, the risk of malignancy increases in line with the size of the nodule. The likelihood of malignancy for peripheral SPNs between 0.8 and 2.0 cm in diameter is reported to be ~18%, and for nodules >2.0 cm, ~50% [7, 8]. Suspicious morphology or upper lobe location are further features that increase the probability of malignant disease in these patients [9].

Diagnosis of solitary pulmonary nodules

One of the challenges in the early diagnosis of lung cancer remains the difficulty in reaching these small lung lesions, detected by radiography or CT, and successfully obtaining adequate tissue samples for pathological diagnosis. Due to the low prevalence of malignancy among small lung nodules <6 mm, nodules of this size are usually followed up by a low-dose CT scan. With both increasing size and pre-test probability of malignancy, *e.g.* due to predisposing risk factors, a nonsurgical biopsy and/or a surgical resection are/is usually recommended [1, 10].

In cases with a high probability of cancer, a direct surgical resection should be considered in order to diagnose and treat the nodule in one session. Ideally, a primary surgical approach would lead to resection of malignant nodules while sparing benign nodules. There are, however, several good reasons to avoid primary surgery and to perform a nonsurgical biopsy:

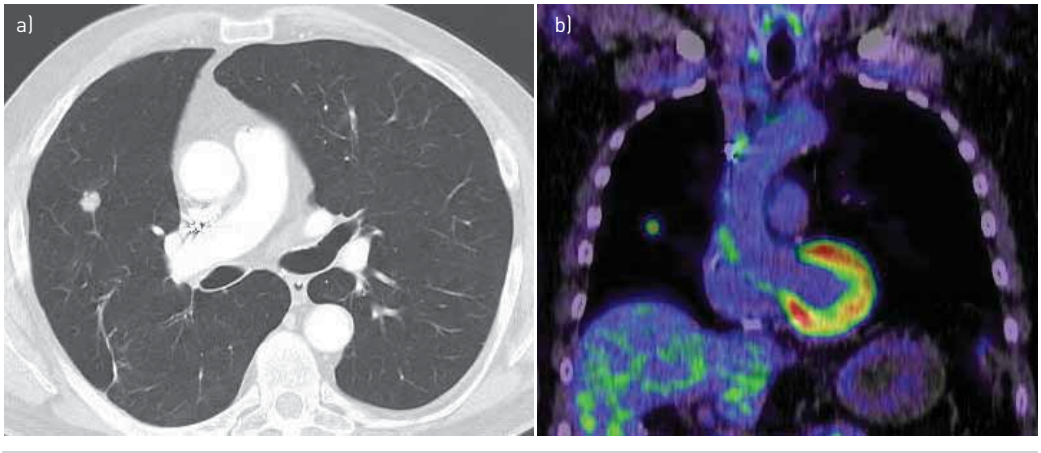

Figure 1. a) CT scan and b) corresponding PET scan from a 56-year-old patient with a 12 mm solitary pulmonary nodule in the middle lobe, suspicious for lung cancer. An acinar adenocarcinoma was diagnosed after surgical resection.

1) some patients may wish to have malignancy confirmed before contemplating surgery; 2) the investigator may be concerned about a benign diagnosis, which would not require resection; and 3) perhaps most importantly, significant patient comorbidities or poor surgical fitness may counsel against a primary surgical approach [11].

In a retrospective analysis of patients referred for surgical resection, 73% were found to be less than ideal candidates for surgery. More than half of the patients had to be excluded due to contraindications against surgery or an unacceptably high peri- or postoperative risk of morbidity and mortality [12]. In cases like these the confirmation of malignancy prior to any treatment should be attempted with minimally invasive methods.

The two standard approaches for diagnosing peripheral pulmonary lesions by minimally invasive methods used currently are transthoracic needle biopsy and bronchoscopy with TBB. A nonsurgical biopsy should be considered whenever imaging results and pre-test probability are discordant and the probability of malignancy is low to moderate [10, 12] or when comorbidities and surgical risk counsel against a surgical approach. Although no studies directly comparing these two approaches are available, the methods appear to be complementary. In general, transthoracic needle biopsy is preferred when the nodule is more peripheral or in the subpleural space, whereas a bronchoscopic approach is favoured for more centrally located lesions, especially where a bronchus sign is present, *i.e.* a bronchus is seen to lead towards the SPN [13].

The advantage of transthoracic needle biopsy under CT guidance is the high sensitivity with a specificity of nearly 100%. The sensitivity for malignancy is between 74% and 96%, and depends on the size of the lesion, location and distance to the pleura as well as the biopsy technique employed [10, 14]. The most common complication is a post-interventional pneumothorax; the risk is related to the size of the lesion, number of biopsies, distance to the pleura and degree of accompanying lung emphysema. A meta-analysis of 15 865 patients showed a pneumothorax rate of 15% and an insertion of a chest tube was needed in >6% of all procedures. The frequency of haemoptysis after transthoracic needle biopsy was ~1% [15].

The standard endoscopic approach for diagnosing SPN is bronchoscopy with TBB using forceps. Other techniques described are cryobiopsy, TBNA or catheter aspiration [16–18]. A meta-analysis has shown that TBNA alone or combined with forceps is superior to TBB by forceps alone in diagnosing SPNs [18].

The bronchoscopy is usually performed under fluoroscopic guidance to aid steering the biopsy tool to the peripheral lung lesion. The value of this method depends on the size of the lesion, relationship of the nodule to the airways and visibility under fluoroscopy. In a meta-analysis the diagnostic yield for peripheral lesions >2.0 cm was 63%, whereas for nodules <2.0 cm the diagnostic yield dropped to 33% [19].

The use of CT for steering the biopsy tools to the lesion improves both the image quality and visual control, but despite that does not appear to improve the diagnostic yield or reduce the complication rate [20, 21]. Furthermore, the radiation exposures for the patient and staff as well as the demand on CT scanner time limit its usefulness in routine practice.

The advantage of the bronchoscopic approach in diagnosing SPNs over CT-guided transthoracic needle biopsy is its lower complication rate, with a pneumothorax rate of <3% [22]. However, the diagnostic yield has historically been lower than with CT-guided

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transthoracic needle biopsy. Bronchoscopic biopsies using forceps can be performed under medication with acetylsalicylic acid 100 mg·day^{-1}, but should be considered carefully under clopidogrel due to the higher risk of bleeding [23, 24].

Navigational bronchoscopy

Improving the diagnostic yield of bronchoscopic sampling while preserving its advantage of lower complication rates when compared with a transthoracic approach remains a challenge, and will depend on improved techniques for navigation towards the lesion and better manoeuvrability of the sampling probes.

Radial EBUS

One of these technologies is radial EBUS, which can be used to locate and assess peripheral pulmonary lesions. Although EBUS probes have been developed for assessing the central airways and the mediastinum, the smaller calibre radial ultrasound probes can be placed through the working channel of a flexible bronchoscope into the peripheral lung, and can also be used to detect and analyse peripheral pulmonary lesions.

Technical aspects

These so-called miniprobes are available in different sizes with an external diameter of 1.4 or 1.9 mm (Olympus, Tokyo, Japan) or 1.7 mm (Fujinon, Tokyo, Japan). The most commonly used ultrasound frequency is 20 MHz, which provides high resolution and allows detailed imaging of the internal structures of peripheral lung lesions. In normal, ventilated and air-filled lung parenchyma, all ultrasound waves will be reflected and the miniprobe produces a snowstorm-like "white-out" ultrasound picture, even when the lesion is close to the tip of the probe, but separated by a small intervening layer of air. If the lesion can be reached endobronchially and the tip can be placed within or adjacent to the lesion, the image will change (figure 2).

Solid tumours are usually clearly distinguishable against the normal lung tissue by a bright border. The sono-morphological image of a tumour appears grey and mostly homogeneous,

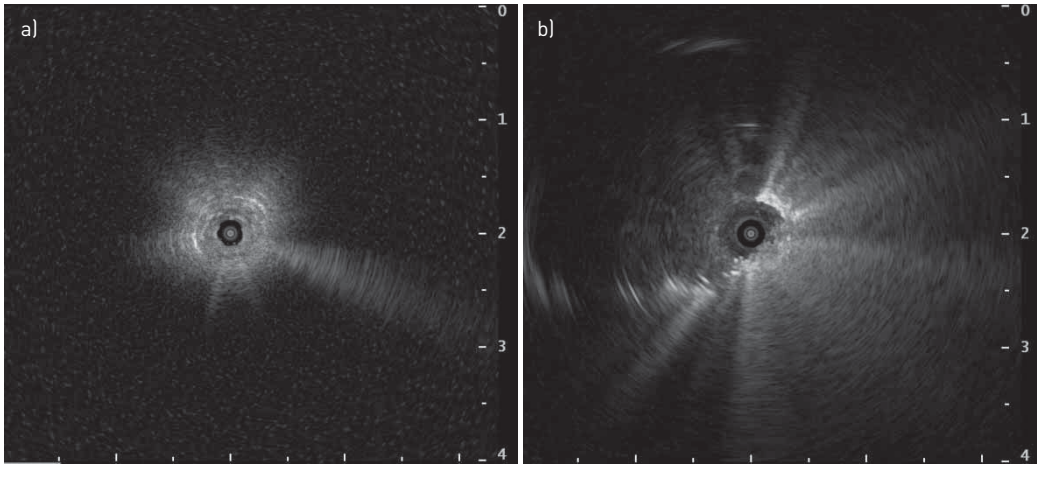

Figure 2. a) Ultrasound image of a peripheral aerated lung: the ultrasound waves are reflected completely and only a whitish snowstorm-like image is visible. b) After reaching the peripheral lesion, the image changes and the pulmonary nodule is visible adjacent to the probe.

although necrotic areas and vessels can be seen as circumscribed black areas. Furthermore, the existence of a continuous hyperechoic margin and the absence of a linear-discrete air bronchogram should raise the suspicion of malignancy. In contrast, ultrasound images of inflammatory tissue or atelectasis have a heterogeneous appearance, caused by the various different structures of the lung. Small bronchi containing trapped air are visible as sharp, white echo spots; the fluid-filled areas appear dark and the borders are slightly blurred (figure 3) [25–27]. However, in patients with lepidic growth pattern carcinoma, the ground-glass opacities have an appearance similar to inflammatory tissue, and a distinction between benign and malignant appearances is not possible here.

Although the use of radial miniprobes in the peripheral lung is technically straightforward, it can sometimes be difficult to interpret the findings. Fluids appear black in the EBUS images, but no Doppler mode is available in the radial ultrasound to differentiate between necrotic areas and vessels. Here, tracing the course of the structure or looking for arterial vascular pulsation can be instructive. Trapped air leads to sharp, white spots with a "comet tail" sign behind which should not be confused with calcifications. Any strong reflections will create repeating echoes that can be recognised by their consistent interval distance.

EBUS-guided bronchoscopy

The EBUS miniprobes can be used like a flexible forceps probe and can be advanced into the relevant subsegmental bronchi where the lesion is suspected. This can be difficult when the probe has to be flexed; in addition, excess friction has to be avoided to protect the transducer and the connecting driving wire from damage. A water-filled balloon over the transducer is not usually necessary in the peripheral lung. The pulmonary nodule has been reached when the ultrasound image shows a solid round or oval lesion. Unfortunately, the biopsies cannot be taken under real-time visual control. The miniprobe has to be removed before introducing a biopsy tool into the working channel. The difficulty of then having to navigate back to the lesion can be reduced by using a guide sheath.

Following EBUS guidance, TBB using flexible forceps is the most common sampling technique. The diagnostic yield depends on the size and the visibility of the pulmonary

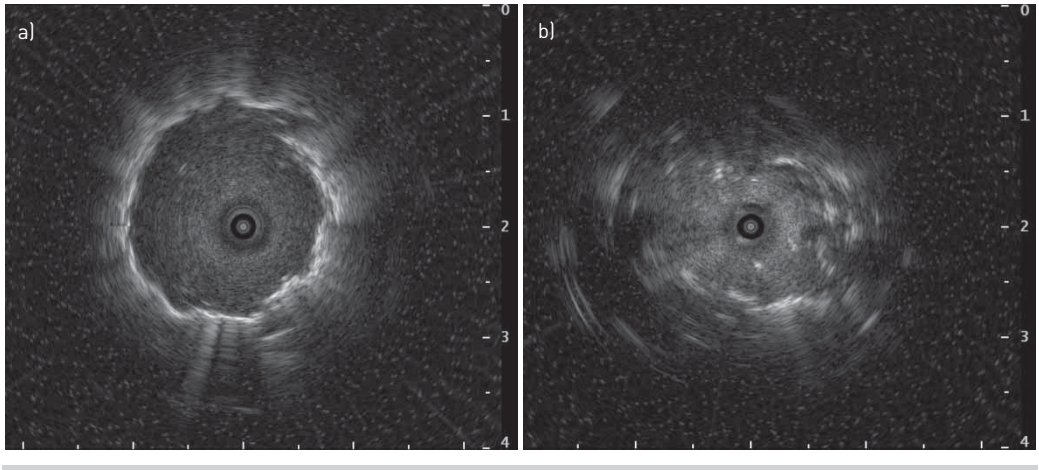

Figure 3. a) Typical EBUS image of a malignant tumour (nonsmall cell lung cancer) with solid structure and clear borders to the surrounding lung. The miniprobe is placed within the lesion. b) EBUS image of a pneumonic infiltrate with white spots and blurred borders.

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nodule in the ultrasound image. Smaller SPNs are more difficult to reach, but the yield will be higher if a bronchus leads directly to the lesion and the probe can be placed within the lesion [28]. However, alternative or additional biopsy tools can be used. The additional use of a TBB needle (TBNA) or a thin aspiration catheter increases the diagnostic yield. This applies in particular if the miniprobe can only be placed adjacent to, but not directly inside, the nodule [16, 29]. Cryoprobes are used widely for taking endobronchial biopsies or TBBs to diagnose endobronchial tumours or ILDs [30, 31]. These probes are also effective in sampling peripheral lung nodules. The advantage of cryobiopsies are the lager size of the samples, better preserved histological architecture with fewer crush artefacts and possibility to obtain tissue from beyond the bronchial wall of the leading bronchus [17]. However, the bronchoscope has to be removed altogether with the cryoprobe and attached sample, which then requires repeated navigation towards the lesion.

The first description of the use of radial miniprobes for detecting peripheral lung lesions was in 2002 [32]. Currently, three different techniques for EBUS guidance are available: The first is to take biopsies "blindly" from the same subsegment after detecting the lesion and removing the EBUS probe. The second and most common approach is to use fluoroscopy to direct the miniprobe to the lesion and to check that the biopsy tool is in the same position that the EBUS probe was in at the time of tumour imaging, before then taking biopsies. The third technique involves advancing the EBUS miniprobe inside a guide sheath catheter used as an extended working channel (EWC). The probe is inserted into a small catheter and both together are advanced through the working channel of the bronchoscope to the peripheral lung [33]. The miniprobe is removed after reaching the lesion, whereas the guide sheath is left in place close to or within the nodule. It is then possible to introduce various biopsy tools through this EWC directly to the region of interest. This technique can also be used for diagnosing peripheral pulmonary lesions that are not visible under fluoroscopy or that are <20 mm [34, 35].

Steinfort *et al.* [36] undertook a systematic review and meta-analysis of 13 studies and 1090 patients undergoing EBUS-guided bronchoscopy for diagnosing peripheral lung lesions. Although significant interstudy variation in the EBUS method was noted, the authors found a pooled sensitivity of 73% and specificity of 100% for radial EBUS-guided biopsies. The pneumothorax rate was 1.0% and no severe bleeding was observed. Moreover, the complications should be attributed to the use of forceps biopsy *per se* and not the use of radial miniprobes, and if the assessment time is limited no increased complication rate should be expected due to a prolonged sedation time. Therefore, EBUS is a safe and relatively accurate tool in the investigation of SPNs, increasing the likelihood of achieving a diagnosis and decreasing the need for surgical biopsy. In a retrospective analysis of four randomised trials with 481 patients, Ye *et al.* [37] found that fluoroscopic TBB plus EBUS was superior to TBB under fluoroscopy alone and the clinical benefit was higher in smaller lesions.

The diagnostic sensitivity of EBUS is also influenced by the prevalence of malignancy in the patient cohort being examined. The yield for EBUS-guided TBB was only 57% in a clinical registry [38]. However, this can in part be explained by selection bias, because the choice of technique for diagnosis was not prescribed and varied from CT-guided biopsy or conventional TBB to TBB with EBUS guidance. In addition, EBUS was used particularly in smaller lesions.

The use of radial EBUS as an adjunct imaging modality is recommended in patients suspected of having lung cancer in the current guidelines of the American College of Chest Physicians, if the technology is available [10].

Combining radial EBUS with other navigational techniques may further improve diagnostic accuracy in peripheral pulmonary lesions.

Virtual bronchoscopy

Ultrathin bronchoscopes with an outer diameter of 3–4 mm have now been available for a few years. These bronchoscopes can be advanced far into the peripheral lung, which may improve access to more peripheral SPNs. However, the anatomical variability of bronchi increases with each generation of subsegments and orientation towards the target becomes increasingly difficult with each bifurcation passed, even for very experienced operators.

Raw CT scan data can be used to generate a three-dimensional virtual bronchoscopy with visual representation down to the sixth generation of bronchi, which allows planning of a virtual pathway towards the target lesion [39]. Following this virtual pathway towards the lesion will significantly simplify navigation in the periphery for the operator and has the potential to enable good results even for less experienced operators, without much additional training required. At present, two different systems are commercially available: LungPoint (Broncus Medical, Mountain View, CA, USA) and Bf-NAVI (Cybernet Systems, Tokyo, Japan). The latter has recently been replaced by the DirectPath system (Cybernet Systems). Generally, two phases can be distinguished: 1) the planning of the pathway and 2) the actual bronchoscopy procedure with biopsy sampling.

Virtual bronchoscopy planning

Although a virtual bronchoscopy can be easily reconstructed with raw diagnostic CT data, the use of virtual bronchoscopy-guided bronchoscopy for diagnosis of peripheral pulmonary nodules is not widespread. For high-quality virtual bronchoscopy a slice thickness of the CT of <1 mm is necessary to achieve a virtual bronchial tree far enough into the peripheral lung [39]. Thicker CT slices, breathing artefacts and/or excessive endobronchial secretion all shorten the visual reconstructed bronchial tree. The CT data have to be uploaded in the DICOM format (Digital Imaging and Communications in Medicine; National Electrical Manufacturers Association, Rosslyn, VA, USA).

The LungPoint computer-based navigation system allows reconstruction of the thorax and the pulmonary nodule in three dimensions. The peripheral lesion can be marked and several possible pathways can be calculated prior to performing the bronchoscopy. The pathway will be laid over the virtual bronchoscopy images and the distance from the point of view to the target can be shown.

An endobronchial pathway to a defined target can be calculated in similar fashion with the Bf-NAVI virtual bronchoscopy system. The CT data requirements are also similar. Nonvisible bronchi can be added using a manual editing or extraction process. The bronchial bifurcations as well as the airways to be intubated will be displayed in the planning of the route.

Virtual bronchoscopy-guided bronchoscopy

Performing virtual bronchoscopy-guided bronchoscopy is similar to that of normal bronchoscopy, but with the use of a thin or ultrathin bronchoscope. Repeated rotation of the instrument is needed in order to advance into more and more peripheral bronchi. This makes it much more difficult for the physician to maintain orientation within the bronchial tree.

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In the LungPoint system the virtual bronchoscopy as well as the real endoscopic image are visible simultaneously. After initial synchronisation of the virtual and real images both the position and the rotation of the virtual bronchoscopy picture will be adapted automatically. The calculated pathway towards the target lesion that has to be followed by the investigator is projected over the images as a blue line (figure 4) [35]. After steering the bronchoscope as close as possible to the lesion, a biopsy can be taken through the working channel at the defined point of entry.

Bf-NAVI depicts the bifurcations during the bronchoscopy. The investigator has to go forward to each next bifurcation in a stepwise approach. The virtual images can be rotated and so adapted to the real endoscopic image. The bronchus to be inserted is marked and after advancing the scope to the next bifurcation, the procedure has to be repeated (figure 5). Direct feedback about the real position of the bronchoscope in the bronchial tree is not available with this method. Artefacts, such as mucus in the airway, can be misrepresented by the virtual bronchoscopy software as a bifurcation, which can increase the difficulty of the technique.

Virtual bronchoscopy is mostly used for diagnosing endoscopically nonvisible lesions in the peripheral lung. This technology can be used on its own or in combination with fluoroscopy, CT guidance and/or radial EBUS to confirm that the nodule has been reached before taking biopsies. CT guidance is particularly suitable for small, low-density lesions, which are not visible under fluoroscopy. A diagnostic yield of up to 82% has been reported in the literature [39]. However, excessive radiation exposure as well as logistical challenges limit its routine use. For that reason virtual bronchoscopy is more frequently used in combination with fluoroscopy using a C-bow. The sensitivity for virtual bronchoscopy plus fluoroscopy in diagnosing SPNs is between 62.5% and 78.7%; even for smaller SPNs <2 cm it is between 54.5% and 76.9% [39].

With the additional use of virtual bronchoscopy with ultrathin bronchoscopes for diagnosing peripheral pulmonary nodules under fluoroscopy the diagnostic yield, especially

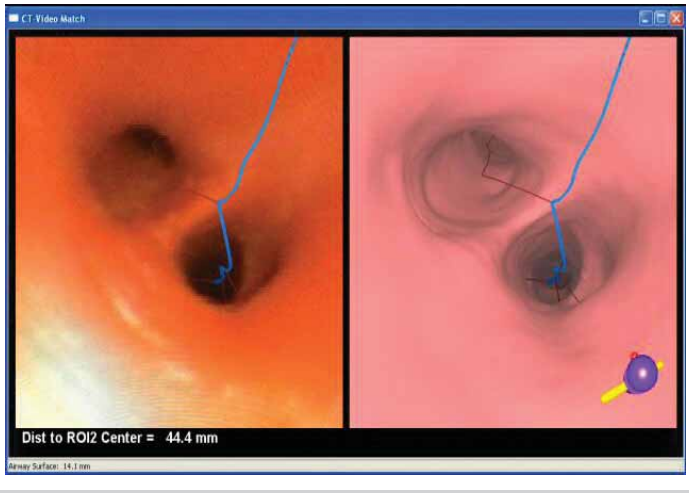

Figure 4. Virtual bronchoscopy with the LungPoint system (Broncus Medical, Mountain View, CA, USA). Both the endoscopic and virtual image are visible simultaneously. The pathway to the lesion is overlaid as a blue line. ROI: region of interest. Figure reproduced and modified with kind permission of Broncus Medical.

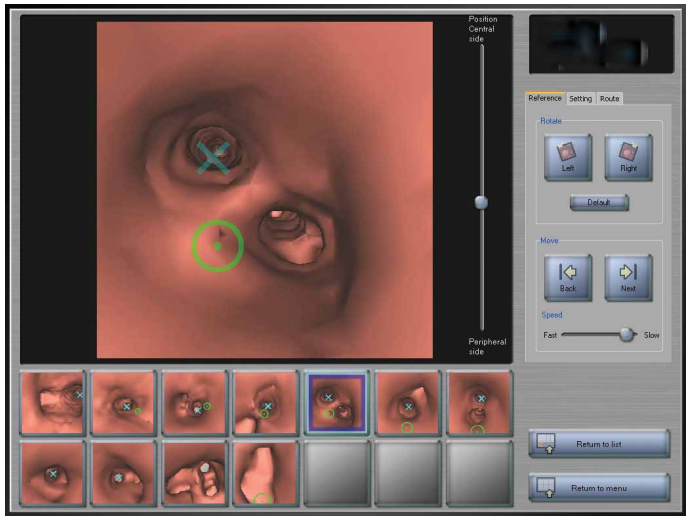

Figure 5. Virtual bronchoscopy with the Bf-NAVI system (Cybernet Systems, Tokyo, Japan). The next bifurcation is visible and the bronchus leading towards the target nodule is marked with a cross.

for radiologically nonvisible and/or lesions located in the outer third, can be increased [40]. Furthermore, it was shown in a randomised controlled trial that the combination with radial EBUS can improve the diagnostic value of virtual bronchoscopy, although the miniprobe could not be used through a guide sheath depending on the outer diameter and the size of the working channel of the ultrathin bronchoscope used [41]. The reported sensitivity for SPNs <20 mm was significantly higher for the combination of virtual bronchoscopy with EBUS compared with virtual bronchoscopy alone (80.4% *versus* 67.0%; p=0.032), whereas the additional use of virtual bronchoscopy did not show a significant difference in SPNs ⩾20 mm.

Overall, the application of virtual bronchoscopy to improve orientation in the peripheral airways does not affect the safety of the bronchoscopic procedure. However, if the quality of the CT scan does not meet the technical requirements, the CT has to be repeated and this additional radiation exposure should be considered when selecting patients for virtual bronchoscopy-guided bronchoscopy. Another limitation is the small diameter of the working channel of ultrathin bronchoscopes. Only very small samples can be taken with the forceps suited to this thin channel. The development of an ultrathin cryoprobe, enabling larger biopsies, may overcome this limitation.

Electromagnetic navigation

Electromagnetic navigation bronchoscopy (ENB) represents another approach for diagnosing SPNs. ENB allows image-based steering of the bronchoscope to a target lesion in the peripheral lung, similar to the techniques described earlier, but with additional real-time confirmation of the position of the probe within the body using an electromagnetic field.

Technical aspects

The superDimension navigation system (Medtronic, Minneapolis, MN, USA) consists of a electromagnetic board, a special sensor catheter and a software system. The electromagnetic

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board, which has to be placed under the patient on the examination table, generates a low-frequency electromagnetic field surrounding the thorax of the patient. Due to the possible influence of metallic objects the field has to be calibrated for every endoscopic suite [42].

A sensor at the tip of a steerable locatable guide can be detected within the electromagnetic field and hence within the patient. In addition, the spatial positioning and the rotation of the sensor can be captured and displayed. This allows precise steering within the airways and a guided advance of the catheter system into target bronchi. The locatable guide is steerable to some degree and permits intubation of airways that come off at an angle, which is an advantage over other guided procedures where this scenario can represent a significant challenge. This locatable guide is inserted through a dedicated guide sheath/catheter, which can be used as an EWC after removing the sensor.

Using CT-DICOM data, multiplanar images with a three-dimensional reconstruction of the bronchial tree can be created in software prior to starting the assessment. The CT quality requirements are similar to the other virtual bronchoscopy systems. During the procedure the virtual images and the position of the sensor are presented in three dimensions on a screen in real-time. For the exact positioning of the probe, the virtual bronchial tree has to be matched with the position of the patient at the beginning of the procedure. This is done automatically by inserting the sensor probe into several airways. The calculated registration error should be kept as small as possible to enable precise navigation to the nodule.

ENB-guided bronchoscopy

During the a planning procedure the target lesion is marked and a virtual pathway is generated, which the investigator then follows during the procedure. The position of both the sensor tip and the target zone are visible on the screen simultaneously and are projected over the virtual bronchoscopy images (figure 6). After reaching the target, the sensor probe is removed with the EWC left in place, through which various biopsy tools can be advanced to the lesion for repeated sampling [16, 42]. To exclude inadvertent dislocation of the EWC during sampling, the sensor probe should be re-inserted intermittently or at the end of the procedure. The accuracy of the electromagnetic navigation system is sufficient to enable ENB without additional fluoroscopic control [43, 44].

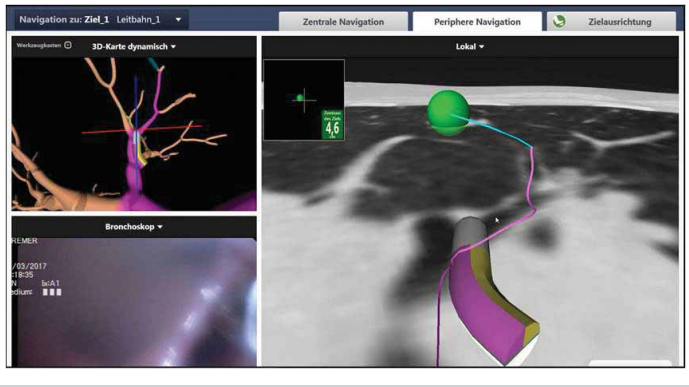

Figure 6. Electromagnetic navigation bronchoscopy with the superDimension system (Medtronic, Minneapolis, MN, USA). The pathway is visible in the CT image as well as in the reconstructed bronchial tree in front of the locatable guide.

A meta-analysis of 1033 SPNs in 14 studies showed the average diagnostic yield was 64.9% (range 55.7–87.5%) with a diagnostic accuracy of 73.9% [45]. The mean lesion size was 25 mm and the median distance to the pleura was 11 mm. The reported diagnostic yield was higher than in historical studies where TBB was solely undertaken under fluoroscopic guidance. The quality and design of the studies was very heterogeneous, *e.g.* although TBBs were performed in all studies, different biopsy tools were used additionally in some trials. In a recent prospective multicentre study, 964 subjects with 1129 lesions underwent ENB for lung biopsy. More than 50% of SPNs were <20 mm in size and the majority of nodules were located in the peripheral third. Adequate tissue sampling was possible in 94.4%; of these, 45.8% and 40.9% were interpreted as malignant and benign, respectively, whereas 13.3% were classified as inconclusive. A final diagnostic yield has not yet been reported due to the short follow-up. ENB was safe with a rate of haemorrhage of 1.0% and a pneumothorax rate of 4.9%. The latter is comparable to previous studies, where pneumothorax occurred in 3.1% of patients, requiring chest tube drainage in 1.6% of cases [45].

One advantage of ENB is the possibility to combine the procedure with EBUS, which allows confirmation that the lesion has been reached, before taking biopsies. This may increase the diagnostic yield further, because the steerability of the sensor probe and the visibility of the lesion in the ultrasound image will overcome the respective limitations of each navigation technique [38, 46]. Nevertheless, the costs for the navigation system itself and for each steerable locatable catheter set limit the frequent of use of this promising technique in daily practice.

Conclusion

While fluoroscopy is widespread, the use of other navigational techniques such as EBUS, virtual bronchoscopy and/or ENB is currently limited to specialised centres. In reality not all of these methods are used every time, even where available. A pragmatic approach to the diagnosis of peripheral nodules is to use fluoroscopy guidance and/or radial EBUS for larger lesions with a clear bronchus sign and to reserve the use of a guide sheath (time of set up, additional cost) and virtual navigation tools (planning, CT requirements) for more peripheral, smaller lesions with more complex navigation demands. ENB with its steerable probe is particularly useful in situations where the leading bronchus comes off at an angle, but is comparatively expensive. Using these additional methods, the diagnostic yield for diagnosing SPNs <30 mm can be increased to 70% [47]. This seems to be independent of which technique is used. A further increase beyond that seems to be difficult to achieve, because the yield depends on the relationship of the lesion to the airways and the possibility to reach the peripheral nodule with a bronchoscope and through the bronchial system. A new approach is to attempt bronchoscopic transparenchymal nodule access [48]. After perforation of the bronchial wall at a defined point of entry, a catheter is advanced to the peripheral nodule directly through the lung parenchyma. The catheter can be used as an EWC and biopsy tools can be advanced through the EWC to the lesion. However, this approach is still in an experimental phase 22 [49].

Due to the increasing number of incidental pulmonary nodules and considering patient comorbidity, improvements in the endoscopic diagnosis of SPNs are needed, in addition to improvements in bronchoscopic therapeutic methods for ablating small malignant tumours. This approach may be an alternative to surgery or external beam radiotherapy in the future. ENB is already used for placing fiducial markers to improve the accuracy of stereotactic

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radiation [50]. Endobronchial brachytherapy under combined EBUS/ENB guidance may be suitable for selected patients, but comes with high costs and significant logistical complexity [51]. Initial publications on bronchoscopic RFA to treat small lung tumours in humans are available and further emerging techniques are under development [52]. The possibility of applying RFA or other curative treatments bronchoscopically to small pulmonary nodules in nonsurgical lung cancer patients would increase the treatment options available to pulmonologists. This may be a particularly attractive option for patients with multiple lesions and limited surgical fitness or previous radical treatment.

In the future, the goal should be to diagnose and to treat early stages of lung cancer endoscopically in one "seek and destroy" procedure [53].

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Chapter 12

Thoracoscopy

Pyng Lee

With thoracoscopy the physician is provided with a window into the pleural space. It allows biopsy of the parietal pleura under direct visualisation with good accuracy, and achieves fluid drainage, guided chest tube placement and pleurodesis. Over a century ago, Hans-Christian Jacobaeus described thoracoscopy as a technique used to collapse the underlying tuberculous lung; this fell out of use owing to effective anti-tuberculous drugs. Thoracoscopy later reappeared as minimally invasive surgery, also known as medical thoracoscopy (MT) and VATS. VATS is performed under general anesthesia using single-lung ventilation. MT is performed by the pulmonologist in an endoscopy suite using non-disposable-rigid or flexi-rigid instruments, local anaesthesia and conscious sedation. MT is less invasive than VATS, and a comparable diagnostic yield is achieved with flexi-rigid instrument as with VATS. Flexi-rigid pleuroscopy can be used as an out-patient procedure and is well tolerated under local anaesthesia. Use of accessories that are compatible with the flexi-rigid pleuroscope (*e.g.* insulated-tip knife and cryoprobe) can enhance biopsy quality. This chapter will discuss indications, complications and advances in thoracoscopy.

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Thoracoscopy, VATS, medical thoracoscopy (MT) and pleuroscopy are minimally invasive procedures that provide access to the pleural space. They differ only in their approach to anaesthesia. In this chapter, our focus will be on diagnostic MT.

VATS is performed by a surgeon in the operating room using single-lung ventilation, three entry ports and rigid instruments. VATS is used for: stapled lung biopsy, resection of pulmonary nodules, lobectomy, pneumonectomy, oesphagectomy, pericardial windows, guided parietal pleural biopsy, drainage of pleural effusion or empyema, and pleurodesis [1, 2].

MT is conducted by a pulmonologist in an endoscopy suite; local anaesthesia and conscious sedation are used. MT allows biopsy of the parietal pleura under direct visualisation with good accuracy, and achieves fluid drainage, guided chest tube placement and pleurodesis [3]. In Europe, MT sympathectomy is used for essential hyperhidrosis, and lung biopsy is used for diffuse lung disease [4].

Table 1 provides a comparison of VATS and MT.

Division of Respiratory and Critical Care Medicine, National University Hospital, Singapore.

Correspondence: Pyng Lee, Yong Loo Lin Medical School, National University of Singapore, Division of Respiratory and Critical Care Medicine, Dept of Medicine, National University Hospital, 1E Kent Ridge Road, NUHS Tower Block Level 10, Singapore 119228. E-mail: mdclp@nus.edu.sg

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Table 1. VATS *versus* medical thoracoscopy

Procedure	VATS	Medical thoracoscopy
Where	Operating room	Endoscopy suite or operating room
Who	Surgeons	Trained non-surgeons
Anaesthesia	General anaesthesia	Local anaesthesia
	Double-lumen intubation	Conscious sedation
	Single-lung ventilation	Spontaneous respiration
Indications	Parietal pleural biopsy	Parietal pleural biopsy
	Pleurodesis	Pleurodesis
	Decortication	Chest tube placement under direct visualisation
	Stapled lung biopsy	
	Lung nodule resection	
	Lobectomy	
	Pneumonectomy	
	Pericardial window	
	Oesophagectomy	

In 1910, Swedish internist Hans-Christian Jacobaeus described examination of the thoracic cavity with a rigid cystoscope attached to an electric lamp as "thorakoscopie". He later advanced the technique to include lysis of pleural adhesions with galvanocautery, also known as the Jacobaeus operation, to collapse the tuberculous lung as part of anti-tuberculous therapy [5, 6]. At a presentation to the American College of Surgeons, Jacobaeus suggested that when "making a differential diagnosis between tumours and pleurisy of other origin, thoracoscopy is of no small value" [7]. He was a strong advocate of thoracoscopy-guided biopsies in the evaluation of pleural effusions of unknown aetiology, and applied thoracoscopy as a diagnostic and therapeutic tool [7].

Equipment

Rigid instruments

Historically, rigid instruments such as stainless steel trocars and telescopes are central to the technique (figure 1) [3–9]. Rigid thoracoscopy requires a cold xenon light source, an endoscopic camera attached to the eyepiece of the telescope, a video monitor and a recorder. The 0-degree telescope is used to provide a direct view of the pleural cavity; the oblique (30- or 50-degree) and periscope (90-degree) telescopes provide a panoramic view of the pleural cavity [8, 9]. Trocars of varying sizes (5–13 mm in diameter) and of either disposable plastic or reusable stainless steel, as well as rigid telescopes providing different angles of vision, can be used depending on the operator's preference and patient considerations. Examination quality can be improved using a bigger trocar that accommodates a larger telescope with better optics. Compression of the intercostal nerve during manipulation of the trocar can increase discomfort, especially if MT is conducted under local anaesthesia and conscious sedation. The preferred instruments for rigid thoracoscopy are a 7-mm trocar, a 0-degree viewing 4-mm or 7-mm telescope, and 5-mm optical forceps [4, 8, 9].

In 2003, in a group of patients with small loculated pleural effusions that were inaccessible to standard-sized instruments, Tassi and Marchetti [10] reported excellent views of the pleural space using a 3.3-mm telescope. Two 3.8-mm trocars were used: one for a 3.3-mm

Figure 1. Rigid trocars, telescopes and accessories.

telescope and the other for 3-mm biopsy forceps. The diagnostic yield of 93.4% was comparable with that achieved using conventional 5-mm biopsy forceps.

Flexi-rigid pleuroscope

The flexi-rigid pleuroscope represents an advance in the field of MT as it is fashioned like a bronchoscope thereby allowing the operator to scale up the learning curve quickly. The autoclavable flexi-rigid pleuroscope (LTF 160 or 240, Olympus, Tokyo, Japan) has a handle and a shaft that is 7 mm in outer diameter and 27 cm in length (figure 2a). The proximal 22 cm is rigid, while the distal 5 cm is flexible with two-way angulation (160 degrees up and 130 degrees down). It has a 2.8-mm working channel that can accommodate biopsy forceps, needles, cryo- and electrosurgical accessories (figure 2b–d), and that can interface with existing processors (CV-160, CLV-U40,) and light sources (CV-240, EVIS-100 or 140, EVIS EXERA-145 or 160) made by the same manufacturer available in most endoscopy units at no additional cost [3, 13, 14]. Flexi-rigid pleuroscopy is generally performed in the bronchoscopy suite on patients under local anesthesia and conscious sedation [3, 14]. A single 1-cm skin incision to accommodate the disposable flexible trocar is required to perform flexi-rigid pleuroscopy. The flexi-rigid pleuroscope is also equipped with NBI, a technology that highlights mucosal abnormalities and vascular patterns associated with malignancy. NBI can aid the detection and biopsy of early pleural lesions [3]. NBI is discussed further elsewhere in this *Monograph* [15].

Contraindications

The only contraindication is the lack of pleural space due to adhesions, although this can be overcome by enlarging the skin incision or digitally dissecting the lung away from the chest wall. MT requires special skills and should not be undertaken without proper training. Marchetti *et al.* [16] advanced the technique further by performing MT in patients without pleural effusion but with demonstrable lung sliding on thoracic ultrasound. As MT is performed in a spontaneously breathing patient under conscious sedation who has suffered partial or near-total lung collapse, it is important that the patient

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Figure 2. a) Flexi-rigid pleuroscope (LTF 160 or 240; Olympus, Tokyo, Japan). Similar in handling to a flexible bronchoscope and compatible with an existing processor and light source. The working channel can accommodate accessories such as b) a spray catheter, c) an insulated-tip knife (Olympus) or d) a cryoprobe (Erbe, Tübingen, Germany). b) Reproduced and modified from [11] with permission. c) Reproduced and modified from [12] with permission. d) Reproduced with kind permission of Erbe.

does not have hypoxia unrelated to pleural effusion, unstable cardiovascular status, bleeding diathesis, refractory cough or allergy to medications that are administered during MT.

Patient preparation

Taking a patient's history and performing a physical examination are vital to any pre-operative evaluation. The entry site is selected after careful review of the chest radiograph, decubitus films, ultrasound and CT. Before MT takes place, 200–300 mL of fluid is aspirated from the pleural cavity using a needle, angiocatheter, thoracentesis catheter or Boutin pleural puncture needle. A pneumothorax is induced by opening the needle to the air until stable equilibrium is achieved. Air causes the lung to collapse away from the chest wall, which aids trocar insertion. The operator may choose to perform MT directly with ultrasound, which has been shown to reduce access failure and diminish the need for iatrogenic pneumothorax [16, 17].

Anaesthesia

Benzodiazepines (midazolam) combined with opioids (demerol, fentanyl, morphine) provide good analgesia and sedation. Patient comfort during manipulation of the thoracoscope can be achieved through meticulous administration of local anaesthesia to the epidermis, aponeurosis, intercostal muscles and parietal pleura at the entry site [18].

In recent years, propofol has been increasingly used to enhance patient comfort during talc poudrage. However, in many countries, propofol use has to be monitored by anaesthesiologists. In patients who receive propofol titrated according to comfort, 64% develop hypotension, with 9% of these requiring corrective measures [19]. In a comparison of propofol and midazolam, increased hypoxaemia (27% *versus* 4%) and hypotension (82% *versus* 40%) were observed in the propofol group, leading the authors to conclude that propofol should not be the first choice of sedation for MT [20].

Good pain control for talc poudrage was achieved by combining opioids with benzodiazepines and anaesthetising the pleura with 250 mg of 1% lidocaine *via* spray catheter [21]. Pre-operative anaesthesia should be individualised according to the patient's general condition and expectations; however, physicians must be aware of the potential adverse events associated with anaesthetic drugs and should be ready to manage them.

Technique

The patient is positioned in the lateral decubitus position with the affected side up. Continuous monitoring of the electrocardiogram, blood pressure and pulse oximetry is carried out throughout the procedure. Although the entry site depends on the location of the effusion or pneumothorax, hazardous sites (*e.g.* anterior chest where the internal mammary artery courses, axilla with lateral thoracic artery, infraclavicular area with subclavian artery, diaphragm) should be avoided. The preference for diagnostic MT is a single port between the fourth and seventh intercostal spaces of the chest wall and along the mid-axillary line. A second port might be necessary to facilitate adhesiolysis, drainage of complex fluid collections, lung biopsy or sampling of pathological lesions located around the first entry site. If rigid instruments are used, double port access may be necessary, particularly around the posterior and mediastinal aspects of the hemithorax that are inaccessible due to partial collapse of lung, or when the lung parenchyma is adherent to the chest wall [4, 8].

When using the flexi-rigid pleuroscope, a single port would suffice as its flexible tip allows easy manoeuverability within a limited pleural space and around adhesions [13, 14, 21]. At the end of diagnostic MT, a chest tube is inserted and the air is aspirated. The tube is removed as soon as the lung has re-expanded, and the patient can be discharged after a brief period of observation in a recovery area [22]. If talc poudrage or lung biopsy has been performed, the patient should be hospitalised for a period of monitoring and chest tube drainage [4, 14].

Thoracoscopic guided biopsy of parietal pleura

It is preferable to perform biopsy of the parietal pleura over a rib in order to avoid the neurovascular bundle (figure 3). The forceps probe for the rib, grasp the overlying parietal

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pleura and tear, rather than "grabbing and pulling". Specimens that are obtained with rigid forceps are larger than those achieved with the Abram's or Cope needle. Biopsies performed using the flexi-rigid pleuroscope are small as they are limited by the size of the flexible forceps, which in turn depends on the diameter of the working channel. The flexible forceps also lack the mechanical strength required to obtain pleural specimens of sufficient depth, which may pose a challenge if mesothelioma is suspected. This technical hitch can be overcome by taking multiple (eight to 12) biopsies of the abnormal area as well as several "bites" of the same area to obtain representative tissue.

Comparative studies show no difference in diagnostic yield between biopsies performed with flexible and rigid forceps, even in mesothelioma [23]. Full thickness parietal pleural biopsies can be obtained using the insulated-tip diathermic knife during flexi-rigid pleuroscopy. One study reported that the diagnostic yields using the insulated-tip knife and the flexible forceps were 85% and 60%, respectively. The authors noted that the insulated-tip knife was useful when smooth, thickened parietal pleura was encountered, of which

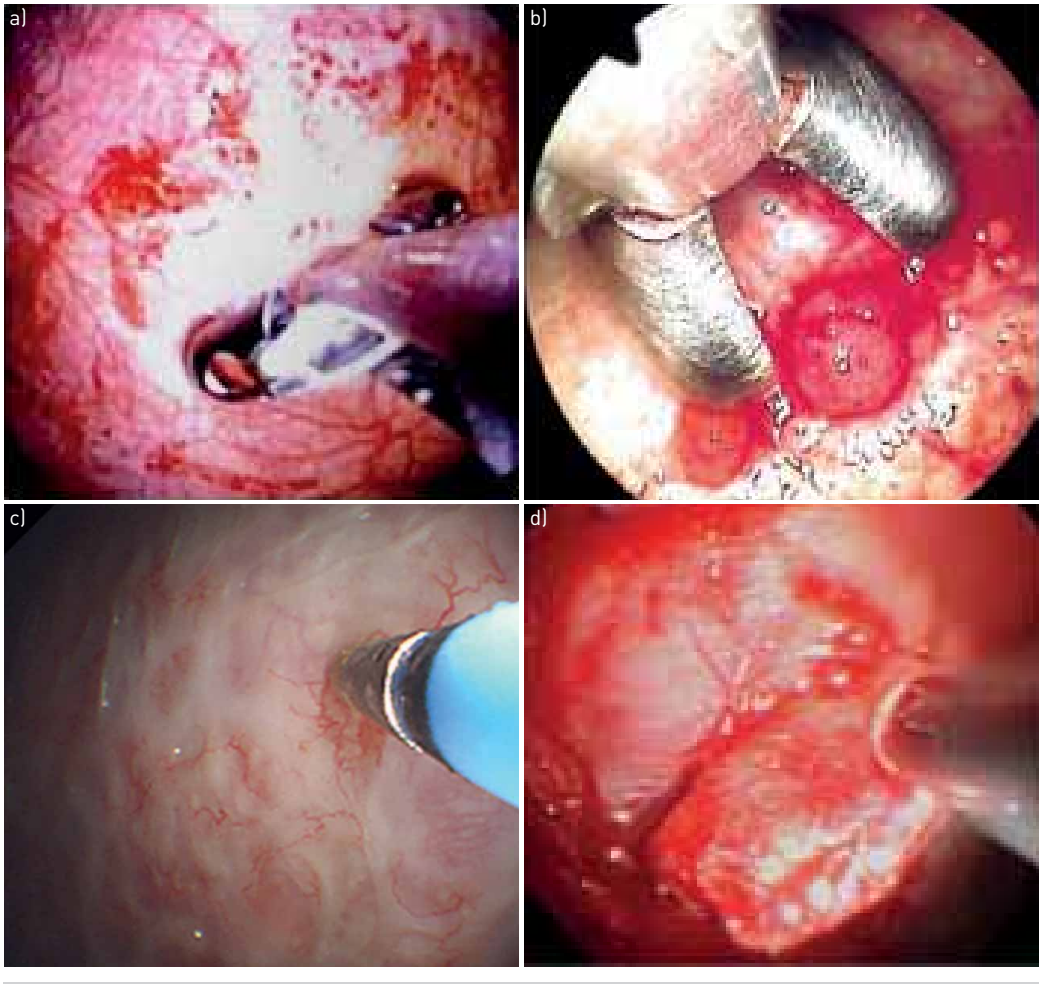

Figure 3. Biopsy of parietal pleura using a) flexible forceps, b) rigid forceps, c) a cryoprobe and d) an insulated-tip knife.

nearly half were malignant mesothelioma [12]. Cryobiopsy is another method that achieves larger specimens and better preserves the cellular architecture and tissue integrity [24].

Management of haemorrhage

A principal danger is haemorrhage from inadvertent biopsy of an intercostal vessel. External finger compression of the intercostal space over the bleeding site is the first intervention while another access port is made. The physician should then use two entry sites to examine and cauterise tissues at the same time. Direct pressure with gauze mounted on the forceps can be applied from the inside; in addition, connecting the chest tube to underwater seal re-expands the lung, which tamponades the bleeding site. If the bleeding does not cease, the surgeon might have to ligate the bleeding vessels using endoclips, enlarge the incision to facilitate repair and even consider thoracotomy.

Thoracoscopic talc poudrage

Chemical pleurodesis has an integral role as malignant pleural effusion (MPE) tends to recur unless the primary tumour is chemosensitive. Prevention of recurrence using chemical pleurodesis is also a primary goal for secondary spontaneous pneumothorax. Chemical pleurodesis is performed *via* instillation of a sclerosant through an intercostal tube or small-bore catheter or *via* talc poudrage during thoracoscopy. Thoracoscopic talc poudrage is performed after fluid aspiration and pleural biopsy, and can be administered using various delivery devices, such as a talc spray atomiser or a bulb syringe. Thoracoscopic talc poudrage is discussed further elsewhere in this *Monograph* [25].

Complications

Mortality from rigid thoracoscopy ranges 0.09–0.34% [26, 27]. Talc poudrage was associated with 0.69% mortality, and a trial conducted in the USA using non-graded talc contributed to nine out of 16 deaths [28].

Major complications (prolonged air-leak, haemorrhage, empyema, pneumonia and port site tumour growth) occur in 1.8%, while minor complications (subcutaneous emphysema, wound infection, fever, hypotension and cardiac arrhythmia) are observed in 7.3% of MT [28, 29].

A serious but rare complication associated with pneumothorax induction is air embolism (<0.1%) [26]. During MT, litres of pleural fluid can be removed with minimal risk of re-expanding pulmonary oedema due to the immediate equilibration of the pressures provided by air through the trocar into the pleural space. Fever that occurs after talc poudrage generally resolves within 48 h; in comparison, bronchopleural fistula that requires prolonged chest drainage and suction may occur after thoracoscopic lung biopsy for ILD. Wound infection, pneumonia and empyema can develop as a result of long-term tube drainage [28, 29]. In cases of mesothelioma, prophylactic radiotherapy should be carried out within 2 weeks of MT to prevent tumour growth at the incision site [30].

Complications associated with the flexi-rigid pleuroscope are rare. No mortality was reported in a recent meta-analysis of 755 patients who underwent flexi-rigid pleuroscopy [13, 31]; however, training in the proper techniques cannot be overemphasised. Table 2 describes the type of patient suitable for rigid or flexi-rigid pleuroscopy.

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Clinical applications

Pleural effusion of unknown aetiology

Thoracentesis is the first step in the evaluation of a pleural effusion. As more than half of exudative effusions in developed countries are due to malignancy, pleural fluid cytology is a simple definitive test [32]. Diagnostic yield of thoracentesis depends on the nature of the primary malignancy and the extent of the disease [33]. A single pleural aspiration diagnoses malignancy in 60% of cases and mesothelioma in 30% of cases [32, 34]. A second sample increases the yield by 15% and a third sample is non-contributory even when large volumes (>50 mL) are submitted [35].

"Blind" or closed needle biopsy (CNB) is positive in 40% of MPE due to patchy pleural involvement. Malignancy tends to affect the costophrenic recess and diaphragm, which are inaccessible to biopsy, and adding CNB to pleural fluid cytology increases the yield by 7–27% for malignancy and 20% for mesothelioma [36, 37]. Contrast-enhanced thoracic CT is superior to standard CT, and nodularity, irregularity and pleural thickness measuring >1 cm are highly suggestive of malignancy [32, 38, 39]. Pleural imaging can be performed at the patient's bedside using ultrasound, and ultrasound is increasingly used to the select appropriate sites for thoracentesis, tube thoracostomy and MT. As ultrasound has been shown to improve safety and decrease access failure, national guidelines recommend its use to guide all pleural procedures [14, 16, 32]. Ultrasound features such as pleural nodularity, pleural thickening of >10 mm and diaphragmatic thickening of >7 mm, are diagnostic of

Table 2. Indications for rigid thoracoscopy or flexi-rigid pleuroscopy

Clinical scenario	Type of procedure
Diagnostic thoracoscopy for indeterminate, uncomplicated pleural effusion where suspicion of mesothelioma is not high	**Flexi-rigid pleuroscopy** or use of rigid telescope under local anaesthesia
Trapped lung with radiographically thickened pleura	**Rigid optical biopsy forceps** or flexi-rigid pleuroscopy with flexible forceps, either performing multiple bites over the same area to obtain specimens of sufficient depth or using flexible forceps, an **insulated-tip knife** or **cryobiopsy**
Suspected mesothelioma	**Rigid optical biopsy forceps** or flexi-rigid pleuroscopy with **insulated-tip knife** or **cryobiopsy**
Pleuro-pulmonary adhesions	Fibrous: **rigid optical biopsy forceps** or flexi-rigid pleuroscopy with electrocautery accessories Thin, fibrinous: flexi-rigid pleuroscopy with flexible forceps
Empyema, split pleural sign, loculated pleural effusion	**Rigid instruments (VATS)** or conversion to thoracotomy for decortication
Pneumothorax with bulla or blebs	**Rigid instruments (VATS)** for staple bullectomy

Bold denotes preferred procedure.

malignancy with 73% sensitivity and 100% specificity [40]. An "echogenic swirling pattern" described as numerous free-floating echogenic particles swirling in the pleural cavity during respiration or heartbeat is another sign suggestive of MPE [41]. CT and ultrasound features may suggest pleural metastasis but pathological diagnosis is necessary, and where MT is not readily available, CT- or ultrasound-guided pleural biopsy is superior to CNB. In a randomised trial, CT-guided biopsy of pleural thickenings measuring >5 mm achieved an 87% yield for malignancy *versus* 47% with CNB using Abram's needle [42]. Ultrasound-guided biopsy of pleural lesions of >20 mm with a 14-gauge cutting needle gave an 85.5% yield for malignancy, a 100% yield for malignant mesothelioma and a 4% yield pneumothorax rate [43]. The type of needle appeared important; a tru-cut needle was better than a modified Menghini needle for malignancy (95.4% *versus* 85.8%) [44], Abram's needle is superior if tuberculous pleural effusion is suspected [45].

Abnormal pleural appearances are not always seen on contrast-enhanced CT. In a study where CT-reported diagnoses were compared with histological results using MT, the sensitivity for CT report of malignancy was 68%, which implied that a significant number of patients had malignancy despite negative CT report. Reliance on CT alone to stratify who should undergo invasive pleural biopsies must be re-evaluated, and studies defining the diagnostic pathway are therefore required [46, 47].

Despite repeated use of thoracentesis and image-guided needle biopsy, ~20% of pleural effusions remain undiagnosed. And this is where MT plays an important role [28, 48]: it enhances diagnostic capabilities where other minimally invasive tests fail. If a neoplasm is strongly suspected, the diagnostic sensitivity of thoracoscopic exploration and biopsy approaches 90–100% [10, 13, 22, 23, 28, 31]. Endoscopic characteristics (nodules, polypoid masses and "candle wax drops") strongly suggest malignancy (figure 4) but early stage mesothelioma can resemble pleural inflammation [48, 49].

Chrysanthidis and Janssen [50] conducted a study to determine whether autofluorescence mode (DAFE system, Richard Wolf GmbH, Knittlingen, Germany) could differentiate early malignant lesions from non-specific inflammation, thereby targeting sites for biopsy and delineating tumour margins for more precise staging. Using 300W xenon lamp in the violet–blue range (390–460 nm), a colour change from white/pink to red was demonstrated in all cases of malignant pleuritis (100% sensitivity). Use of autofluorescence thoracoscopy made them easier to identify and improved delineation of their margins. Colour change from white/pink to orange/red was observed in two cases of chronic pleuritis (75% specificity). Chrysanthidis and Janssen [50] concluded that there was little value in autofluorescence thoracoscopy for patients with extensive pleural involvement that was easy to diagnose using white light thoracoscopy, but that autofluorescence mode might be useful for early pleural malignancies.

NBI is a feature of the flexi-rigid pleuroscope (Olympus LTF 160; Olympus). NBI uses unfiltered narrow bands in blue (415 nm) and green (540 nm) light wavelengths, which coincide with the peak absorption of oxyhaemoglobin and thereby enhance the vascular architecture of the tissues. In 26 patients with malignant involvement of the pleura (9 mesothelioma), no difference was found in the diagnostic accuracy of NBI and white light video pleuroscopy (figure 5) [51]. Similar observations were made in 45 patients; 32 had pleural metastases, 12 had tuberculous pleuritis and one had non-specific pleuritic (unpublished data; P. Lee, National University Hospital, Singapore). Although pleural vasculature was well imaged with NBI, it was difficult to discriminate tumour

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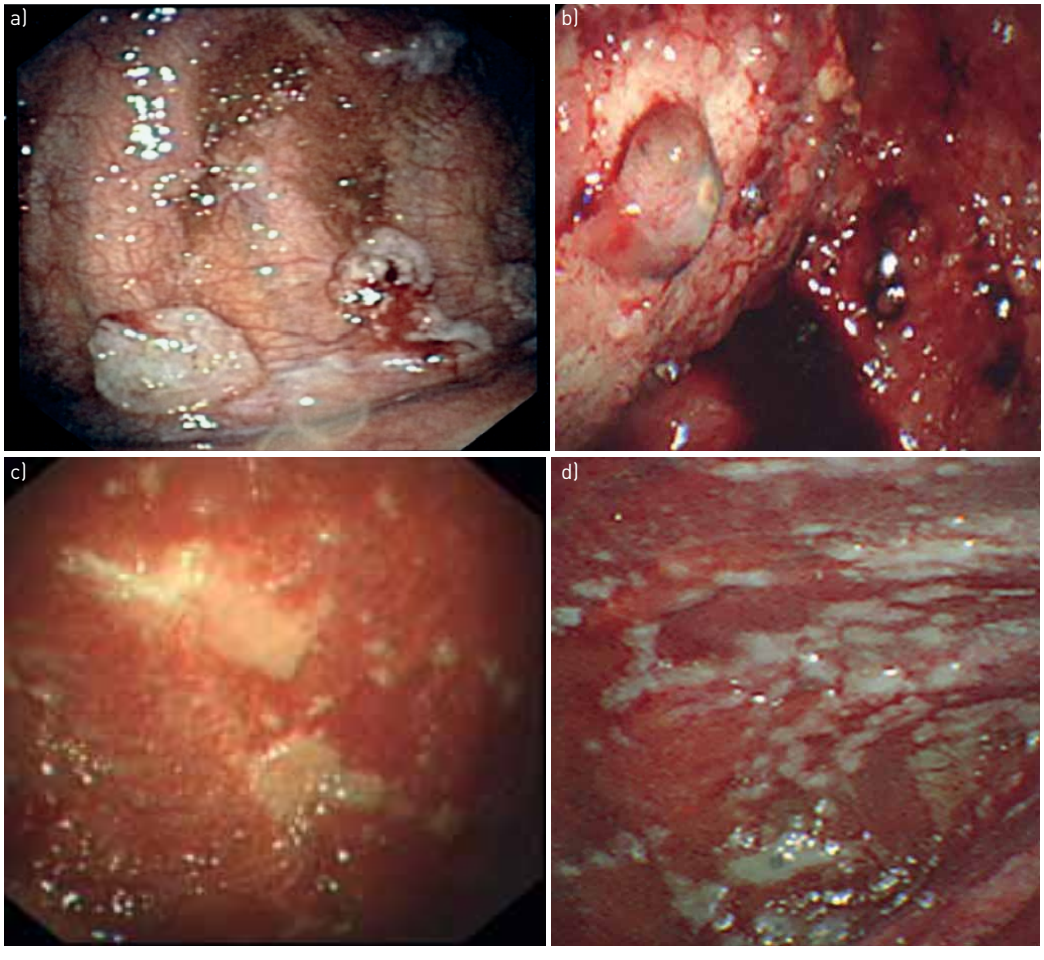

Figure 4. Endoscopic views of a and b) polypoid masses and c and d) candle wax nodules.

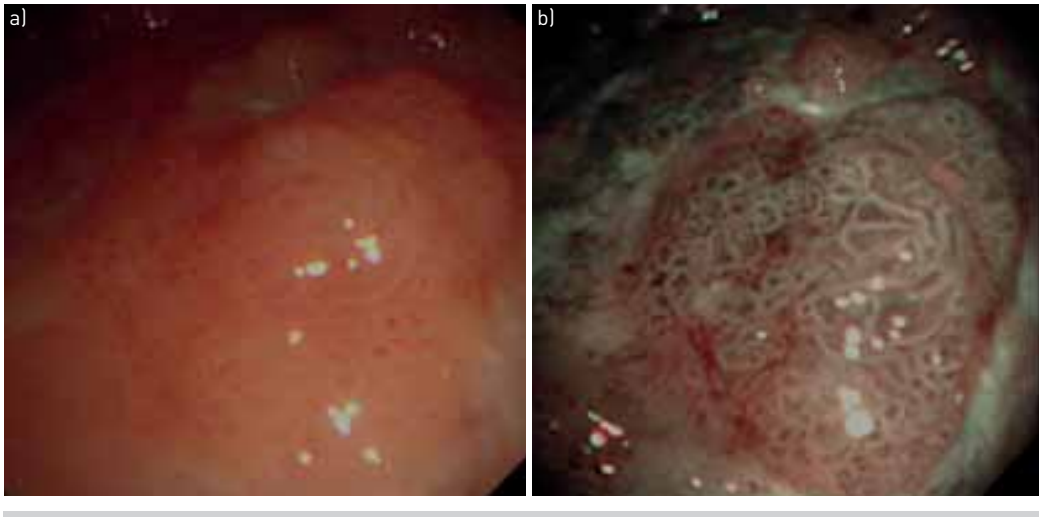

Figure 5. a) White light and b) NBI of pleural metastasis due to breast cancer.

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neovascularisation from inflammation based on vascular patterns. In patients with metastatic pleural malignancy, NBI demarcated tumour margins clearly but failed to demonstrate differences in the quality of biopsies obtained.

A study by Baas *et al.* [52] investigated administration of 5-aminolaevulinic acid (ALA) prior to VATS, and whether this could lead to the improved detection and staging of thoracic malignancy. Per oral 5-ALA was administered 3–4 h before VATS; the pleural cavity was then examined, first with white light then using fluorescence thoracoscopy (D light Autofluorescence System; Karl Storz GmBH and Co., Tuttlingen, Germany). Tissue samples were taken from all abnormal areas, and histological diagnoses were compared with thoracoscopic findings. Although fluorescence was not superior to white light thoracoscopy, it led to upstaging in four out of 15 patients with mesothelioma due to better visualisation of visceral pleural lesions that were otherwise undetectable by white light. Although several postoperative complications were reported, Baas *et al.* [52] concluded that fluorescence thoracoscopy using 5-ALA was feasible with minimal side-effects, and it could have potential applications in the diagnosis and staging of mesothelioma.

Lung cancer

Cancer-related pleural effusions occur as a result of direct invasion, tumour embolisation to visceral pleura with secondary seeding of the parietal pleura, haematogenous or lymphatic spread. Elastin staining and careful examination for invasion beyond the elastic layer of the visceral pleura should be carried out for lung cancer resections, as visceral pleural invasion is important for staging in the absence of nodal involvement. Pleural metastasis as defined using TNM (tumour, node and metastasis) staging is M1a instead of T4, and represents change from stage IIIB to stage IV [53]. It is rare to find resectable lung cancer in the setting of an exudative pleural effusion despite negative cytologic examination. MT can assess surgical operability by determining whether the pleural effusion is para-malignant or caused by metastases [28]. If pleural metastases are found, they denote disseminated disease with reduced life expectancy, and talc poudrage or tunnelled pleural catheter can be performed at the same setting [54].

Malignant mesothelioma

The average survival of a patient diagnosed with malignant mesothelioma is 6–18 months, with death occurring as a result of respiratory failure [55]. Malignant mesothelioma is suspected in patients with asbestos exposure and chest radiographs characteristic of pleural effusion without contralateral mediastinal shift. Diagnosis by pleural fluid cytology CNB is difficult, which prompts some physicians to advocate open biopsy using mini or lateral thoracotomy in order to obtain specimens of sufficient size and quantity for immuno-histochemical stains [56]. Pleural fluid mesothelin (>2 $nmol \cdot L^{-1}$) and megakaryocyte potentiating factor (>12.4 $ng \cdot mL^{-1}$), which originate from a common precursor protein, have shown 65% sensitivity and 95% specificity for pleural mesothelioma in a large study of 507 patients [57].

MT is favoured over thoracotomy as the pleural specimens obtained with 5- or 7-mm rigid forceps are comparable with open biopsies [58]. MT allows staging to be performed in a minimally invasive manner, and 5-ALA fluorescence VATS may be a technique that can improve its staging accuracy [52]. Adequacy of the tissue obtained using flexible forceps

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can cause concern and the rigid 5-mm optical forceps, insulated-tip knife or cryobiopsy may be preferred [12, 24, 58, 59]. As mesothelioma is notorious for seeding, biopsy, MT and chest tube sites should be chosen carefully to allow excision if subsequent therapeutic resection is performed [60]. Boutin *et al.* [27] previously recommended prophylactic irradiation of 7Gy for 3 consecutive days within 2 weeks of MT; however, a recent randomised trial comparing immediate drain site radiotherapy (21Gy in 3 fractions) to best supportive care in 61 patients failed to show any difference in the occurrence of tract metastases [61]. Prophylactic radiotherapy at MT and drain sites therefore remains controversial [62]. As only 5% of patients are suitable for curative surgery [63], a palliative approach towards aggressive relief of dyspnoea by removing pleural fluid, talc poudrage, pain control and prophylactic irradiation of incision sites has provided good symptom control [64]. In recurrent symptomatic pleural effusions, the tunnelled pleural catheter may represent a viable option [62].

Tuberculous pleural effusion

The diagnostic yield of CNB in tuberculous pleural effusions is variable. In a prospective study of 100 tuberculous effusions in Germany, an immediate histological diagnosis was established in 94% using MT compared with 38% using CNB (figure 6). The positive yield from tissue cultures was also higher with MT-guided biopsies than with CNB tissue and pleural fluid combined [65]. Similar results were reported in another study performed in a tuberculosis-endemic country, where MT-guided pleural biopsies achieved a yield superior to CNB using Abram's needle (98% *versus* 80%). MT has a role when large quantities of pleural tissue are required for culture in suspected drug-resistant cases, and when adhesiolysis is used to promote drainage of fluid loculations [66].

Conclusion

Diagnostic MT is effective in the evaluation of pleural and pulmonary diseases when routine fluid analysis and cytology fail. In many institutions where facilities for MT are

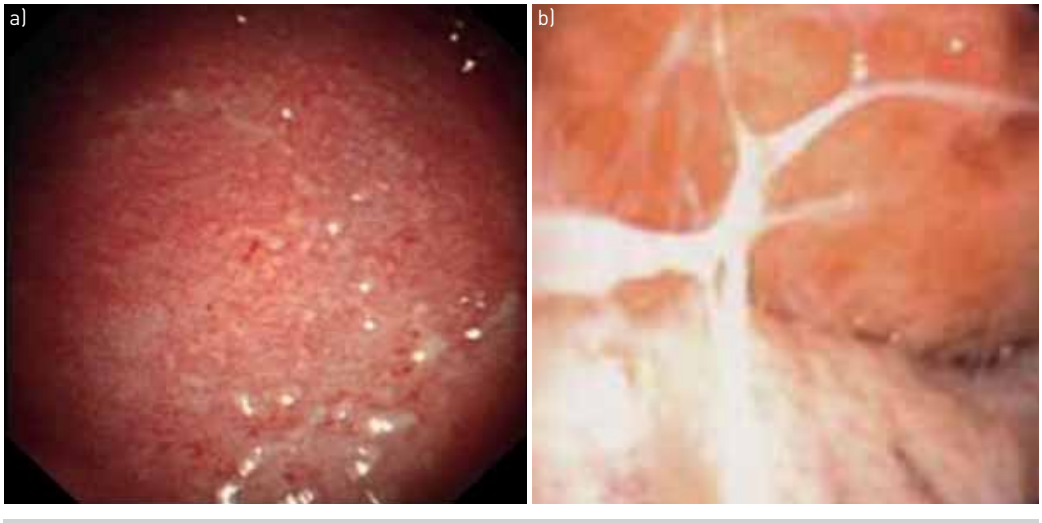

Figure 6. a) Sago nodules and b) fibrinous adhesions in tuberculous effusion.

available, it replaces second-attempt thoracentesis and CNB in patients with exudative effusions of unknown aetiology. MT also offers the non-surgeon a way to breakdown loculations in complicated parapneumonic effusions, and to perform talc poudrage for recurrent malignant effusions and pneumothoraces. Therapeutic thoracoscopy is discussed in another chapter in this *Monograph* [25].

Training in MT is required. The American College of Chest Physicians recommends that 20 supervised procedures are performed before operators are considered competent, and 10 procedures should be performed each year to maintain competency [67]. The flexi-rigid pleuroscope is a significant invention in the era of minimally invasive pleural procedures and is likely to replace traditional biopsy methods [68]. The future of MT will define "when and how" to apply flexi-rigid and rigid instruments to the evaluation of pleuro-pulmonary diseases.

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Chapter 13

Haemoptysis

George Z. Cheng and Momen M. Wahidi

Haemoptysis is a common clinical entity encountered in pulmonology. Its presentation ranges from blood-streaked sputum to massive haemoptysis. Appropriate assessment and management of this potentially life-threatening entity can lead to improved clinical outcomes. Here, we focus on the definition, anatomy, aetiology, diagnosis and management of massive haemoptysis. We evaluate the utility of bronchoscopy and CT scans in the diagnostic evaluation pathway. We also discuss bronchoscopic, radiological and surgical approaches in haemoptysis management. Most importantly, we stress the multidisciplinary approach in management to achieve the desired clinical outcomes.

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Haemoptysis is a commonly encountered clinical entity in pulmonary medicine. Ranging from self-limited blood-streaked sputum (85–95%) to massive bleeding (5–15%), haemoptysis has variable presentations and, ultimately, different management approaches based on the severity of bleeding [1]. Massive haemoptysis can rapidly compromise airways, resulting in asphyxiation rather than exsanguination. Therefore, it should be viewed as a medical emergency requiring prompt intervention. Untreated massive haemoptysis has a mortality rate approaching 50% [2]. A patient with massive haemoptysis should be managed with appropriate positioning, securing the airway to maintain respiratory and cardiovascular function, and correcting any coagulopathy that may contribute to the bleeding [3]. This is quickly followed by evaluation for the source of the bleed *via* bronchoscopy and HRCT. Bronchoscopy is essential for localisation, isolation and control of the haemorrhage source in the case of endoluminal lesions. HRCT provides a global assessment of the lung tissue, vital mediastinal structures and parenchymal bleeding source [4]. Here, we review the definitions, anatomy, aetiology, and diagnostic and management approaches to haemoptysis with a special focus on massive haemoptysis.

Definitions

Haemoptysis, derived from the Greek root of *haima* for blood and *ptysis* for the act of spitting, can be mild to massive. Mild or nonmassive haemoptysis is not life-threatening

Dept of Medicine, Duke University Medical Center, Durham, NC, USA.

Correspondence: George Z. Cheng, Duke University Medical Center, DUMC Box 102356, Durham, NC 27710, USA. E-mail: george.cheng@duke.edu

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and often self-limited. The patient maintains adequate ventilation and oxygenation, usually does not require hospitalisation, observation is often the mainstay of management, and additional outpatient workup should be individualised with regard to the patient's comorbid conditions. Massive haemoptysis is often life-threatening and requires prompt intervention; however, there is no consensus on its definition [5].

Using the amount of expectorated blood as a measurement of haemoptysis is challenging in clinical practice. Patients do not quantify the amount of perceived haemoptysis in millilitres. The description is often more colloquial, in terms of cups or the amount and frequency of haemoptysis, thus leading to grossly inaccurate measurements. The published literature does not have a consensus on what is considered to be massive haemoptysis. Threshold ranges from 100 to 1000 mL over 24 h have been proposed, but none has been universally accepted [1, 6–9].

Pathophysiologically, the conducting airway (*i.e.* anatomical dead space) volume is ~150 mL. Therefore, if blood was to fill the conducting airways, there would be significant airway obstruction and interference with ventilation and oxygenation. Furthermore, the clinical response of a patient with haemoptysis often depends on their underlying cardiopulmonary reserve and comorbidities. Any disease states (*i.e.* neuromuscular weakness, tracheal stenosis and COPD) that interfere with the ability to effectively clear the airway will change the threshold for considering intervention [10, 11]. Therefore, if there is evidence of abnormal gas exchange or haemodynamic instability secondary to haemoptysis, we propose to consider intervention regardless of the amount of bleeding. However, in a patient without gas exchange abnormalities, we proposed to use 100 mL in 1 h (two-thirds of the anatomical dead space) or 300 mL in 24 h (two times the anatomical dead space) as the threshold for intervention.

Anatomy

The lung and its conducting airways receive dual circulation from the bronchial arteries and the pulmonary arteries. There are wide anatomical variations in the origins of bronchial arteries. Generally, bronchial arteries originate from the descending thoracic aorta, most often at the T5–T6 level and less frequently from vertebral or intercostal arteries. Typically, one bronchial artery supplies the right lung and two bronchial arteries supply the left lung. These vessels supply the airways from the trachea to the terminal bronchioles, hilar lymph nodes, visceral pleura and other mediastinum structures (the middle third of the oesophagus, vagus nerve, vasa vasorum of the aorta and pulmonary trunks). Of note, in ~5% of individuals, the spinal artery originates from the bronchial artery, which has implications for procedures involving embolisation of bronchial arteries [2, 12–15]. The pulmonary arteries carry deoxygenated blood to the alveolar capillary bed and supply the lung parenchyma and the respiratory bronchioles, where anatomical anastomosis with bronchial arteries exists. While bronchial arteries carry only 1% of the total lung blood flow, this is a high-pressure system compared with pulmonary arteries, which form a low-pressure system. As such, 90% of massive haemoptysis has a bronchial artery origin compared with 5% attributable to pulmonary circulation [3, 16]. Of note, chronic inflammatory, infectious or vascular lung diseases can cause significant alterations in vascular anatomy, resulting in enlargement, marked tortuosity and altered anastomosis of bronchial arteries, which lead to increased arterial blood flow and risk of bleeding [13].

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Aetiology

There are many causes for haemoptysis originating from the lower respiratory tract, including but not limited to infectious, inflammatory, malignant, haematological, vascular, iatrogenic and toxin-related categories. Historically, three aetiologies account for 90% of massive haemoptysis, *i.e.* bronchiectasis, tuberculosis and lung abscess [1]. However, more recent epidemiological data suggest that the causes of haemoptysis are evolving, with bronchogenic carcinoma, mycetomas and cryptogenic haemoptysis becoming more prominent [17–19].

Bronchiectasis

Bronchiectasis is the result of recurrent infectious and inflammatory processes, characterised by abnormal bronchial wall thickening with a dilated lumen, chronic sputum production associated with cough and airflow obstruction. Chronic airway inflammation in bronchiectasis leads to increased tortuosity and enlargement of the bronchial arteries to the affected bronchial tree. In addition, there is a corresponding increase in the submucosal and peribronchial capillary plexus. Rupture of either the bronchial artery or the capillary plexus will lead to significant haemoptysis. This pattern often occurs in patients with disease entities that predispose them to recurrent infections, such as cystic fibrosis, rheumatological disease, allergic bronchopulmonary aspergillosis, immunodeficiency, ciliary dysfunction, haematological malignancies, recurrent aspiration and nontuberculous mycobacteria infection [20, 21].

Tuberculosis

While the incidence and distribution of tuberculosis have changed in recent decades secondary to advances in antimycobacterial therapy, it remains a prominent cause of massive haemoptysis in areas of the world where tuberculosis is prevalent, such as South-East Asia and Africa [6, 22, 23]. Tuberculosis can lead to haemoptysis both in prior and active infection. With prior tuberculosis infection, massive haemoptysis can occur when calcified lymph nodes or broncholiths erode into an airway interrupting a bronchial artery, due to bronchiectasis as a result of prior tuberculosis infection or as a result of a superimposed fungal infection within the lung cavity due to prior pulmonary tuberculosis. With active tuberculosis infection, significant bleeding often occurs due to the necrosis of bronchial vessels adjacent to the airway involved in active infection, which can occur in both cavitary and noncavitary disease. Active tuberculosis can also lead to Rasmussen's aneurysm, where infectious processes lead to slow expansion of the pulmonary artery, resulting in eventual rupture of the vessel wall due to chronic inflammation [24, 25].

Fungal infections

Fungal infections leading to massive haemoptysis in patients with cavitary lung disease are most often attributed to *Aspergillus*. Aspergilloma or mycetoma is formed from *Aspergillus* hyphae, cellular debris, fibrin and mucin within a lung cavity. The chronic inflammatory process leads to bronchial artery dilation and hypertrophy surrounding these cavities, and predisposes these areas to bleed. Patients with aspergilloma report haemoptysis very frequently, ranging from 50% to 90% during their disease course [1]. Angio-invasive fungal infections from *Aspergillus* or *Mucor* in immunocompromised hosts (such as those

undergoing stem cell transplantation) can result in haemoptysis during the engraftment phase when the neutrophil count begins to rise. Neutrophil infiltration of the infected lung parenchyma initiates the inflammatory response that leads to disruption of bronchial vessels and results in massive haemoptysis [26–29].

Lung abscess

Lung abscesses arise from polymicrobial/anaerobic infections secondary to aspiration or necrotising pneumonias and can result in massive haemoptysis due to either tissue necrosis or bronchial artery rupture. The risk factors for developing haemorrhage from a lung abscess include thrombocytopenia or coagulopathy from systemic disease such as liver failure or bone marrow suppression [30]. In a recent review of patients who underwent anatomical lung resection for haemoptysis, lung abscess was an independent predictor of death along with advanced age, renal failure, sarcoidosis and extent of resection [31].

Bronchogenic carcinoma

Roughly 20–60% of lung cancer patients will experience varying degrees of haemoptysis, with ~7–10% at the time of presentation [1]. Recent evidence suggests that lung cancer patients represent over half of the patients who present with massive haemoptysis [32, 33]. Among patients with massive haemoptysis, eight out of 10 had sentinel-bleeding events in the weeks prior to presentation. Large, endobronchial, centrally located tumours (such as squamous cell carcinoma) are more likely to be associated with haemoptysis. This is especially true with the use of bevacizumab (an antiangiogenesis agent that leads to tumour cavitation) in squamous cell lung cancer, where six out of 66 patients had haemoptysis and there were four fatal outcomes during the phase II trial [34]. Furthermore, metastatic lesions to the lung are also associated with haemoptysis. Melanoma, colon, breast and prostate cancer have a propensity for endobronchial metastasis, whereas renal cell carcinoma, thyroid cancer and sarcomas tend to form parenchymal lesions in the lung. These lesions have a tendency to cause bleeding due to necrosis, mucosal invasion or local angiogenesis [10].

Cryptogenic haemoptysis

Cryptogenic or idiopathic haemoptysis refers to haemoptysis without a clear aetiology after clinical assessment, radiographic studies and fibreoptic bronchoscopy evaluation. In the reported literature, cryptogenic haemoptysis encompasses 7–42% of haemoptysis cases. When these patients with cryptogenic haemoptysis are followed, 6–10% will eventually be diagnosed with lung cancer, especially in smokers and those over 40 years old [17, 35, 36]. Cryptogenic/idiopathic haemoptysis is a diagnosis of exclusion. Immunological lung diseases (*e.g.* Goodpasture's syndrome, granulomatosis with polyangiitis, microscopic polyangiitis and systemic lupus erythematosus) or cardiovascular defects (*e.g.* pulmonary arteriovenous malformations, bronchial Dieulafoy's lesion, mitral stenosis, pulmonary hypertension, pulmonary emboli and aortic aneurysms) should be excluded prior to reaching a diagnosis. In young female patients, thoracic endometriosis (catamenial haemoptysis) or lymphangioleiomyomatosis (spontaneous pneumothorax and haemoptysis in the setting of cystic lung disease) should be considered [11].

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The aetiology of haemoptysis is variable. A useful approach is to consider anatomical location and the disease process that is involved (table 1). Clinical suspicion will ultimately direct diagnostic and management approaches.

Diagnostic approaches

When evaluating a patient with haemoptysis, it is essential to determine that the haemorrhage is coming from the lung and not from the supraglottic airway (*i.e.* epistaxis) or gastrointestinal tract (*i.e.* haematemesis). If pseudohaemoptysis is suspected, then evaluation by otolaryngology or gastroenterology will be essential for diagnosis and management. Typically, haemoptysis is alkaline, bright red colour with oxygen saturation close to that of arterial blood, whereas haematemesis tends to be acidic, dark coffee ground colour with oxygen saturation close to that of venous blood. Careful examination of the oral and nasal passage can provide clues to bleeding in the naso- or oropharynx [9].

History and physical examination are important to haemoptysis evaluation, in that pertinent findings will guide clinical evaluation and therapeutic intervention. For example, a history of infectious exposure, fever and cough will lead one to consider pulmonary cavitary lesions, whereas a history of haemoptysis corresponding with menstruation will lead one to consider catamenial haemoptysis. Clinical presentation of the patient will ultimately triage the urgency of diagnostic workup and management.

Table 1. Haemoptysis aetiologies

Anatomical location	Disease
Airway	Trauma (blunt or penetrating)
	Bronchitis
	Bronchiectasis
	Cystic fibrosis
	Bronchovascular fistula
	Neoplasm (bronchial carcinoma, carcinoid or metastasis)
	Dieulafoy lesion
	Foreign body
Parenchyma	Infection (abscess, necrotising pneumonia, mycetoma, tuberculosis or parasites)
	Inflammation (diffuse alveolar haemorrhage, Goodpasture's syndrome, microscopic polyangiitis, granulomatosis with polyangiitis or systemic lupus erythematosus)
Vascular	Congenital heart disease
	Mitral stenosis
	Pulmonary arteriovenous malformation
	Pulmonary artery pseudoaneurysm
	Pulmonary hypertension
	Pulmonary embolism
Miscellaneous	Iatrogenic (stent, bronchoscopic biopsy, pulmonary artery catheter injury, tracheo-innominate fistula or transthoracic needle aspiration)
	Drugs (bevacizumab or cocaine use)
	Thoracic endometriosis
	Pseudohaemoptysis

Laboratory evaluation of a patient presenting with haemoptysis should be targeted. A complete blood count, coagulation studies, a basic metabolic panel, a hepatic function panel, arterial blood gases, urinalysis, and blood typing and cross-matching should be obtained as the initial assessment. Correction of underlying coagulopathy will aid in controlling haemoptysis. Urinalysis will provide clues to possible pulmonary renal syndromes (*i.e.* presence of blood in the urine may trigger a workup for vasculitis).

Radiological workup

Chest imaging is one of the cornerstones of diagnostic evaluation in haemoptysis. The goal is to localise the bleeding site so as to direct management. Chest radiography is inexpensive, ubiquitous and can rapidly provide lateralising information. While chest radiography is commonly the initial imaging study, it has significant limitations. In one series, chest radiography only provided the location in 46% and the cause in 35% of haemoptysis cases [37]. Furthermore, patients with haemoptysis secondary to malignancy had normal chest radiography ~25% of the time [36]. Therefore, when evaluating haemoptysis, a normal chest radiograph is not sufficient and should warrant additional workup either with bronchoscopy or a multidetector CT (MDCT) scan.

MDCT or HRCT scan

A CT scan should be performed in the setting of gross or recurrent haemoptysis, especially in patients with increased cancer risk (*i.e.* more than 30 pack-years smoking history, over 40 years of age), suspected bronchiectasis or with unrevealing chest radiography. A HRCT scan without contrast is ideally used in patients with self-limiting haemoptysis without risk factors for cancer and those with renal dysfunction. An MDCT scan with contrast or angiography should be done for patients with active bleeding or those with a high risk of cancer who are being considered for embolisation procedures [38–40]. MDCT angiography is noninvasive and highly accurate in characterising thoracic, bronchial, ectopic nonbronchial and pulmonary arteries that may be involved in bleeding, correctly identifying the bleeding vessel up to 85% of the time [40]. Pathological characteristics of bronchial arteries include increased tortuosity and diameter $\geqslant$2 mm. High-resolution volumetric reconstructions of bronchial arteries can effectively aid in procedural planning [2]. The major limitations of CT scans are the time that is required to obtain the image and the supine position of the patient that may impair airway clearance.

Bronchoscopy

Flexible and rigid bronchoscopies are essential techniques for identifying and treating haemoptysis causes in the airway. Flexible bronchoscopy is able to localise the bleeding source in 73–93% of patients [37, 41]. Studies have demonstrated that early bronchoscopy (*i.e.* during active bleeding episodes or within 48 h of cessation) can better localise the active bleeding source; however, clinical diagnosis and outcome did not vary [42, 43]. Importantly, rigid bronchoscopy should be considered as the first line for evaluation and treatment of massive haemoptysis, as it affords adequate suction for evacuating blood and clots, and concurrent ventilation and airway maintenance. However, use of rigid bronchoscopy is limited by the need for general anaesthesia, experience in its use, and the restricted airway accessibility to the trachea and main bronchi. Therefore, flexible

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bronchoscopy is often performed through the rigid bronchoscope to achieve adequate airway evaluation and bleeding control involving distal airways (figure 1a) [44–47].

Diagnostic complements

Bronchoscopy is complementary to the use of a CT scan. Bronchoscopy is better for detection of airway bleeding sources, whereas a CT scan provides information on lung parenchymal and vascular abnormalities. One study showed that a CT scan more effectively identified the cause of the bleed (77% *versus* 8%), but was not superior to bronchoscopy in detecting the bleeding site (70% *versus* 73%) [37]. However, in patients with no appreciable bleeding source on a CT scan, bronchoscopy can aid in detecting the source of the bleed [48]. Most importantly, bronchoscopy can obtain samples from lavage and tissue for microbiology, cytology and histopathology examination.

Management

Patients with haemoptysis are triaged based on severity of bleeding. Not all patients who present with haemoptysis require hospitalisation; in particular, those with self-limiting and

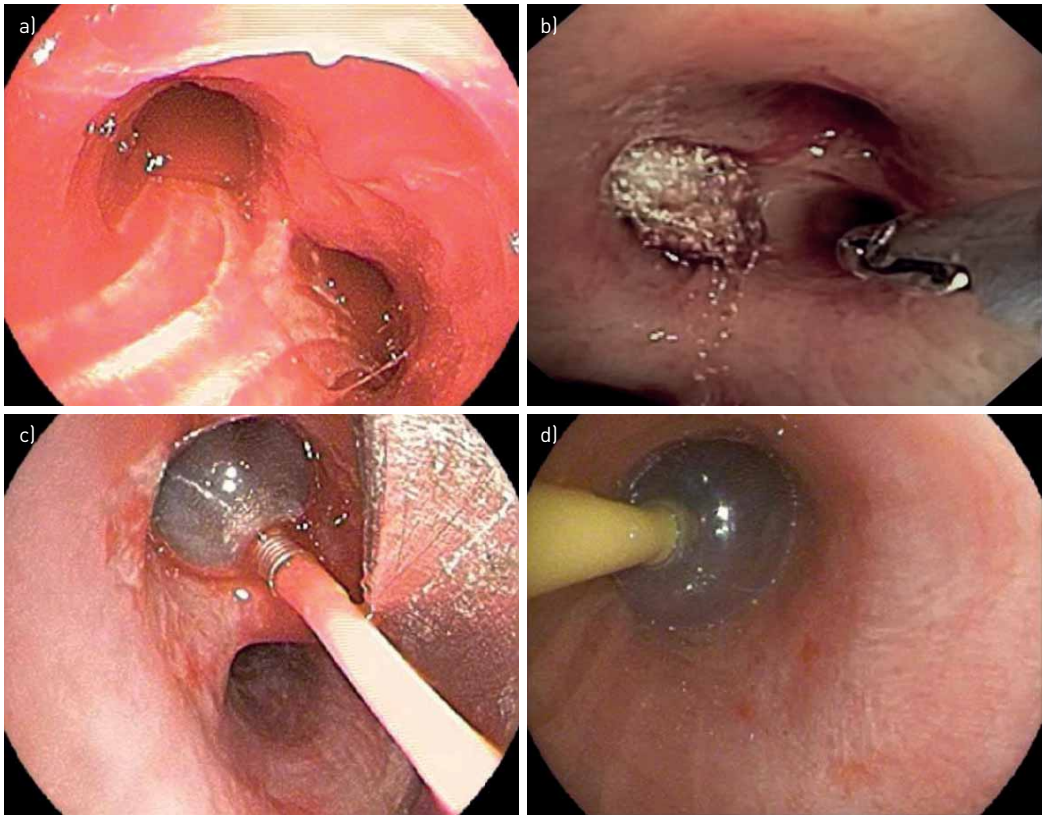

Figure 1. a) Massive haemoptysis with refresh blood coming from both the left and right mainstem. b) SURGICEL application (Ethicon, Somerville, NJ, USA) to the anterior segment of the right upper lobe. Reproduced with kind permission of J. Cárdenas-García (Penn State Milton S. Hershey Medical Center, Hershey, PA, USA). c) Fogarty balloon occlusion to the right upper lobe. d) Arndt endobronchial blocker (Cook Medical, Bloomington, IN, USA) to the left mainstem.

intermittent blood-streaked sputum can often be managed as outpatients. However, patients with massive haemoptysis should be considered as a medical emergency and require multidisciplinary management teams, including emergency physicians, intensivists, pulmonologists, interventional radiologists and cardiothoracic surgeons, and the possible involvement of otolaryngologists and gastroenterologists. The therapeutic goal is to maintain airway patency, localise and stop the bleeding source, and monitor for any haemodynamic instability and recurrent bleed [4, 9, 38].

General considerations

The patient presenting with active massive haemoptysis should be admitted to the intensive care unit for close monitoring; it is necessary to provide supplemental oxygen and empiric antibiotics, obtain laboratory studies for workup of haemoptysis, maintain total fasting, and insert adequate large bore intravenous access for resuscitation. It is important to stress that once the side of active bleeding is known, the patient should be placed in the lateral decubitus position with the bleeding side down. With this positioning, one can delay the spillage of blood into the nonbleeding side. In general, intubation should be considered only if the patient cannot maintain his/her airway. As the patient's native cough reflex is often more efficient than the suction catheters available for blood clearance, endotracheal intubation should not be done routinely without consideration. However, if there is any sign of fatigue or ventilation defects, intubation with a large (8.5–9.0 mm diameter) bore endotracheal tube will allow adequate suctioning and therapeutic flexible bronchoscopy. Ideally, in the setting of experienced bronchoscopists, rigid bronchoscopy should be performed to ensure the most efficient means of clearing the airway and treatment of airway bleeding source or blocking off active bleeding lung segments in order to prevent asphyxia.

Bronchoscopic treatment

Several strategies are available for efficient bronchoscopic treatment of the bleeding airway. The operator should be familiar with techniques of effective suctioning, maintaining a clear bronchoscopic visual field and clot evacuation [49]. Endobronchial pharmacological and mechanical therapies are reviewed in the following subsections. In general, pharmacological therapies that can reach distal airways are more effective on peripheral sites of bleeding, while mechanical therapies are often limited to the more central sites of bleeding where visualisation of the bleeding source is required for effective therapy delivery.

Ice saline lavage

Endobronchial irrigation with normal saline at 4°C (ice saline) for massive haemoptysis has been used since the 1980s. The initial report of ice saline treatment for massive haemoptysis examined 12 consecutive patients with at least 600 mL of haemoptysis in 24 h. All patients were treated with rigid bronchoscopy. The bleeding side was repeatedly irrigated with ice saline at 4°C in 50 mL aliquots, where each aliquot was left in for 30–60 s prior to suction removal. On average, 500 mL (range 300–750 mL) per patient was used to stop bleeding. One out of the 12 patients had transient sinus bradycardia that resolved without intervention. Two out of the 12 patients had recurrent bleeding that required repeat ice saline lavage. The mechanism of action of ice saline was attributed to cold-induced vasoconstriction and clot formation [50]. Ice saline irrigation can be used with a flexible bronchoscope *via* a large bore endotracheal tube; however, there is less

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control of selective ventilation and suction. Unfortunately, most of the data with ice saline is from retrospective case series and no current randomised control trial for evaluation of ice saline use in massive haemoptysis has been performed [9].

Pharmacological therapy

Topical epinephrine, tranexamic acid, fibrinogen–thrombin complex, *n*-butyl-2-cyanoacrylate and oxidised regenerated cellulose have been reported in controlling haemoptysis. However, their efficacy in massive haemoptysis is not known due to a lack of high-quality studies. Additionally, topical agents are often diluted and washed away by the blood in the airway, thus decreasing their true efficacy. We will briefly review their use here.

Topical endobronchial application of epinephrine has been used to achieve local vasoconstriction and bleeding control in the setting of endobronchial biopsy or TBB. The safety profile of diluted epinephrine (1:10 000) applied in 2 mL aliquots up to a maximum dose of 0.6 mg has had very long experiential support [51]. However, the use of epinephrine in massive haemoptysis is limited to a case report [52]. Unintended hypertension and tachyarrythmias can also occur, and therefore endobronchial epinephrine should be avoided in the elderly, in patients with coronary artery disease and in the setting of carcinoid tumours [53].

Use of an antifibrinolytic drug, *i.e.* tranexamic acid, *via* oral or *i.v.* administration, in patients following major surgery has been well established [54]. However, there is only limited evidence for its use in controlling haemoptysis from any cause [55]. In recent reports, both topical application (500 mg tranexamic acid in 15 mL of normal saline) and intralesional injection (250–500 mg tranexamic acid in 2.5–5 mL of normal saline) appear to decrease endobronchial bleeding related to malignancy and bronchoscopic biopsies [56, 57]. In a recent randomised study comparing endobronchial epinephrine (1 mg in 20 mL of saline) with tranexamic acid (500 mg in 20 mL of saline) there appears to be no difference in the efficacy between these agents in controlling haemoptysis [58]. Finally, there is one case series of four patients (three with lung cancer and one with bronchiectasis) with moderate haemoptysis (100 mL per 24 h) successfully treated with nebulised tranexamic acid (250–500 mg in 2.5–5 mL every 8 h) [59]. While these are encouraging reports, there is still insufficient data to recommend the routine use of tranexamic acid, especially in the setting of massive haemoptysis. Furthermore, tranexamic acid at a high dose and in susceptible populations (*i.e.* the elderly, renal failure, cardiac disease and those with prior neurological defects) can lead to seizures [60]. This adverse effect has also been reported in haemoptysis treatment with tranexamic acid [61].

Fibrinogen–thrombin complex for endobronchial treatment of haemoptysis has been in clinical use since the 1980s. The initial report of 33 patients (19 treated with thrombin alone and 14 treated with fibrinogen–thrombin complex) showed promising results in managing massive haemoptysis (>200 mL of blood) [62]. In 1998, fibrinogen–thrombin complex became commercially available as TISSEEL in the USA (Baxter International, Deerfield, IL, USA) and TISSUCOL elsewhere in the world. Bronchoscopic application of TISSUCOL achieved immediate bleeding control in 11 patients with massive haemoptysis (>150 mL per 12 h) refractory or unable to undergo bronchial artery embolisation (BAE). However, three patients had a relapse of bleeding within 12 months of treatment [63]. In addition to TISSEEL, glue material such as *n*-butyl-2-cyanoacrylate has been used endobronchially in haemoptysis management [64, 65]. Despite these encouraging reports,

there is a lack of high-quality controlled studies to recommend routine use in patients with massive haemoptysis.

Oxidised regenerated cellulose (SURGICEL; Ethicon, Somerville, NJ, USA) is a topical haemostatic agent that is biocompatible, absorbable, sterile and bactericidal. SURGICEL and its family of products (SURGICEL SNoW, FIBRILLAR and Nu-KNIT) have broad surgical applications. Endobronchial SURGICEL treatment was first described in 57 patients with massive haemoptysis (>150 $mL \cdot h^{-1}$ or >150 mL on one occasion) who were refractory to topical ice saline and epinephrine treatment. SURGICEL mesh was cut into strips (maximum 30×40 mm), pulled into the flexible bronchoscope's working channel with a biopsy forceps and introduced into the bleeding lobar or subsegmental airway to achieve haemostasis. Bleeding was arrested in 56 out of the 57 (98%) treated patients. Six patients had bleeding recurrence within 3–6 days post-treatment. These patients subsequently underwent BAE and two out of six had repeat endobronchial treatment. Five patients developed post-obstructive pneumonia [66]. While the initial experience with SURGICEL is encouraging, the treatment is limited to distal airways and recurrence of bleeding is possible with absorption of the haemostatic SURGICEL plug (figure 1b). Finally, post-obstructive pneumonia risk is significant, especially considering four out of five patients with post-obstructive pneumonia had lobar haemostatic treatment [67].

Mechanical therapy

Physical occlusion of the bleeding airway segment aims to prevent spillage of blood into the healthy lung segments, to allow time for clot formation and to prevent further deterioration of the respiratory status. Once the bleeding side is determined, isolation of the healthy lung can be immediately achieved by selective intubation of the healthy lung with a large bore endotracheal tube. For example, if the blood is coming from the right lung, the left mainstem can be selectively intubated to maintain ventilation of the left lung. Caution should be exercised when selectively intubating the right mainstem due to the close proximity to the right upper lobe take-off. A double-lumen endotracheal tube can be used for selective intubation and lung isolation; however, the use of such tubes is not advocated in haemoptysis due to the small lumen that prohibits therapeutic bronchoscopy. Endobronchial blockers, silicone plugs, and endobronchial stents and valves have been used to achieve airway occlusion in haemoptysis patients. They are reviewed in the following paragraphs.

Balloon occlusion can be used in combination with an endotracheal tube to isolate the bleeding lung and allow therapeutic bronchoscopy treatment. The use of a Fogarty balloon for treatment of massive haemoptysis has been reported since the 1970s [68–70]. However, the Fogarty balloon catheter is placed *via* the bronchoscope's working channel and cannot be left in place (figure 1c). To overcome these limitations, different approaches have been described to enable placement of the Fogarty balloon parallel to the bronchoscope [71, 72]. Several systems have been developed to allow long-term balloon tamponade of the airway. The commercially available systems for balloon occlusion include the Arndt endobronchial blocker (Cook Medical, Bloomington, IN, USA), Cohen Flextip endobronchial blocker (Cook Medical), Rusch EZ-Blocker (IQ Medical Ventures, Rotterdam, The Netherlands) and Fuji Uniblocker (Fuji Systems, Tokyo, Japan). The characteristics of each system are summarised in table 2. To date, there are no studies comparing the effectiveness and ease of placement of the different endobronchial blockers in the setting of massive haemoptysis (figure 1d).

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Table 2 Endobronchial blockers

	Arndt endobronchial blocker	Cohen Flextip endobronchial blocker	Rusch EZ-Blocker	Fuji Uniblocker
Appearance				
Size Fr	5, 7 and 9	9	7	5 and 9
Guidance mechanism	Nylon wire loop coupled with the fibreoptic bronchoscope	Wheel device to deflect the tip, guidance arrow at the tip for direction	Y-shape at the distal end to straddle the carina	Pre-shaped tip to be directed into the desired airway
Recommended endotracheal tube for use mm	⩾5.0 (5 Fr) ⩾7.5 (7 Fr) ⩾8.0 (9 Fr)	⩾8.0	⩾7.5	⩾5.0 (5 Fr) ⩾8.0 (9 Fr)
Maximum inflation volume mL	2 (5 Fr) 6 (7 Fr) 8 (9 Fr)	9	12	3 (5 Fr) 8 (9 Fr)
Centre channel (internal diameter) mm	1.4	1.6	1.4	1.4

Fr: French. Reproduced and modified with kind permission from J.H. Campos (University of Iowa Health Care, Iowa City, IA, USA). Manufacturer details for the endobronchial blockers presented are as follows. Arndt endobronchial blocker: Cook Medical, Bloomington, IN, USA. Cohen Flextip endobronchial blocker: Cook Medical. Rusch EZ-Blocker: IQ Medical Ventures, Rotterdam, The Netherlands. Fuji Uniblocker: Fuji Systems, Tokyo, Japan.

The Endobronchial Watanabe Spigot (EWS; Novatech, La Ciotat, France) is made from implantable medical-grade silicone and dyed with barium sulfate for improved radiological visualisation. It has been used in the treatment of bronchopleural fistula, persistent pneumothorax and haemoptysis [73–76]. The EWS comes in three sizes (5, 6 and 7 mm diameter) and can be deployed in multiple ways [77, 78]. In massive haemoptysis, the EWS has been used as a bridging measure to BAE.

Endobronchial stents and valves have been used in the treatment of haemoptysis in several case reports. With endobronchial stents, covered self-expanding metallic stents were used to either tamponade directly the bleed tumour or to block the orifice of the bleeding segment of the lung [79–81]. Recently, endobronchial valves, both Zephyr (PulmonX, Redwood City, CA, USA) and Spiration (Olympus, Tokyo, Japan), were used to treat recurrent or refractory haemoptysis [82, 83]. While these case reports provide intriguing approaches to management, there are no data regarding the efficacy or safety profile in the haemoptysis patient population.

Adjunctive therapy: laser photocoagulation, APC, electrocautery and cryotherapy

If the bleeding source is a visible lesion in the airway, heat therapy with laser photocoagulation, APC and electrocautery can be used to address the bleed.

Dumon *et al.* [84] introduced the use of the endobronchial Nd-YAG (neodymium-doped yttrium aluminium garnet) (1060 nm) laser in 1982. The first report of using laser photocoagulation to treat massive haemoptysis appeared 1 year later [85]. Using laser treatment for endobronchial lesions often addresses both haemoptysis and airway obstruction [33]. The Nd-YAG laser was used to palliate 110 patients with large airway malignancy; 52 patients had haemoptysis and 49 out of the 52 (94%) patients reported improvement in haemoptysis after treatment. Complete cessation of bleeding occurred in 40 out of the 52 (77%) patients [86]. Over the past couple of decades additional medical lasers have been developed and used endobronchially. Different laser media determine the wavelength of the laser (ranging from argon at 516 nm to carbon dioxide at 10 600 nm) and ultimately the unique tissue interactions. While the newer thulium (1940 nm) and Nd-YAP (neodymium-doped yttrium aluminium perovskite) (1340 nm) medical lasers offer advantages, the use of lasers in the airway is often limited by the costs and availability of laser setup, the requirement for personnel training, and additional precautions for laser operators [87, 88].

APC has been an effective treatment of haemoptysis. In a retrospective study, APC successfully treated 31 patients with haemoptysis and 25 patients with both haemoptysis and airway obstruction. The rate of haemoptysis ranged from >200 to <50 mL per day. Regardless of the amount, bleeding was controlled in all patients with an airway bleeding source. The effect was maintained for an average of 97 days in the follow-up period [89].

Finally, electrocautery has been shown to be safe and effective in the treatment of malignant airway obstruction and associated haemoptysis. In 94 patients who underwent electrocautery as the primary ablation technique, 15% had haemoptysis as the presenting symptom and 71% reported post-treatment overall symptom improvement. However, bleeding magnitude was not reported [90]. Taken together, haemoptysis due to airway lesions, especially related to malignancy, could be effectively addressed with bronchoscopic heat therapy (figure 2) [33].

While cryotherapy is an effective palliative treatment for inoperable airway malignancy, it is not considered a treatment option in massive haemoptysis. Cryotherapy, specifically cryodebridement, is used to facilitate effective blood clot removal in order to maintain airway patency [4, 91].

Bronchial artery embolisation

Since the initial description of BAE in the early 1970s, the BAE procedure has become safer, and has been accepted as the most effective treatment for refractory and massive haemoptysis [2, 92]. Either as the definitive therapy or as a bridging therapy to surgical intervention, BAE provides immediate control of bleeding in 66–96% of patients [93–99]. Increased diameter (>3 mm, normal is 1.5 mm), tortuosity, neovascularity/hypervascularity, extravasation of contrast medium and presence of aneurysm changes are all pathological signs of bleeding vessels (figure 3). Bronchial, nonbronchial or ectopic arteries can be the culprit target; as such, BAE is a highly variable procedure where pre-procedural MDCT angiography can provide valuable information to inform the treatment plan. In general, the

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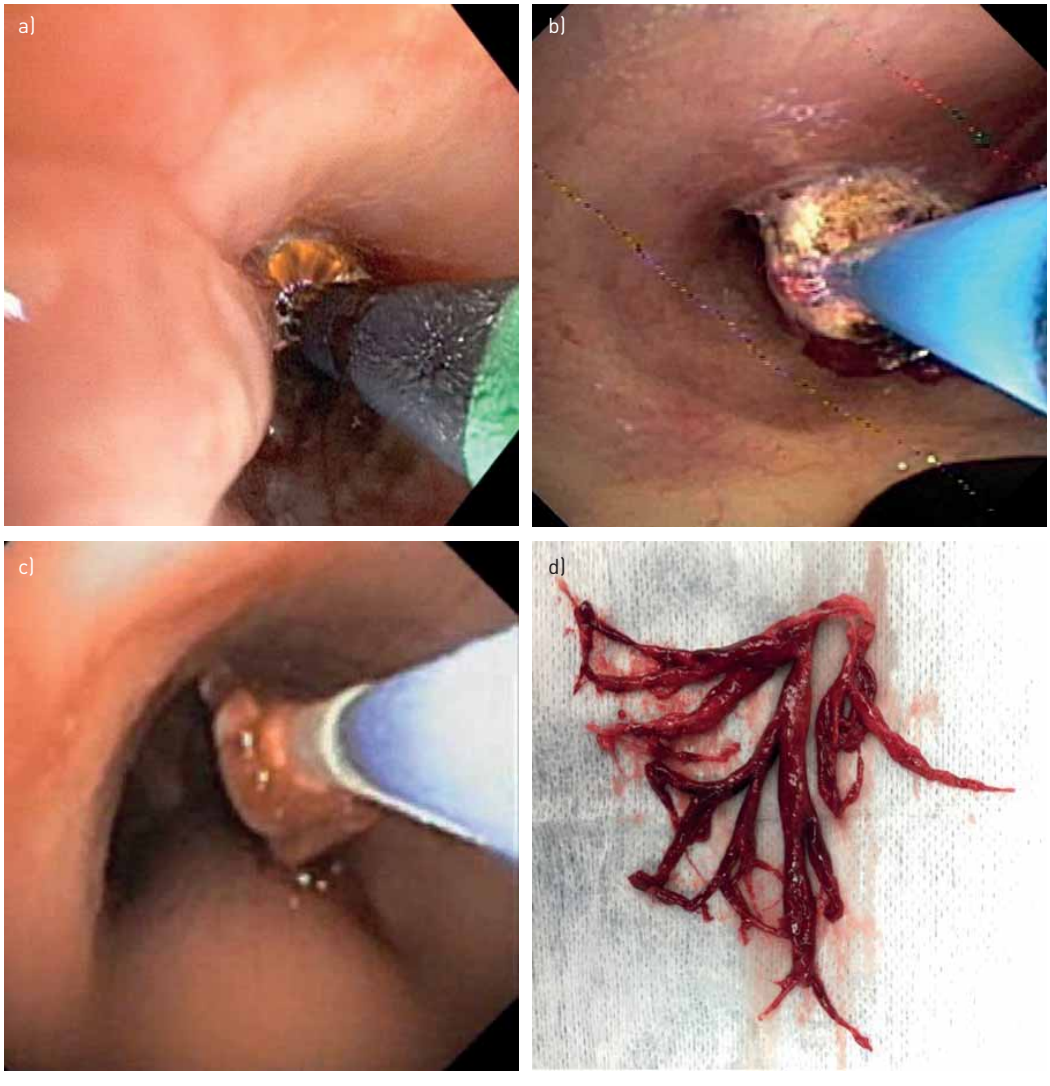

Figure 2. a) Electrocautery to a bronchus intermedius lesion. b) Argon plasma treatment to a tracheal lesion. c) Cryoprobe-mediated clot removal. d) Blood clot forming airway cast post-removal.

femoral or brachial artery is used for arterial access. Femoral arterial access is more commonly used, and is associated with lower morbidity and complication rates [100]. Initial arterial access and bronchial artery origin cannulation is usually obtained with a 5 French (Fr) angiographic pigtail catheter (Cook Medical). Superselective cannulation with a 2.7 Fr (Progreat, Terumo, Japan) or 3 Fr (Cook Medical) microcatheter can be done in a coaxial fashion through the 5 Fr catheter. The coaxial system reduces embolic material reflux into the aorta during the injection process [95]. Arteriography should be performed with low-osmolar or iso-osmolar nonionic contrast material. All pathological vessels are targets for embolisation. However, bleeding recurs in 10–29% of patients due to recanalisation, collateralisation or incomplete embolisation of the targeted vessels. The most common rebleed entity is a mycetoma, which will usually require surgical resection [2, 6, 12, 15, 40, 101, 102]. The most serious complication of BAE is embolisation of the anterior

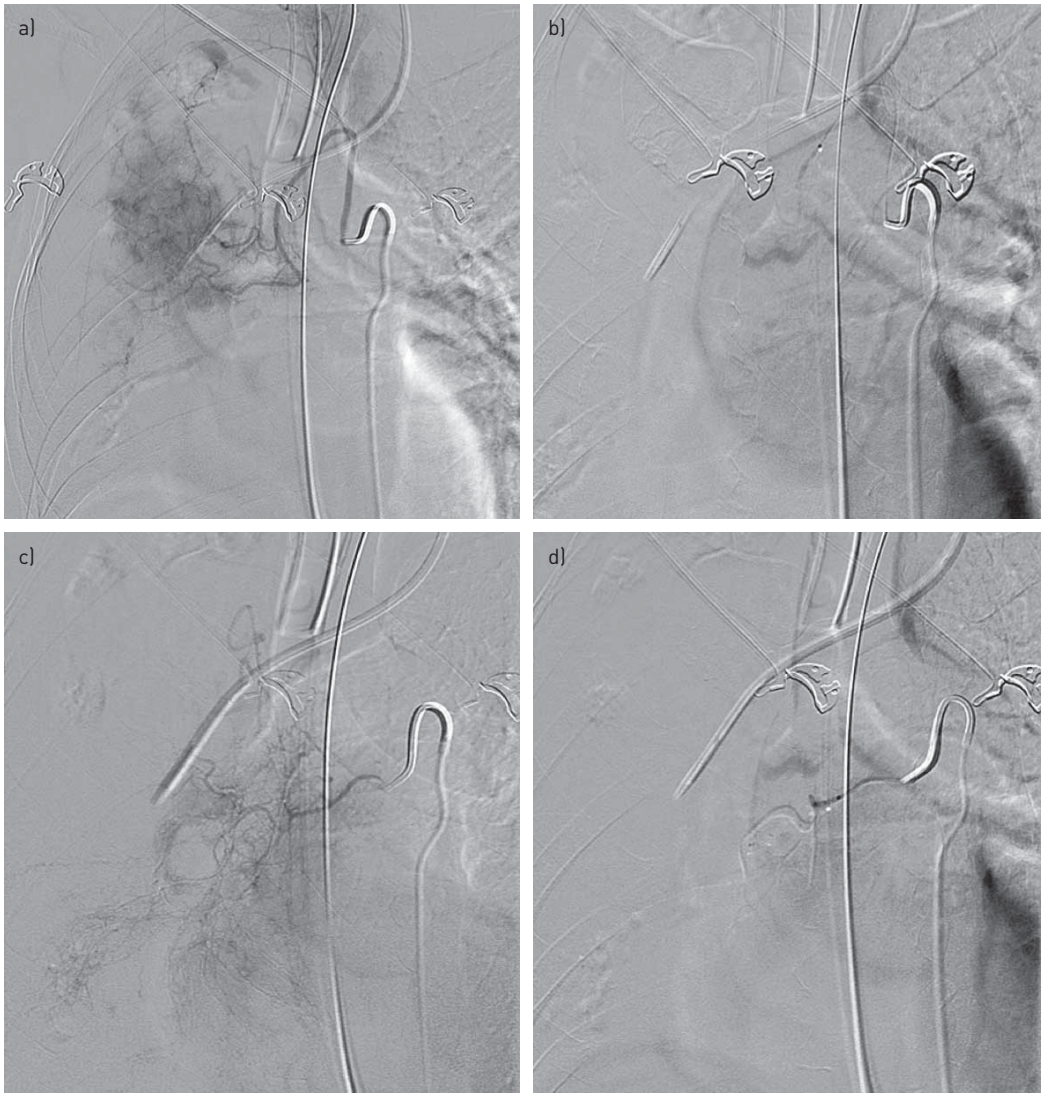

Figure 3. Right upper lobe bleeding lesion. a) Right upper bronchial artery arteriogram demonstrated hypertrophy with prominent tumour blush and tumour vascularity. b) Right upper bronchial artery was embolised to stasis. c) Right lower bronchial artery arteriogram demonstrated branching into abnormal vessels suspicious for tumour vascularity. d) Right lower bronchial artery was embolised to stasis.

spinal artery (artery of Adamkiewicz), leading to anterior spinal cord syndrome. Fortunately, the use of a microcatheter allows cannulation of the bronchial artery distal to the origin of the anterior spinal artery and the use of low-osmolar or iso-osmolar nonionic contrast material appears to reduce this neurological complication [103].

Several agents have been used for embolisation. Two of the most commonly used agents are GELFOAM (Pharmacia & Upjohn, Kalamazoo, MI, USA) and polyvinyl alcohol (PVA) particles (Boston Scientific, Natick, MA, USA). GELFOAM is an absorbable gelatine sponge that results in temporary arterial occlusion, but has a high rate of recanalisation and often requires repeated embolisation procedures. PVA particles, whose size ranges from 250 to

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500 µM, are nonabsorbable and can afford a more durable vascular occlusion. Use of a particle size >325 µM is needed to ensure no significant bronchial–pulmonary shunting that can result in pulmonary or systemic infarction. Microspheres (BioSphere Medical, Rockland, MA, USA) are hydrophilic cross-linked gelatine spheres (500–700 µM) that have a more uniform spherical shape that reduces clumping and these have been shown to achieve similar short-term clinical success as PVA particles. Liquid embolic agents such as *n*-butyl-2-cyanoacrylate (Trufill; Johnson & Johnson/DePuy, Raynham, MA, USA) or ethylene vinyl alcohol polymer (Onyx; eV3 Neurovascular, Irvine, CA, USA) have been used successfully in BAE. Finally, metallic coils can be used for proximal vessel occlusion for patients with persistent and recurrent haemoptysis [14, 95]. The choice of which agent to use is dependent on operator experience and availability of the embolic material.

Surgical management

Historically, emergent surgical intervention in massive haemoptysis carried a high mortality rate (25–50%); thus, it is only considered in refractory bleeding secondary to pulmonary artery rupture, chest trauma, necrotising infection (mycetoma) or complex arteriovenous malformations [3, 6, 104]. The rate of complications and mortality is significantly decreased when the surgery is performed in a planned fashion after a period of clinical stability afforded by BAE or endobronchial treatments [104]. In a recent study of national registry data, patients who underwent urgent or emergent lobectomy and pneumonectomy

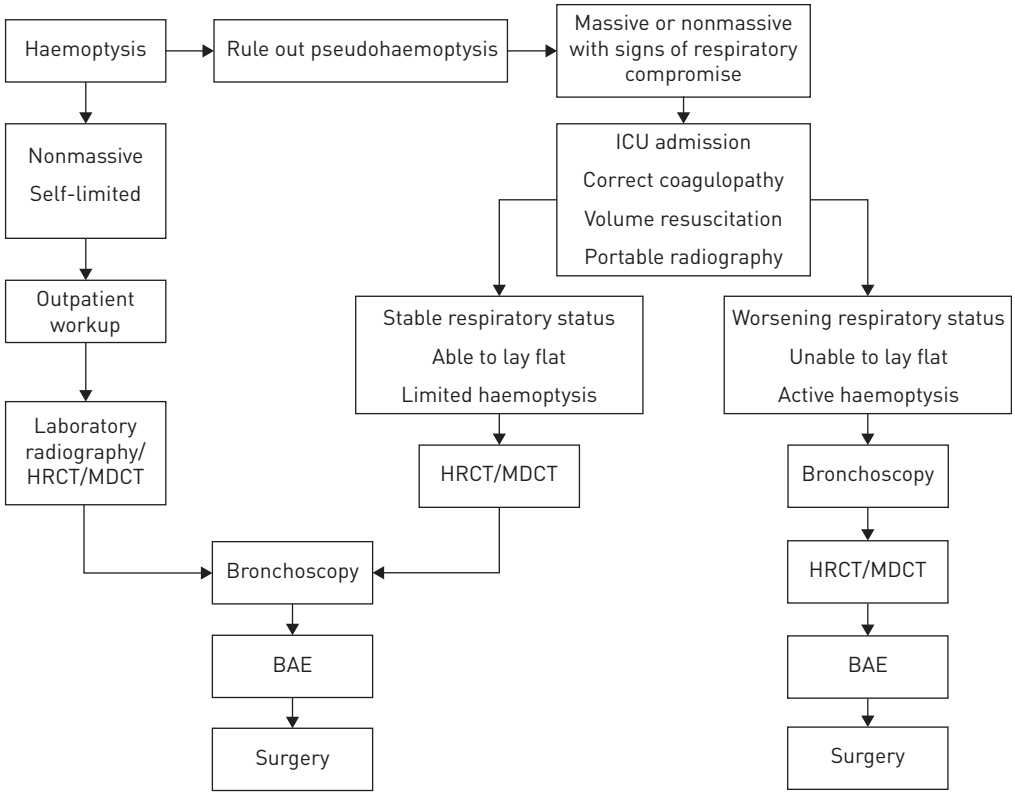

Figure 4. Haemoptysis management flowchart. ICU: intensive care unit; MDCT: multidetector CT; BAE: bronchial artery embolisation.

had mortality rates of 6.6% and 15.2%, respectively. Of note, risk factors associated with poor outcome include advanced age, concurrent infections, necrotising infections, extent of resection, and diagnosis of sarcoidosis and renal failure [31]. Thus, surgical intervention is a salvage treatment for refractory haemoptysis, and is associated with increased mortality and morbidity.

Conclusion

While there is no consensus on the definition of massive haemoptysis, the clinical importance of recognising this life-threatening condition is not disputed. A practice algorithm can significantly streamline the management of these patients. We propose the algorithm outlined in the flowchart in figure 4 as an example for the management of haemoptysis. Patients who present with haemoptysis should be triaged based on severity and respiratory status, with consideration given to baseline pulmonary reserve. For patients with massive haemoptysis, correction of underlying coagulopathy, providing appropriate resuscitation, frequent monitoring in the intensive care unit and identifying the bleeding side are the initial clinical aims. If the patient is not able to maintain their airway, intubation with a large bore endotracheal tube followed by bronchoscopy should be performed. When available, a combination of rigid and flexible bronchoscopy is preferred over flexible bronchoscopy through a large bore endotracheal tube. Once the bleeding source or side is identified, a variety of endobronchial approaches can be applied to temporise the haemorrhage and stabilise the patient for radiological evaluation and treatment with BAE. In selected patients, surgical intervention should be considered in an elective nonurgent setting.

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Chapter 14

Early cancer therapies

Marta Díez-Ferrer[1], Cristina Gutierrez[2] and Antoni Rosell[1]

Bronchoscopic therapies for early lung cancer have shown very promising results but strong evidence comparing available treatments is still lacking. Endobronchial therapies have been attempted in proximal lesions, including Nd-YAG laser therapy, electrocautery, cryotherapy, brachytherapy, APC and PDT. Approaching the lung periphery is still challenging and peripheral lesions in patients who cannot undergo surgery often have to be managed using a CT-guided percutaneous approach. Percutaneous techniques include laser ablation, RFA, microwave ablation, cryotherapy and PDT. Newer bronchoscopically guided and navigational technologies may be able to deliver these therapies effectively to peripheral lesions in the near future with fewer complications than the percutaneous approach.

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Newer therapies for early lung cancer have emerged and should be made available when surgery and radiotherapy are contraindicated, *e.g.* in patients in whom the amount of normal tissue that has to be removed or denaturalised is too large according to their lung function, those with unresectable central tumours or in cases where further intervention might be needed due to the presence of metachronous lesions. Therefore, the use of bronchoscopic therapies in the management of lung cancer that is limited to the airways has shed new light on the management of early lung cancer.

Several techniques (many of which are covered elsewhere in this *Monograph* [1]) are available to treat endoluminal superficial lesions, including laser therapy, electrocautery, APC, PDT, cryotherapy and brachytherapy. The curative potential of all these therapies has been demonstrated, as all of them are able to effectively destroy tumours of up to a depth of 5 mm in central early lung cancer. However, positioning endoscopic therapies in the management of early lung cancer remains challenging. The heterogeneity of the inclusion criteria in the reported studies as well as the difficulty of conducting randomised controlled trials comparing natural outcomes of early stage superficial lesions with the different therapies are the main reasons for the limited weight of current evidence.

[1]Bronchoscopy Unit, Dept of Respiratory Medicine, Hospital Universitari de Bellvitge, Universitat de Barcelona, IDIBELL, L'Hospitalet de Llobregat, Barcelona, Spain. [2]Brachytherapy Unit, Dept of Radiotherapy and Oncology, Institut Català d'Oncologia, L'Hospitalet de Llobregat, Barcelona, Spain.

Correspondence: Antoni Rosell, Bronchoscopy Unit, Dept of Respiratory Medicine, Hospital Universitari de Bellvitge, Universitat de Barcelona, IDIBELL, Feixa Llarga s/n, L'Hospitalet de Llobregat, 08907 Barcelona, Spain. E-mail: arosell@bellvitgehospital.cat

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The definition of early lung cancer used in the studies of bronchoscopic therapies does not correspond exactly to the current definitions of the TNM (tumour, node and metastasis) classification and differs among authors. In 1989, NAGAMOTO *et al.* [2] observed that squamous cell carcinoma (SCC) ⩽3 mm thick and with a longitudinal extension <20 mm was associated with no nodal involvement. In 1999, KONAKA *et al.* [3] suggested that hypertrophic lesions (*i.e.* those with only superficial thickening of the epithelium) <1 cm^2 in surface area are either carcinoma *in situ* (CIS) or micro-invasive tumours within the muscle layer, while nodular and polypoid lesions ⩾1 cm^2 in surface area are more likely to be invasive beyond the cartilaginous layer. Accordingly, in 2003, MATHUR *et al.* [4] defined early stage cancer as radiographically occult SCC that is endoscopically superficial, <2 cm^2 in surface area with clearly visible margins and not invading beyond the bronchial cartilage. Later, in 2010, the Japan Lung Cancer Society defined the bronchoscopic criteria of central-type early stage lung cancer as that located subsegmentally or more proximally, <2 cm^2 in surface area with bronchoscopically recognisable margins and proven SCC [5]. However, evidence shows that pre-invasive bronchial lesions should also be detected and treated due to their higher risk for cancer [6, 7].

The current edition of the International Association for the Study of Lung Cancer TNM classification incorporates new definitions in the early stages, including some special situations [8]. Superficial spreading tumours in the central airways are those confined to the tracheal or bronchial wall regardless of size and location, and are labelled T1a *ss*. CIS (classified as Tis) now includes both SCC *in situ* (or squamous dysplasia) and adenocarcinoma *in situ* (AIS, which is localised, ⩽3 cm and shows pure lepidic growth, lacking stromal, vascular, alveolar space or pleural invasion). Minimally invasive adenocarcinoma is classified as T1a(mi) and corresponds to solitary adenocarcinoma ⩽3 cm with a predominantly lepidic pattern and ⩽0.5 cm invasion. The invasive component is defined as a histological type other than lepidic or tumour cells infiltrating myofibroblastic stroma. In our setting, it is important to note that examination of small biopsy specimens cannot exclude or quantify invasive components for AIS and T1a(mi), respectively. Although there can be a high suspicion of AIS with biopsies with a pure lepidic pattern, together with a CT correlation of the ground-glass component, AIS and T1a(mi) require examination of the entire resection specimen [8, 9].

The accuracy of the techniques used for diagnosing early lung cancer is crucial for defining the lesions suitable for endobronchial therapy. High-definition bronchoscopy, AFB and NBI have been used for defining the margins of the lesion, the latter having a higher specificity [10]. To evaluate the shallowness of the tumour, radial EBUS and OCT have been used [11]. The combination of AFB and OCT has also shown good results for both the detection and characterisation of pre-malignant lesions of the central airways [12]. Thin-section CT (⩽1 mm) and PET-CT might also be useful in the evaluation of pre-malignant lesions [13, 14]. A comprehensive review of early stage cancer diagnostic techniques can be found elsewhere in this *Monograph* [15].

Treatment success is directly dependent on lesion accessibility and the ability to correctly delineate the margins and shallowness of the lesions [16]. Given the accumulated evidence, it is logical to think that pre-malignant lesions and those limited to the tracheal and bronchial wall (*i.e.* T1a *ss* tumours) might be suitable for endoscopic curative treatments, granted that lesion margins and shallowness are correctly delineated. Once the limits of the lesion are defined, and according to current evidence, choosing one technique over another depends mainly on the expertise of the bronchoscopist and the availability of the therapy. However, some of the practical characteristics of each technique should be considered.

Finally, due to the high risk of primary and second primary lung cancer in patients with pre-malignant lesions, as well as cancer progression and recurrence, follow-up is another key issue to be determined. In this sense, bimodal surveillance with AFB and CT has shown the highest detection rate, which was 34% in a 10-year follow-up [6]. However, more efficient strategies should be explored.

Here, we review the available bronchoscopic therapies for the management of endobronchial early cancer limited to the proximal airways (table 1). We will also briefly present the percutaneous therapies that are currently available for the management of peripheral lung cancer (table 2).

Laser therapy

"Laser" is an acronym for "light amplification by stimulated emission of radiation". Briefly, stimulation of an active substance produces photons that are reflected inside the laser cavity, producing new photons which make up the laser beam. Laser light energy is used for thermal tissue ablation (figure 1). The wavelength of a particular laser is determined by the stimulated substance. The power settings of the laser machine (measured in watts) can also

Table 1. Endobronchial therapies for early lung cancer

Therapy	Principle	Depth	Main risks	Considerations
Laser	Thermal ablation with laser light	Up to 10 mm (but variable)	Airway perforation, haemorrhage, airway fire, respiratory failure	As for thermal therapies[#]
Electrocautery	Thermal ablation through electric current flow	Up to 10 mm (but variable)	Airway perforation, haemorrhage, airway fire, respiratory failure	As for thermal therapies[#]; caution with pacemakers; cheaper than laser therapy
APC	Thermal ablation with electric current through argon gas	2–3 mm	Airway fire, respiratory failure	As for thermal therapies[#]; caution with pacemakers
PDT	Nonthermal ablation with light in previously photosensitised tissues	3 mm	Respiratory failure	Produces intense photosensitivity; delayed results and need for repeat bronchoscopy
Cryotherapy	Rapid tissue freezing causing cell death and ischaemic necrosis	3 mm	Respiratory failure	Delayed results
Brachytherapy	Radiation therapy applied directly to tumour through endobronchial catheter	Variable	Ulcers, fibrosis, stenosis, haemoptysis	Accumulative radiation dose; high complexity and need for multidisciplinary team

[#]: thermal therapies should be applied with an oxygen concentration <30–40% due to ignition risk and rigid bronchoscopy considered, although laryngeal masks can be used and are safer than ETTs.

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Table 2. Percutaneous treatments for peripheral pulmonary lesions

Therapy	Application	Principle	Main risks
Laser	Nd-YAG laser applied through outer sheath	Thermal ablation with laser light	Pneumothorax
RFA	RFA applied through an electrode placed in the tumour	Thermal ablation with kinetic energy	Pneumothorax, pleuritic chest pain, haemoptysis, pleural effusion
Microwave	Microwave energy applied through a needle placed in the tumour	Thermal ablation with kinetic energy	Pneumothorax
Cryotherapy	Cryoablation probe placed in the tumour	Ablation through tissue freezing	Pneumothorax, bleeding
PDT	PDT applied through catheters placed in the tumour	Thermal ablation with light in previously photosensitised tissues	Pneumothorax

be regulated. Finally, the exposure time or so-called laser energy (measured in joules), the density of the impact surface, the distance from the laser fibre to the target, the colour of the tissue surface and the angle of incidence also determine the effect of the laser beam on the tissue. This effect can be relatively superficial and is then used for coagulation; however, when higher temperatures are obtained, a deeper resection and vapourisation effect is produced on the tissue [17]. Although laser therapy is a very precise technique, there is also some degree of delayed effect of the laser on the surrounding tissues due to heat energy absorption [18]. Of all the lasers, the Nd-YAG (neodymium-doped yttrium aluminium garnet) laser is the most commonly used due to its resection and vapourisation properties. The Nd-YAG laser emits in the infrared range at 1064 nm and therefore a red helium–neon beam is used to mark the area of application that would otherwise be invisible.

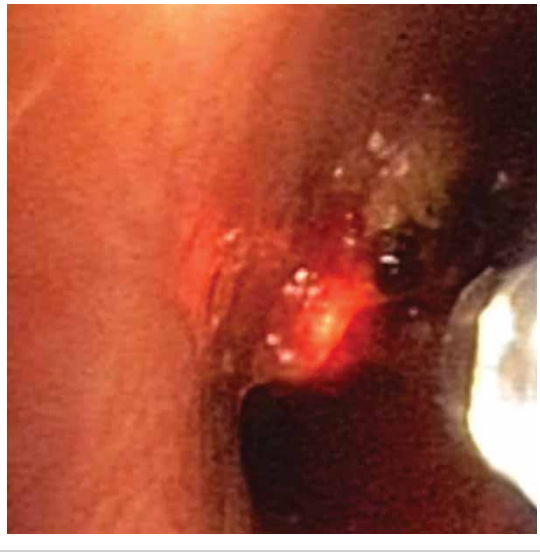

Figure 1. Nd-YAG laser application on a tumour.

Laser therapies are most commonly applied using a rigid bronchoscope under general anaesthesia, either directly through the rigid bronchoscope or through the working channel of a flexible bronchoscope. Laser therapy is mainly indicated in the acute treatment of life-threatening central airway obstructions (CAOs), mainly for the palliation of symptoms derived from a malignant infiltration of the main airways, although it can also be used in benign stenosis. However, there are some reports on the use of laser therapy for the management of early lung cancer that is limited to the inner lumen of the proximal airways. Cavaliere *et al.* [19] investigated the use of Nd-YAG laser therapy to treat 19 CIS over a 10-year period. They reported no recurrence of CIS in any case, although they only specified a follow-up period in one case, which was of 4 years [19]. A number of other cases have been reported, including an epithelial–myoepithelial carcinoma with a PET-CT negative control after treatment [20] and a case of multiple poorly differentiated SCC lesions treated with an Nd-YAG laser with no recurrence after a 1-year follow-up [21]. Vonk-Noordegraaf *et al.* [22] also reported a case that was successfully treated with Nd-YAG laser therapy, although they did not specify histology or the follow-up period, which was at least 2 years. Finally, Van Boxem *et al.* [23] reported the successful treatment of three out of four endoluminal typical carcinoids.

Electrocautery

Electrocautery uses an electric current to produce thermal ablation of the tissues (figure 2). The effects of electrocautery on tissue include coagulation, vapourisation and fulguration (according to the nature of the lesion); tissue penetration is determined by the adjusted frequency of the waveform and the peak voltage. As with laser therapy, there is some degree of delayed effect of electrocautery on the surrounding tissues due to heat energy absorption. Electrocautery is most often applied with unipolar electrodes through the working channel of a flexible bronchoscope and under conscious sedation, although rigid probes with several configurations exist that can be used through rigid bronchoscopes

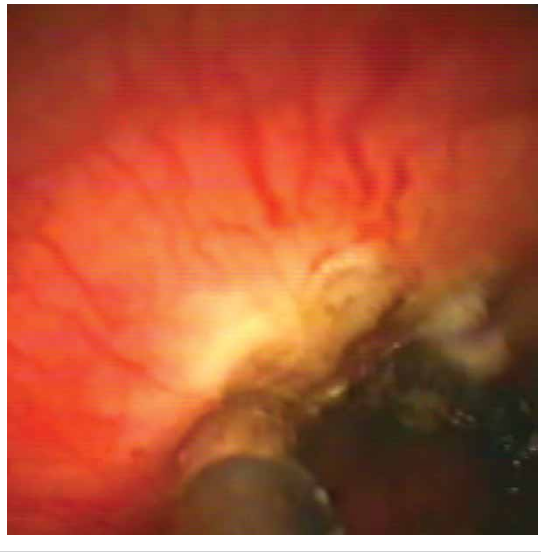

Figure 2. Thermal ablation of a tumour with electrocautery.

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under general anaesthesia. The probe is placed in contact with the tissue in order to produce the desired effect. It is important for a neutral plate electrode to be fully attached to the patient to complete the path for the current to flow through and prevent cutaneous burns [17, 18].

As with laser therapy, electrocautery is mainly used in the acute management of CAO. However, some groups have used electrocautery in the treatment of endobronchial early lung cancer. Van Boxem *et al.* [24] used electrocautery in the treatment of 13 cases of early SCC (T1N0M0) and two CIS, and reported complete remission in nine lesions after a median follow-up of 22 months (a remission rate of 80%). The same group also reported the effective treatment of 10 out of 14 intraluminal typical carcinoids [23]. Vonk-Noordegraaf *et al.* [22] reported 24 cases of SCC and adenocarcinoma treated with electrocautery with complete remission in 16 cases over a follow-up period of 2–10 years, with three patients presenting local recurrence, which was successfully treated.

Argon plasma coagulation

APC uses electric current flow through argon gas (also known as argon plasma) to produce thermal ablation of the tissues (figure 3). As opposed to electrocautery, APC is a non-contact-mode technique as it uses argon plasma emitted through a Teflon tube to conduct the electric current to the tissue. The APC probe is inserted through the working channel of a bronchoscope. The effects of APC on tissue are shallower than laser and electrocautery, and therefore APC may be less efficient for tissue debulking but more efficient for treating superficially spread lesions. Therefore, APC is better for achieving haemostasis and carries a lower risk of airway perforation [17].

As with laser and electrocautery, APC is mainly used in the acute treatment of CAO. Nevertheless, a number of reports exist on the successful treatment of early lung cancer with APC. Vonk-Noordegraaf *et al.* [22] reported two cases of intraluminal micro-invasive cancer that were successfully treated with APC after a 2-year follow-up. Schuurman *et al.* [25] also reported the successful treatment of the proximal tumour margin in a patient with early stage SCC in whom APC facilitated a less extensive surgical resection.

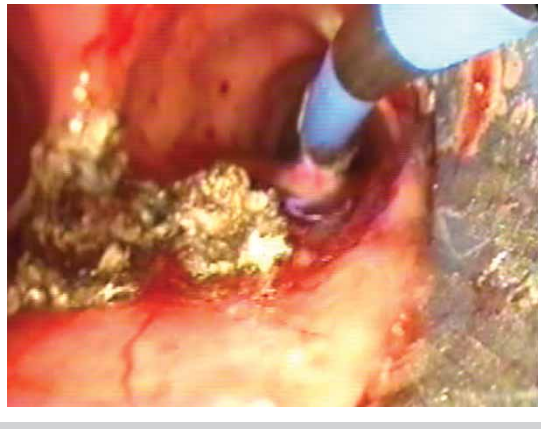

Figure 3. Thermal ablation of the tumour after application of APC.

Photodynamic therapy

PDT uses a specific light wavelength to produce nonthermal ablation in previously photosensitised tissues (figure 4). The photosensitising agent, which accumulates preferentially in tumour cells, is administered intravenously 48 h prior to the PDT session. After 48 h most of the photosensitiser is eliminated by normal cells, while it remains for a longer period in abnormal or proliferating cells. A red laser light of 630 nm wavelength is then applied to the abnormal tissue, producing a photo-oxidative reaction (or photodynamic reaction) that results in tissue necrosis.

PDT is a minimally invasive and selective therapy that does not produce long-term side-effects, can be repeated many times and does not compromise future treatments. Therefore, this therapy is widely used in many tumours other than lung cancer. The PDT probe is connected to the light source and inserted through the working channel of a flexible or, less commonly, a rigid bronchoscope. The photosensitiser remains in the tissues for up to 3 weeks, allowing PDT to be repeated during this period. At least one routine bronchoscopy should be performed a few days after each therapy session to remove secretions and sloughed tissue. Porfimer sodium (Photofrin) is the most commonly used photosensitiser for lung cancer treatment. Other photosensitisers approved to treat lung cancer include temoporfin, talaporfin and HPPH (2-(1-hexyloxyethyl)-2-devinyl pyropheophorbide-a) [26]. More recently, the second-generation chlorine derivative NPe6 has been used [27]; its accumulation in tumour tissues is more selective and occurs 2–3 h after infusion, and it is completely eliminated in 24 h. This is related to fewer side-effects, including photosensitivity. Conversely, only one session can be performed after infusion. Some authors have successfully used low-energy irradiation to define the area to be irradiated, monitor treatment response and detect those patients in whom PDT is ineffective due to a lack of fluorescence [28].

As opposed to laser therapy, electrocautery and APC, the effect of PDT is delayed but longer lasting and shallower. Therefore, PDT has been used extensively for treating bronchoscopically visible lung cancers ⩽1 cm with no extracartilaginous invasion and no

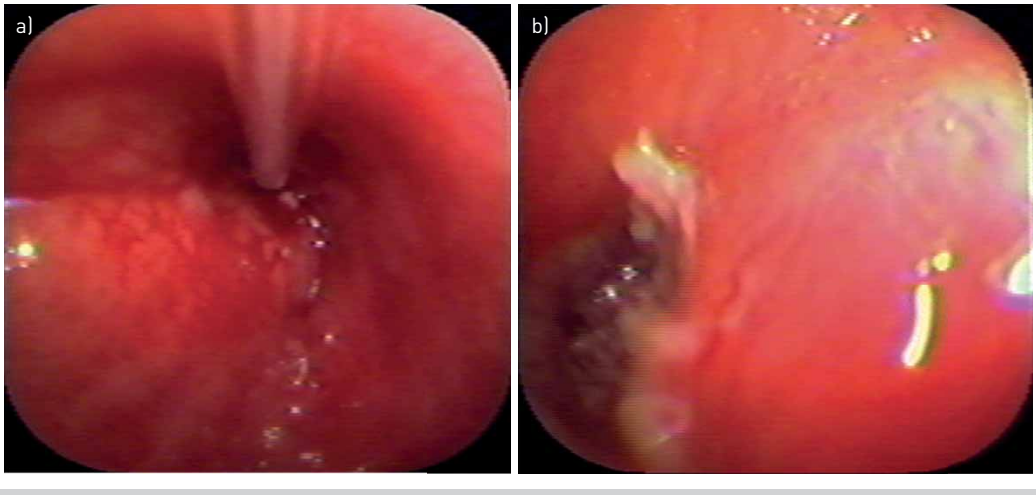

Figure 4. PDT. a) Light application on photosensitised tissue. b) Sloughed tissue after therapy. Reproduced with the kind permission of Pablo Díaz-Jiménez (Clínica Corachan, Barcelona, Spain).

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lymph node involvement [29]. The Japanese guidelines for PDT included SCC ⩽2 cm [30]. 715 lesions were included in a review of studies with more than 10 patients only between 1987 and 2007 [31]. Haematoporphyrin derivative and Photofrin were used as photosensitisers. The majority of patients included in these studies were ineligible for or declined surgery and the objective of PDT was the complete local response of an early central lung cancer. The follow-up period differed among studies, running from 2 months to 10 years, with a complete response oscillating between 30% and 100%; the estimated 5-year survival rate was 61% [31].

Furthermore, PDT has been used for the treatment of multiple primary lung cancer, showing promising results in a clinical scenario in which treatment strategies are limited. Usuda *et al.* [27] reported 22 patients with multiple primary lung cancer: 11 patients underwent both surgery and PDT using the photosensitiser NPe6 for the management of different early lung cancer lesions, and 11 patients underwent PDT alone. All 39 synchronous or metachronous lesions included in their report exhibited a complete response after PDT [27]. In addition to these promising results with PDT, larger phase III trials are needed in order to place PDT as an alternate therapy in the management of early lung cancer.

Cryotherapy

Cryotherapy (discussed in detail elsewhere in this *Monograph* [32]) produces tumour ablation by means of tissue freezing (figure 5). Briefly, cryotherapy is based on the Joule–Thomson effect by which a gas stored in a liquid state at high pressure (most commonly nitrous oxide or liquid nitrogen) is abruptly decompressed, passing to a gaseous state that produces a rapid fall in temperature, typically reaching −40°C. Rapid tissue freezing produces intracellular ice crystals that cause cell death and ischaemic necrosis, while respecting collagen structures. When applying cryotherapy to tumour lesions cell destruction is homogeneously induced around the 3 mm cryoprobe, while surrounding tissue up to a radius of 3–4 mm is less homogeneously affected, and blood vessels and perivascular cells are most affected [17]. Cryotherapy, together with PDT and brachytherapy, belongs to the group of delayed-effect ("slow") techniques. As opposed to laser therapy, electrocautery and APC, the effect of cryotherapy is not immediate and full tissue necrosis takes a few days.

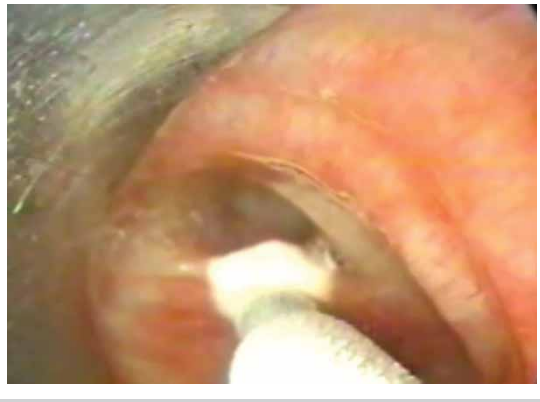

Figure 5. Cryotherapy application on carcinoma *in situ*.

Cryoprobes can be rigid or semirigid and can therefore be used through the working channel of a flexible or a rigid bronchoscope. A routine bronchoscopy can be performed a few days after cryotherapy to remove sloughed tissue. Percutaneous cryotherapy has been widely studied. Deygas *et al.* [33] published a series of 35 patients with early superficial bronchogenic carcinoma treated with cryotherapy through a rigid bronchoscope. They reported no adverse events and a complete response in 91% at 1-year follow-up. Only 28% of patients had local recurrence within 4 years and long-term survival was observed in 50% [33]. Although there have been promising results, further studies including randomised controlled trials are needed to place cryotherapy in the treatment algorithms of early lung cancer.

Brachytherapy

Brachytherapy is a method of administering radiation therapy directly to the tumour. Only tumours <4 cm in length and <1 cm deep and located away from large vessels can be treated with this modality. In addition to small cell carcinoma, any histology can be treated.

A catheter is introduced inside the tracheobronchial tree through the working channel of a flexible bronchoscope and placed at least 2 cm past the lesion under bronchoscopic and fluoroscopic control. When treating early lung cancer, caution is needed to adequately place the catheter as close as possible to the lesion. For lesions located in a spur, treatments can be applied from both sides of the bronchi. For lesions that appear on a suture, placing the catheter can be technically impossible. A dummy source is placed inside the catheter, attached to the connector and fixed to the nostril with tape. A CT scan is then performed for therapy planning on the reconstructed CT images in order to fully cover the tumour and limit the dose to critical structures [34]. The planning system allows the pulmonologist and radiation oncologist to determine the area to treat by defining a planning target length that must encompass the gross tumour volume plus 2 cm, *i.e.* 1 cm for the clinical target volume and an extra 1 cm to cover for possible catheter shifts. Care should be taken when delineating neighbouring structures in order to limit dosing to organs at risk. Unless a device is used to place the catheter in the centreline of the airway, such as a balloon, special attention should be paid to protecting the airway wall. A standard distance of 10 mm is prescribed from the centre of the source with the planning target length ranging from 4 to 6 cm, although CT planning does allow for more accurate prescriptions, *e.g.* when a pronounced curvature is found. In such cases, a higher dose should be prescribed in the concave curvature and a lower dose over the convex part [35]. After planning, the catheter should be checked for possible shifts. If no movements are noted the catheter is then connected to the high-dose-rate boost and the desired fraction administered over a few minutes in the same position as CT acquisition (figures 6–8).

Dosage should be reported for the target volume and up to 1 cm from the centre of the catheter as well as for neighbouring organs at risk. The use of standard 2 Gy equivalent dose fractions ("EQD2") is encouraged for dose reporting [35]. The most common scheme is of six weekly fractions of 5 Gy, although other schemes have been reported with no differences in overall survival [34–36]. Marsiglia *et al.* [37] reported 34 patients with early stage lung cancer with a complete response rate of 85% seen over 2 years of follow-up. Perol *et al.* [38] reported 19 patients with early stage lung cancer and a complete response rate of 83%, which fell to 75% at 1-year follow-up.

This method is expansive and needs coordination with the radiotherapist. It remains suited for deeper lesions compared with the techniques described earlier. Radiation bronchitis and

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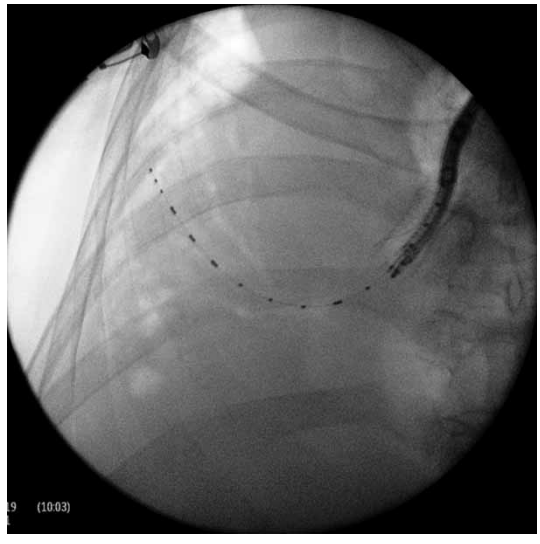

Figure 6. Brachytherapy applicator placement under fluoroscopic control.

stenosis may occur as early and delayed complications, and interventional bronchoscopy techniques are sometimes required. The assessment of treatment outcomes is made by bronchoscopy at least 3 weeks after the last treatment session.

Complications of endobronchial therapies

The treatment of superficial endoluminal lesions is seldom associated with complications. Specific risks differ among therapies (table 1). Airway perforation is the most relevant, and

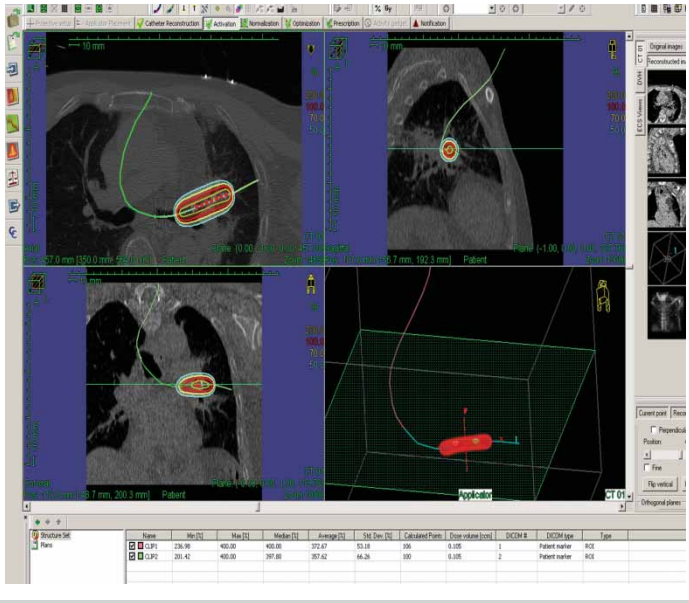

Figure 7. Brachytherapy planning and dose distribution.

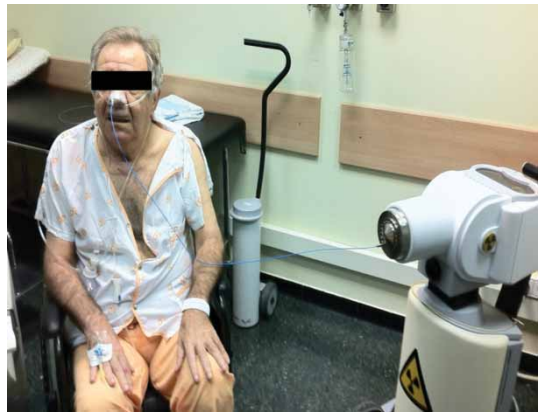

Figure 8. Application of brachytherapy in the bunker.

is mainly associated with laser therapy and electrocautery. Haemorrhage is also associated with both laser therapy and electrocautery due to their effect on deep tissues, although they are also effective for the control of bleeding. Another relevant complication is airway fire, which is associated with thermal therapies (laser, electrocautery and APC). In order to avoid airway fires, thermal therapies should be applied with an oxygen concentration <30–40%, which is a limitation in the treatment of patients with respiratory failure who cannot tolerate such low oxygen concentrations during the procedure. Airway scarring and subepithelial fibrosis leading to airway stenosis have also been described, and are more frequent in patients treated with Nd-YAG laser therapy and PDT compared with those treated with electrocautery [39]. Photosensitivity skin reaction (sunburn) is a specific side-effect of PDT and the most frequent complication of this therapy, reported in 5–28% of cases [30]. PDT is a rare cause of respiratory complications, especially if proper bronchial toilette is performed after each session. Brachytherapy can produce mucosal ulcers, although this can be minimised by adjusting treatment to bronchial wall distance (4–10 mm). If white membranes develop there is a risk for future fibrosis and stenosis. The most important risk associated with brachytherapy is fatal haemoptysis, which can occur in 32% of cases during or after treatment administration [35, 40]. Therefore, single doses >10 Gy are not recommended [41, 42].

Therapies for peripheral pulmonary lesions

Reaching peripheral pulmonary lesions has been a major challenge in the last few decades. Percutaneous techniques have been superior in reaching the lesions located in the utmost periphery of the lung. This is regardless of the higher risk of complications, mainly pneumothorax, which were reported in 38.4% of patients in a series of 3344 treated with percutaneous lung ablation [43]. Therapeutic advances have focused on percutaneous application due to its superior approach to peripheral pulmonary lesions. Percutaneous therapies are mostly performed under CT guidance, and include laser ablation [44], RFA [45], microwave ablation [46], cryotherapy [47] and PDT [48], which are briefly summarised in table 2.

The emergence of endoscopically guided and navigational technologies has significantly improved the diagnostic yield of bronchoscopy for peripheral pulmonary lesions [49].

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Further improvements in this field are expected and, together with better peripheral pulmonary lesion localisation, the possibility of performing the aforementioned techniques through an endobronchial approach in patients who cannot undergo surgery is becoming increasingly extended. Tanabe *et al.* [50] reported 10 patients with stage IA lung cancer treated with bronchoscopy-guided RFA prior to surgical resection; however, resected tissue contained tumour cells in all patients. The same group later reported 23 early stage peripheral pulmonary lesions in 20 patients treated with bronchoscopy-guided RFA with a 5-year survival of 61.5% [51]. Downie and McGuire [52] also reported a sustained response 5 years after the treatment of a peripheral carcinoid with PDT. Although the risks for a bronchoscopic approach are lower than for a percutaneous approach, further improvements are needed to reach peripheral pulmonary lesions more precisely before these techniques are broadly applied [49, 53].

To date, only a few active clinical trials concerning bronchoscopic therapies for early lung cancer have been registered. A search was performed for studies in ClinicalTrials.gov between January 2014 and June 2017. The trials found include: evaluation of the efficacy and safety of electromagnetic navigation-guided RFA (identifier NCT03009630), safety and feasibility of navigation-guided bronchoscopy coupled with radial EBUS to treat peripheral pulmonary lesions with Photofrin (identifier NCT02916745), and efficacy and safety of bronchoscopy-guided transbronchial ablation with microwave, radiofrequency and SBRT (identifier NCT02972177). A pilot trial on bronchoscopic thermal vapour ablation has also been registered recently (identifier NCT03198468).

Conclusion

Bronchoscopic therapies have shown very promising results in the treatment of early lung cancer that is limited to the central airways. These therapies provide local treatments with few complications. However, further studies are needed in order to place these therapies in the treatment algorithms of early lung cancer. In the near future, newer guided and navigational technologies may be able to deliver these therapies effectively to peripheral lesions with fewer complications than the percutaneous approach.

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Chapter 15

Central airway obstruction

Christophe Dooms[1] and Antoni Rosell[2]

Neoplastic central airway obstruction (CAO) with imminent respiratory failure, stridor and/or severe dyspnoea requires immediate and appropriate care and action. Initial evaluation of CAO involves CT and bronchoscopy in order to decide upon timely referral for interventional pulmonology, consisting of mechanical debulking with or without thermocoagulation to restore airway patency and with or without airway stenting to preserve central airway patency. The assessment and treatment of benign central airway strictures should be reserved for selected centres that provide a multidisciplinary, dedicated interventional approach and are evaluated based on qualitative long-term outcome.

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Patients with central airway obstruction (CAO) often have nonspecific clinical manifestations that are responsible for a delayed diagnosis. The reason for this delayed diagnosis, but often acute presentation, is that symptoms usually begin at 50% airway narrowing and from there airflow resistance increases exponentially as the stenosis becomes more severe. Significant CAO generally presents with severe dyspnoea, stridor, orthopnoea and/or imminent respiratory failure requiring immediate action [1].

How to evaluate a CAO

The central airways are defined as those airways that can be directly visualised by flexible therapeutic bronchoscopy with an outer diameter of 5–6 mm. The central airways of interest for interventional pulmonology are limited to the trachea, mainstem bronchi and lobar bronchi.

CAO can be classified into two distinct patterns, *i.e.* focal airway obstruction and diffuse airway narrowing, which are generally split into malignant and nonmalignant causes of disease (table 1). CT and bronchoscopy are complimentary techniques that play an important role in the assessment, diagnosis and treatment planning for a CAO.

[1]Dept of Respiratory Diseases, University Hospitals KU Leuven, Leuven, Belgium. [2]Bronchoscopy Unit, Dept of Respiratory Medicine, Hospital Universitari de Bellvitge, Universitat de Barcelona, IDIBELL, L'Hospitalet de Llobregat, Barcelona, Spain.

Correspondence: Christophe Dooms, Dept of Respiratory Diseases, University Hospitals KU Leuven, UZ Leuven Campus Gasthuisberg, Herestraat 49, 3000 Leuven, Belgium. E-mail: christophe.dooms@uzleuven.be

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Table 1. Classification of central airway obstructions into two distinct patterns

Focal tracheobronchial airway narrowing
Post-traumatic stricture: post-intubation stenosis, post-tracheotomy stenosis, postoperative airway anastomotic stricture (*e.g.* lung transplantation, sleeve lobectomy)
Post-infectious stricture (*e.g.* tuberculosis, *Aspergillus*, rhinoscleroma)
Neoplasia: benign neoplasia (*e.g.* hamartoma, papilloma, lipoma, *etc.*), primary tracheobronchial carcinoma, metastatic disease to tracheobronchial wall, mediastinal neoplasia with direct tracheobronchial invasion
Inflammatory disease with or without autoimmune disorder: idiopathic subglottic tracheal stenosis, granulomatosis with polyangiitis, rheumatoid arthritis, inflammatory bowel disease, IgG4-related disease, sarcoidosis, amyloidosis
Extrinsic compression (*e.g.* thyroid tissue, mediastinal adenopathy, vascular structure)
Diffuse tracheobronchial narrowing
Post-traumatic stricture: inhalation injury
Post-infectious stricture (*e.g.* tuberculosis, *Aspergillus*, *etc.*)
Neoplasia: malignant or benign (*e.g.* papilloma)
Inflammatory disease with or without autoimmune disorder: granulomatosis with polyangiitis, sarcoidosis, relapsing polychondritis, inflammatory bowel disease, amyloidosis, tracheobronchopathia osteochondroplastica
Dynamic tracheobronchomalacia and expiratory dynamic airway collapse

Contrast-enhanced multidetector CT in deep inspiration acquires 1–5 mm sections throughout the thorax for routine two-dimensional axial, coronal and sagittal multiplanar reconstruction. It also provides a variety of three-dimensional techniques for optimal imaging of the central airways to enhance estimation of the type, length and degree of stenosis, along with visualising the airways distal to the point of obstruction and/or the relationships between central airways and adjacent mediastinal and hilar structures (*e.g.* blood vessels and lymph nodes). Other respiratory disorders can also be detected, such as bronchiectasis, pulmonary embolism and parenchymal disorders. Limitations of the CT scan include the inability to reliably differentiate mucosal from submucosal or extrinsic disease, inability to visualise subtle (sub)mucosal extension, inability to recognise mucus impaction around a CAO and an often inaccurate evaluation of airway patency distal to an occluding CAO. A CT scan might not be possible in some cases of severe orthopnoea where the patient cannot lay flat.

Video bronchoscopy is generally more accurate in assessing the exact location of a tumour (distance from larynx or carina as well as distance assessment in order to evaluate stent compatibility), the degree, length and type of airway stenosis, and distal airway patency. It also has the advantage of facilitating a biopsy for histopathological diagnosis. Video bronchoscopy is the preferred tool to assess whether the CAO consists of intraluminal tumour growth, extraluminal tumour compression or a combination of both. Additionally, tracheomalacia and excessive dynamic central airway collapse are better defined during bronchoscopy.

An excellent standardised qualitative classification scheme designed for grading tracheobronchial stenosis from the pulmonologist's perspective, taking into account the CT scan and bronchoscopy evaluation, was proposed in 2007 with descriptive images and diagrams for rapid and uniform classification of types of central airway stenosis [2]. We recommend its use in daily clinical practice, although the degree of severity criterion is not justified physiologically. There is currently no commonly accepted standardised technique to quantify the severity or degree (percentage cross-sectional area) of large airway luminal

narrowing by bronchoscopic inspection [3]. Preferred techniques vary considerably and are often based on a subjective visual estimation that is poorly reproducible. Using a classification scheme of mild (<50%), moderate (50–70%) and severe (>70%) obstruction to evaluate still bronchoscopic images resulted in 53% incorrectly classified stenoses, of which 9% and 91% were overclassified and underclassified, respectively [4]. Relying upon the degree of obstruction and not taking into account symptoms and patient comorbidity can significantly affect patient care: underestimation can lead to inadequate or delayed therapy, while overestimation may lead to referral for unnecessary invasive interventions.

Studies of virtual bronchoscopy have found fairly good correlation between the degree of endoluminal airway narrowing noted on virtual imaging and bronchoscopy. Virtual bronchoscopy is based on CT scans with 1–1.5 mm sections together with the use of CT segmentation and three-dimensional volume rendering. Advances in real-time objective measurements from video bronchoscopy are also being explored [5]. Finally, a perfect measurement technique should be integrated in each particular clinical scenario with malignant CAO, as it is equally important to consider the functional status of the larynx and small airways, as well as body mass index and other comorbid limitations, when assessing the need for a central airway bronchoscopic treatment.

General algorithm and impact of malignant airway recanalisation

When a patient with suspected significant upper airway obstruction presents acutely at the emergency room, selective supportive measures may be necessary and include the commencement of an inspired helium–oxygen (Heliox) mixture. Heliox is less dense than oxygen and has the effect of predisposing to laminar flow, which can be used to improve airway dynamics in the short term. Securing the airway for adequate oxygenation and ventilation must be guaranteed in the emergency room. This can be achieved by laryngeal mask airway ventilation, by passing an ETT beyond the central airway stenosis or placing the tip of the ETT above the growth while maintaining ventilation, or by referring the patient for urgent rigid bronchoscopy and removal of the tumour. An urgent tracheotomy is generally only considered in clinical cases already evaluated by bronchoscopy and considered for tracheotomy but not for rigid bronchoscopy.

When a patient presents with an upper airway obstruction in a nonacute setting, an elective assessment and management plan should be proposed. Interventional pulmonology as part of this plan must be carefully considered and executed to obtain an optimal outcome, *i.e.* improvement in quality of life and survival [6–9]. A typical interventional pulmonology algorithm for central airway recanalisation encompasses the following five phases:

1) Query whether a symptomatic stenosis is present and/or palliation is required.
2) Identify the cause, morphology, extent and mechanism of the central airway narrowing, together with confirmation of patent distal airways (figures 1a and b, 2a and b, and 3a–c).
3) Treat the intraluminal component when present (figures 1c and d, and 3d).
4) Assess the residual degree of airway narrowing (figures 1e and 2c).
5) Treat the residual stenosis and/or mural component when considered appropriate (figure 2d).

A multicentre national registry in the USA reported a technical success rate to re-open a >50% narrowing of the airway lumen in 93% (range 90–98%) of patients, while a clinically

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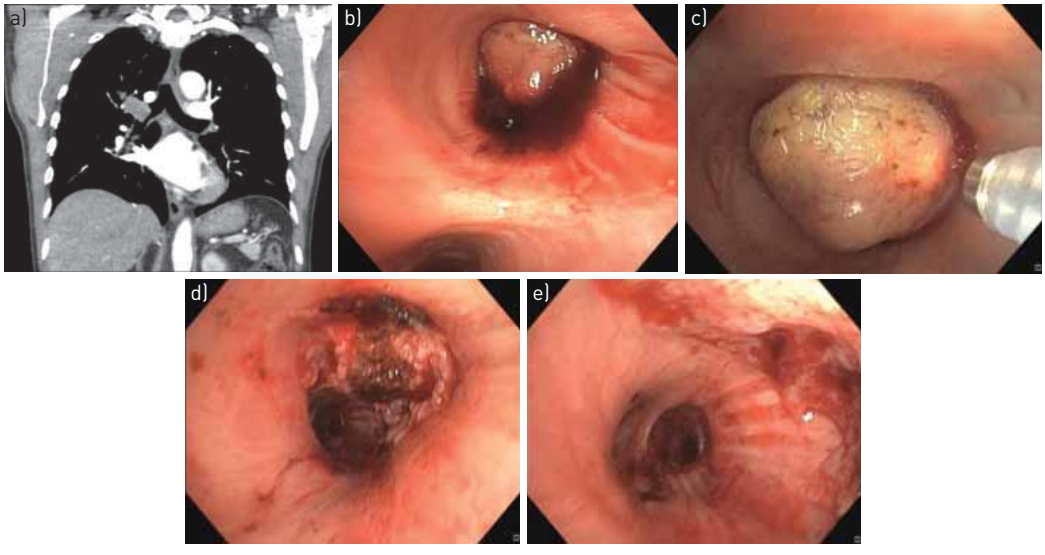

Figure 1. Case illustration of an algorithm for malignant right main bronchus obstruction. a) Coronal CT scan section showing a tumour originating in the ostium of the right upper lobe with right mainstem occlusion. b) Bronchoscopy showing an occlusion of the distal right main bronchus and signs of recent bleeding, demonstrating a squamous cell carcinoma at histopathology. c) Bronchoscopic Nd-YAG laser coagulation of the occluding tumour in order to obtain haemostasis. d) Bronchoscopic status after Nd-YAG laser vapourisation. e) Final status after endoscopic debulking with thermocoagulation showing patent distal airways.

significant improvement was only obtained in 42% and 48% of patients for quality of life and symptoms such as dyspnoea, respectively [10]. Two prospective single-centre cohorts have been published [11, 12]. In both cohorts, the interventional pulmonology procedure was considered successful in 91–92% of patients as a post-intervention lumen patency of at least 50% was achieved for a pre-intervention symptomatic >50% narrowing of the central airway. In one cohort it was reported that a completely restored airway patency (defined as 80–100% patency) was obtained in 41% of patients, while a partially restored airway patency (defined as 50–80% patency) was obtained in 50% of patients [12]. The later might be relevant in order to explain the lower rate of subjective benefits reported. Oviatt *et al.* [11] reported a minimal clinical improvement of 50 m in 6-min walk distance at 30 days in 32% of patients and a minimal clinical improvement in composite dyspnoea scores by European Organisation for the Research and Treatment of Cancer quality of life questionnaires (core QLQ-C30 and lung cancer QLQ-LC13 modules) in 46–49% of patients at 1 month. Stratakos *et al.* [12] compared a group of patients with a symptomatic >50% CAO who declined an endoscopic interventional pulmonology treatment (control group) to a group who underwent a bronchoscopic interventional pulmonology treatment (intervention group). Quality of life significantly improved and dyspnoea decreased in the intervention group, not deteriorating for those who survived up to 12 months post-procedure, whereas patients who declined an interventional treatment (control group) had worse quality of life and dyspnoea at all follow-up time-points [12].

Improvements in functional status after interventional pulmonology treatment may allow further oncological treatment due to the avoidance of CAO-related complications such as retro-obstructive pneumonia or due to the improved performance status in patients initially ineligible due to poor cancer-based performance status. In conjunction with these

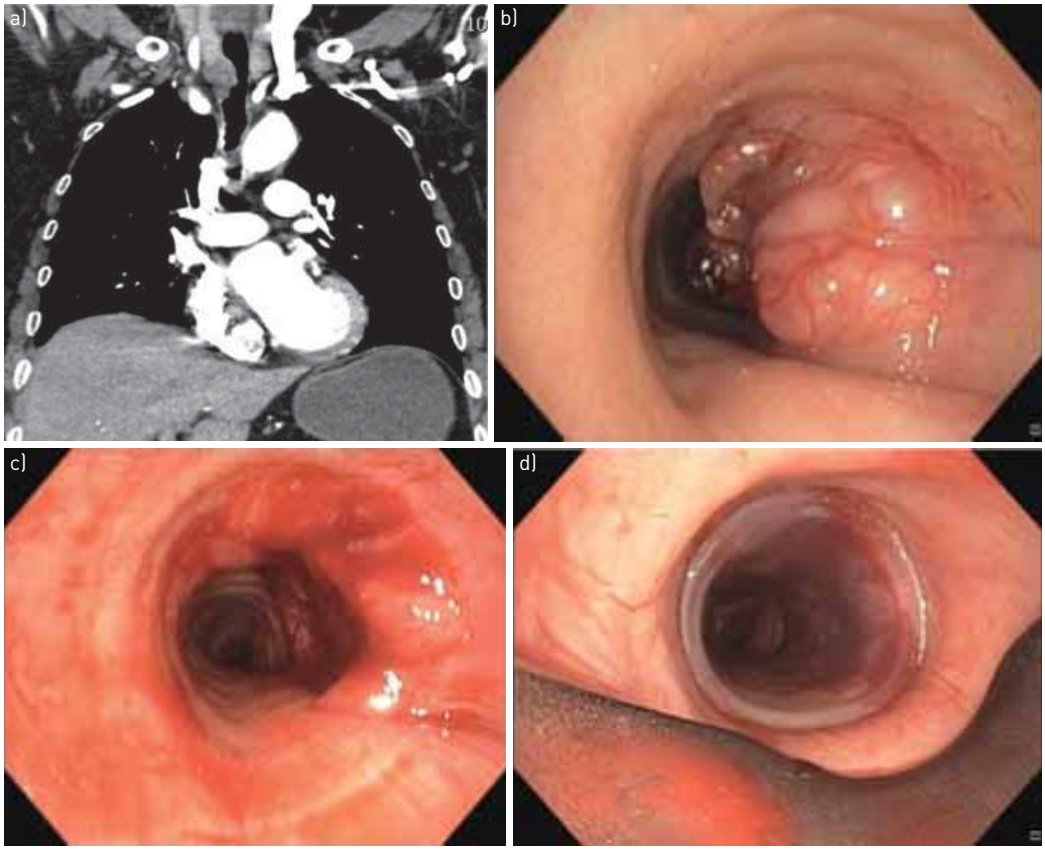

Figure 2. Case illustration of an algorithm for malignant tracheal obstruction. a) Coronal CT scan of a tumour originating at the right lateral tracheal wall with an intraluminal component and 60% airway narrowing. b) Bronchoscopy shows a tumour at the right lateral wall with an intraluminal component and 75% tracheal stenosis, demonstrating an adenoid cystic carcinoma at histopathology. c) Bronchoscopic image of partial Nd-YAG laser recanalisation with 20% residual tracheal narrowing. d) Bronchoscopic image after tubular silicone stent insertion splinting the trachea.

functional benefits it is important to consider the potential impact of a bronchoscopic recanalisation on overall survival. Several studies demonstrated that the survival curve for patients with an unsuccessful airway recanalisation procedure was significantly worse than for those with a successful intervention [6, 9, 12, 13]. These studies also reported no statistically significant difference in survival among patients with inoperable malignant CAO who underwent a successful bronchoscopic recanalisation compared with patients with inoperable cancer without CAO. In addition, it is important to note that it is mainly patients who are considered candidates for any subsequent treatment (either systemic or locoregional) who benefit more from airway recanalisation rather than patients who are only considered for best supportive care [7, 8].

Techniques for malignant central airway recanalisation

Focal CAO can be classified into three distinct types of obstruction, *i.e.* purely intraluminal tumour growth, purely extraluminal tumour compression or a combination of both. These

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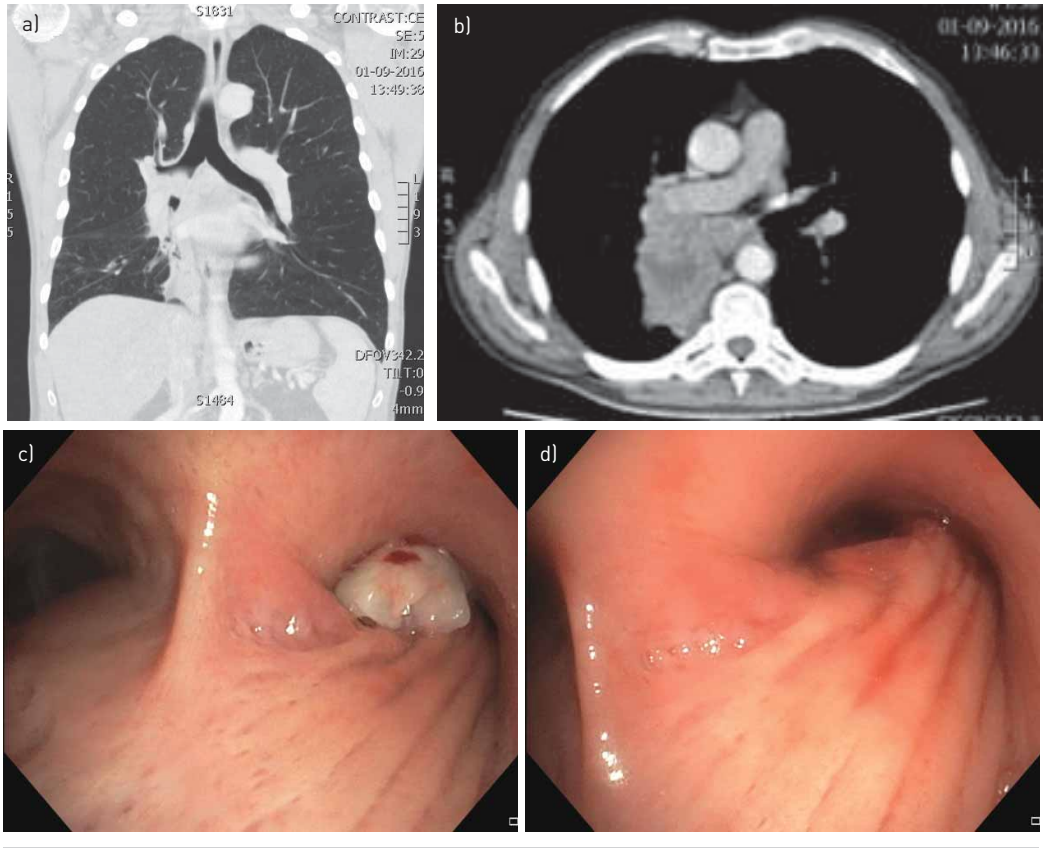

Figure 3. Case illustration of an algorithm for malignant right intermediate bronchus obstruction. a) Coronal CT scan showing a right lower lobe tumour with occlusion of the intermediate bronchus. b) Axial CT scan image showing a 90% narrowing of the intermediate bronchus. c) Bronchoscopy showing a necrotic intraluminal tumour with a smaller airway diameter compared with the left main bronchus due to extrinsic compression, demonstrating a squamous cell carcinoma at histopathology. d) Bronchoscopic image after debulking without an intraluminal residual component but extrinsic compression and tumoural occlusion of the right lower lobe bronchus.

are typically managed with a multimodal approach focusing on an immediate or a delayed effect, comprising mechanical debulking, heat or cold thermotherapy and airway stenting when appropriate (figure 4).

Bronchoscopy

Rigid bronchoscopy (discussed elsewhere in this *Monograph* [14]) with its large working channel is the core of interventional pulmonology as it can guarantee excellent airway control with preserved ventilation, safe manipulation to perform thermocoagulation, and rapid mechanical debulking, dilation and airway stent insertion. Rigid bronchoscopy under general anaesthesia provides more treatment options and greater procedure-related safety than flexible bronchoscopy under moderate sedation (table 2). Alternatively, flexible bronchoscopy through an ETT utilising thermocoagulation, balloon dilation or the insertion of a self-expandable metallic stent can also be used to relieve obstructing airway disorders in centres without rigid bronchoscopy facilities, although more procedures are often required to complete the treatment and safety might be an issue compared with a

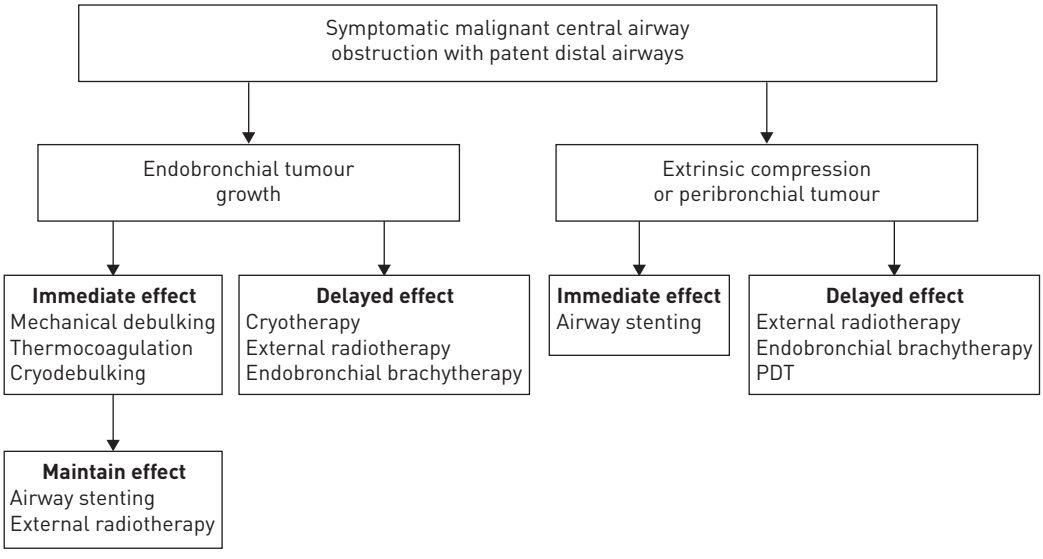

Figure 4. Flowchart of interventional options for symptomatic malignant central airway obstruction.

rigid intervention [15]. Indeed, despite the availability of devices suited for the flexible video bronchoscope, its blocking effect within an ETT may limit ventilation and jeopardise safety. Nevertheless, the ultimate execution of any technique depends on the available facilities and expertise of the team, and not the technique *per se*.

Many of the specific techniques outlined in the following subsections are covered in more detail throughout this *Monograph* [16].

Immediate-effect bronchoscopic techniques

Several immediate-effect bronchoscopic techniques are available. These include hot techniques such as laser therapy, electrocautery and APC, and cold techniques such as cryoextraction and mechanical debulking [1, 17].

Laser resection is the application of laser energy in order to manage endobronchial lesions. Different types of laser are available, *e.g.* Nd-YAG (neodymium-doped yttrium aluminium garnet), Nd-YAP (neodymium-doped yttrium aluminium perovskite), diode and carbon dioxide (CO_2) lasers. Mainly non-contact-mode probes are used with a power setting of 10–40 W and a pulse duration of 0.5–1 s, representing a safe setting to obtain coagulation or devascularisation of the feeding vessels and carbonisation or vapourisation of the tissue, respectively (table 3). Protective eyewear is mandatory when the laser beam is activated outside the context of a working channel of the video bronchoscope and the inspiratory oxygen fraction (FIO_2) should be limited to $\leqslant$40%.

Electrocautery is the use of an electric current for tissue heating through a contact-mode probe. Due to the voltage difference between the probe and tissue, electrons will flow through the tissue acting as a resistance and generating heat for tissue coagulation. The ultimate tissue effect (*i.e.* coagulation or vapourisation) depends on the voltage difference between the probe and tissue, the contact surface area, and the duration of energy

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Table 2. Rigid *versus* flexible bronchoscopy in patients with malignant central airway obstruction

	Rigid bronchoscopy	Flexible bronchoscopy
Mechanical tumour resection	+++	+
Hot thermocoagulation	+++	+/++
Cryodebulking	+++	+
Stent placement	+++ (all)	+/++ (self-expandable)
Dilation	Rigid, balloon	Balloon
Availability/expertise	Uncommon	Common
Anaesthesia	Deep sedation	Conscious sedation
Tools	Rigid/flexible, large/small	Flexible, small
Expense	++	+

+: weak; ++: moderate; +++: strong.

application. Most electrocautery devices used in endobronchial debulking deploy a combination of continuous ("cutting") and intermittent ("coagulation") waveforms. The two main methods of electrocautery are tissue debulking by a cutting loop or snare and direct destruction by a probe or knife, both achieving an effect similar to that seen with laser vapourisation.

APC uses an ionised argon gas jet flow to conduct electrons, allowing a non-contact-mode of treatment. It has a penetration depth in tissue of 2–3 mm and its main effect is tissue coagulation.

Electrocautery and APC require no protective eyewear, but a grounding pad is mandatory when the electric current is activated and F_{IO_2} should be limited to $\leqslant$40%. As there are no published trials comparing the various hot techniques available, current practice is based on the availability of equipment and training.

The clinical utility of cold bronchoscopic cryodebulking or cryoextraction of an obstructive tumour with immediate effect within the central airways can be considered as a cold alternative to the hot techniques in selected lesions consisting of cryosensitive tissue. Typically, cryoresistant tissues are fat, cartilage and connective tissue. In addition, the operator should be aware that vascular thrombosis only occurs in frozen tissue, which will be mechanically extracted by cryodebulking, and not in the warm tumour tissue that remains inside, and thus can be at risk for bleeding. In contrast to hot techniques, cryodebulking preserves tissue integrity, therefore allowing a histopathological diagnosis.

Delayed-effect bronchoscopic techniques

Several delayed-effect bronchoscopic modalities are also available, including brachytherapy and PDT.

Endobronchial brachytherapy was initially a palliative intervention to improve symptoms related to CAO, but high-grade occlusive endotracheal or main bronchus lesions are contraindicated as well as situations at risk for fistula formation between the airway and other structures (*e.g.* major vessels or oesophagus). The subjective outcome was found to vary, with 20–100% of patients obtaining some symptom relief [18]. A Cochrane review

Table 3. Specific features of different types of lasers

Laser	Wavelength nm	Coagulation	Vapourisation
Nd-YAG	1064	+++	+++
Nd-YAP	1340	++	–
Diode	810	++	+
CO_2	10 600	++	–

–: none; +: weak; ++: moderate; +++: strong.

observed no evidence of survival benefit for endobronchial brachytherapy compared with external beam radiotherapy and Nd-YAG laser therapy [18]. The evidence did not provide conclusive results that endobronchial brachytherapy plus external beam radiotherapy improved symptom relief over external beam radiotherapy alone. From heterogeneous information obtained from several small randomised controlled trials, Reveiz *et al.* [18] concluded that external beam radiotherapy alone is more effective for palliation than endobronchial brachytherapy alone. For patients previously treated by external beam radiotherapy who are symptomatic from recurrent endobronchial central obstruction, endobronchial brachytherapy may be considered in selected cases [18].

Bronchoscopic PDT in lung cancer patients is applied ~48–72 h after the intravenous injection of a photosensitising agent to allow the photosensitising material to accumulate in the target lesion and wash out of healthy nonmalignant tissue. Bronchoscopic PDT has been used to palliate central endobronchial obstruction. Diaz-Jiménez *et al.* [19] reported similar efficacy of endobronchial PDT and Nd-YAG laser therapy for the palliation of symptoms caused by malignant endobronchial obstruction.

Airway stents

There is expert consensus that airway stent implantation is required whenever a patient demonstrates a residual airway stenosis of >50% after debulking or a patient presents with a symptomatic >50% extraluminal CAO. Indeed, in trachea narrowing <50% the pressure drop is similar to that which occurs through the normal glottis opening, whereas for airway narrowing ⩾50% the airflow resistance increases exponentially as the stenosis becomes more severe [20, 21]. The work of breathing depends on the degree of pressure drop along a stenosis. This pressure drop is in turn dependent on the degree of stenosis and the flow velocity through the stenotic lesion. It seems that at 50% obstruction patients are usually symptomatic with exertion, whereas at 70% they become symptomatic at rest [20, 21]. Airway stents are extensively discussed elsewhere in this *Monograph* [22].

Airway stenting with a covered stent can protect the airway lumen from tumour ingrowth (barrier effect) and/or counterbalance extrinsic/intrinsic pressures (splinting effect). The role of silicone stent insertion in residual central airway stenosis of <50% after debulking was recently evaluated in the French multicentre randomised controlled SPOC trial. A case illustration is given in figure 2. This randomised controlled trial communicated a trend towards improved airway stenosis recurrence-free survival and an improved benefit on dyspnoea during the first year after stenting [23].

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Techniques for benign CAO treatment

Nonmalignant and iatrogenic-related causes of CAO typically include post-intubation tracheal stenosis (PITS), post-tracheotomy tracheal stenosis (PTTS), idiopathic subglottic tracheal stenosis and anastomotic stricture after sleeve resection or lung transplantation. The role of interventional pulmonology as a definitive treatment might be rather limited as either a conservative approach is preferred in pauci-symptomatic postoperative anastomotic stricture (*e.g.* after sleeve resection or lung transplantation) or an early definitive surgical intervention is often the procedure of choice in the majority of traumatic tracheal stenoses (*e.g.* PITS or PTTS) with excellent long-term outcome profiles. However, the role of interventional pulmonology in the multidisciplinary assessment is key, as well as the intervention to relieve acute stridor or dyspnoea upon presentation.

When a patient with suspected significant upper airway obstruction presents acutely at the emergency room, supportive measures may be necessary (as discussed earlier). The accurate evaluation of a benign central airway stricture usually consists of a bronchoscopic evaluation of the location, degree, extent and dynamics of the stricture itself, and an assessment of laryngeal functioning as well as the assessment of choke point physiology or location of the flow-limiting segment. Only a central airway treatment at the choke point will improve flow limitation (either at higher flow during exercise or at low flow while at rest), by increasing the airway cross-sectional area, and thus improving ventilation and relieving dyspnoea. Treatment options for benign CAO or stricture are typically open surgical techniques or interventional pulmonology techniques, or a combination of both. The optimal treatment choice will depend on patient comorbidities in combination with the stricture characteristics (aetiology, anatomy and physiology), and should be discussed within a multidisciplinary team consisting of at least an interventional pulmonologist, a thoracic surgeon, an ENT surgeon, an anaesthesiologist and a radiologist. The objectives of the treatment should include palliation of respiratory symptoms by providing airway patency, a long-term solution at low risk for recurrence, maintenance of adequate voice and swallowing functioning, and avoidance of a definitive tracheostomy.

The interventional pulmonology treatment for an obstructing benign, mainly intraluminal lesion, such as a hamartoma or lipoma, aims at rapid debulking using a combination of mechanical and thermal techniques similar to those discussed for malignant CAOs. The interventional pulmonology treatment techniques of benign strictures used in practice vary widely. Interventional pulmonology typically consists of a laser cut to release tension in circumferential focal strictures by performing radial incisions. The thermal injury to the submucosal tissue may perpetuate inflammation and scarring, and therefore CO_2 laser scar vapourisation with its superficial thermal effect is preferred above other laser techniques such as the Nd-YAG laser with a deep thermal effect. In PITS or idiopathic subglottic tracheal stenosis the laser cut can be preceded by an intralesional infiltration with corticosteroids and followed by a gentle rigid or balloon dilation, although there is no consensus on these techniques [24]. An endobronchial or endotracheal stent is generally not indicated in benign airway strictures unless a surgical intervention is deemed technically impossible or medically contraindicated, or when no safe airway can be guaranteed after an endoscopic laser cut. It should be realised and discussed with the patients that, although bronchoscopic stenting has a rewarding short-term success rate, recurrence of stenosis after stent removal (*e.g.* after 6–12 months) is high and/or that high complication rates (obstructive granulation, stent-related infection, further damage to cartilage enlarging the damaged segment, *etc.*) for long-term indwelling airway stents have been consistently reported.

Building an interventional pulmonology practice for the treatment of CAO

An interventional pulmonology practice should only be developed when there is a locoregional unmet medical need and when a dedicated interventional pulmonology unit can be guaranteed. The practical and financial advantages and disadvantages of its implementation should be positively evaluated in advance. The start-up and maintenance costs are generally high, and returns on investment are not always positive. Furthermore, performing these interventional procedures requires a team (which must include at least two well-trained interventional pulmonologists, specialised endoscopy nurses and anaesthesiologists) and these procedures can be time-consuming [25–27]. In addition, these departments should be available 7 days a week, and should provide a fast and appropriate response to referrals in emergency cases.

Data from other specialities (cardiology and surgery) illustrate that procedural volume or a high-volume hospital is associated with better outcome [28, 29]. Setting up criteria regarding the procedural volume would punish institutions performing highly qualitative but smaller volumes. As the number of procedures performed does not solely define competence, participation in outcome databases evaluating quality presents a more attractive model than procedural volume alone. We believe this will automatically lead to centralisation of more advanced procedures to centres where qualitative performance of interventional procedures within a multidisciplinary setting is guaranteed. This is crucial, as interventional pulmonology is associated with significant risks and as a speciality is probably more complex than often assumed. Prospective risk-adjusted and disease-specific outcome analysis after interventional bronchoscopic procedures in experienced centres demonstrated that complications are common (morbidity 20%) and 30-day mortality can be high (mortality 8%) [10, 30].

Conclusion

The morphology, location, extent, mechanism and histological type of a symptomatic CAO are factors that determine patient selection for a bronchoscopic intervention. A multidisciplinary outlook and multimodality approach is often required, as the prospects for certain diseases are evolving. Interventional pulmonologists should be aware of this, and consider the ability of their intervention to intervene with acute palliation, anticipate long-term complications and contribute to qualitative survival.

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Chapter 16

Airway stents

Marc Fortin[1] and Hervé Dutau[2]

In this chapter, we review the most frequent indications for airway stenting, the types of airway stents available and the data about potential new airway stenting technologies (biodegradable, drug-eluting and three-dimensional printed airway stents). We also discuss the complications associated with airway stenting and the necessary surveillance after airway stenting.

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The first anecdotal reports of airway stent insertion date back as early as the 19th century [1, 2], but it was not until the 1960s when a dedicated airway stent became available and was widely used. The Montgomery T-tube, a silicone T-tube with an external side limb that protrudes through a tracheostomy, was the first available dedicated airway stent. Its use was limited to the upper trachea due to its side limb and method of insertion. Attempts to solve the problem of more distal airway stenosis were subsequently made by deploying modified vascular metal stents, which were unfortunately associated with unacceptable complications rates [3]. In 1987, a revolution in airway stenting occurred with the introduction of Dumon stents (Novatech, La Ciotat, France), dedicated silicone stents for the trachea and bronchi [4]. This innovation marks the beginning of interventional pulmonary medicine for many. These stents rapidly became widely used. Later in the 1990s, SEMS designed for the airways provided better clinical results than the previously used modified vascular stents and also gained in popularity [5]. Many stents are now available with different characteristics. A significant quantity of data about airway stenting has been collected over recent decades. Here, we review the indications and complications for airway stenting, the types of stents currently available and their characteristics, as well as future avenues for airway stenting.

Indications

Malignant airway obstruction

Malignant airway obstruction (MAO) represents the most frequent indication for airway stenting (figure 1). Lung cancer is by far the most frequent cause of MAO; however, other

[1]Dept of Pulmonary Medicine and Thoracic Surgery, Institut Universitaire de Cardiologie et de Pneumologie de Quebec, Quebec City, Quebec, Canada. [2]Dept of Thoracic Oncology, Pleural Disease and Interventional Pulmonology, Hôpital Nord, Marseille, France.

Correspondence: Hervé Dutau, Dept of Thoracic Oncology, Pleural Disease and Interventional Pulmonology, Hôpital Nord, Chemin des Bourrely, 13015 Marseille, France. E-mail: hdutau@ap-hm.fr

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cancers can directly invade or compress the airway (*e.g.* oesophageal and thyroid cancer or mediastinal lymphomas) and almost any cancer can cause distant metastasis to the airway. Patients present most frequently with dyspnoea, cough, symptoms of post-obstructive pneumonia and stridor.

MAO can be intrinsic, extrinsic or mixed. In cases of intrinsic stenosis, *i.e.* cases where the tumour has invaded the airway, the tumour should be debulked first. Once the tumour is debulked the clinician has to make the decision to stent the airway or not. In cases where significant residual stenosis is present, stenting is necessary. In cases where patency of the airway has been regained, the decision will depend on the expected response to upcoming therapies and the risk of stenosis recurrence. As an example, if complete patency of the airway has been obtained and the patient has a confirmed small cell lung cancer that will undergo rapid treatment, stent insertion is not required. In the opposite situation, where a patient has a nonsmall cell lung cancer and has already received multiple lines of chemotherapy and a maximal dose of radiation to the treated area, stenting is indicated due to the high risk of restenosis. A grey area between these two cases exists.

We participated in a randomised controlled trial of airway stenting *versus* no stenting in MAO [6]. Airway stenting after relieving the obstruction significantly improved quality of life for a longer period of time over no airway stenting in patients with MAO, but the effect of stenting on quality of life was not statistically significant in patients that had not undergone any prior chemotherapy or radiation therapy. Except in occasional situations where it is used as a bridge to another therapy, such as chemotherapy or surgery, airway stenting in MAO is a palliative procedure and its role is to alleviate symptoms; hence, no intervention is required in asymptomatic patients.

Factors have been identified to help predict symptomatic response to airway stenting. There must be normal parenchyma distal to the obstruction. If atelectasis distal to the airway obstruction is present, traditional teaching has been that it should not have been present for

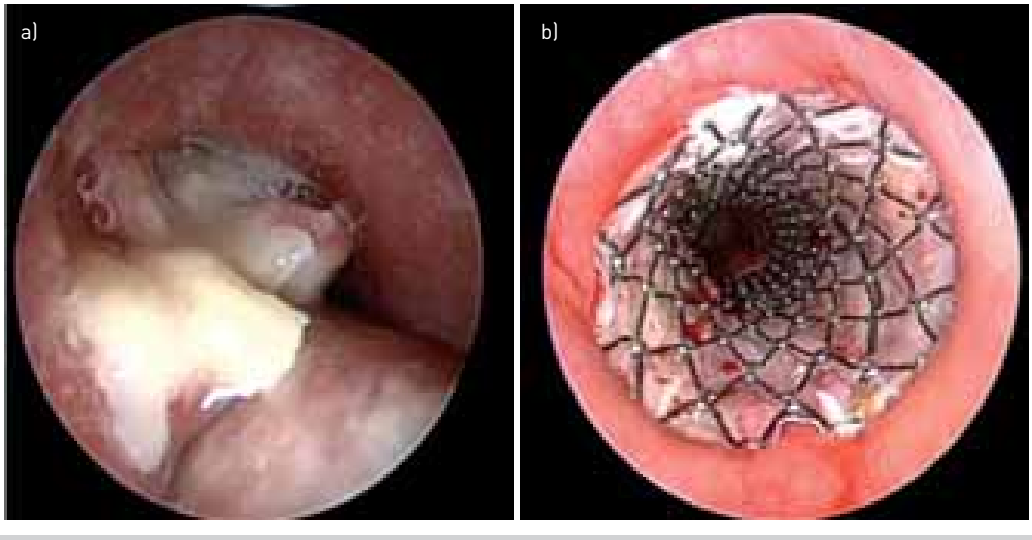

Figure 1. Tracheal invasion from an oesophageal cancer a) before and b) after mechanical debulking and fully covered SEMS placement.

many months as surfactant becomes dysfunctional and parenchyma cannot re-expand. Experience from endobronchial valves for lung volume reduction can lead us to reconsider this as atelectasis has been demonstrated to resolve after being present for prolonged periods. The time after which lung parenchyma will not re-expand even if the occluded airway is reopened is not clear. Perfusion to the parenchyma to which the obstructed airway leads must be sufficient. Hypoxic vasoconstriction caused by decreased ventilation in MAO may improve after alleviating the airway obstruction; however, if perfusion to the concerned area is absent due to vascular obstruction by the malignant tissue, perfusion will not improve after relieving the airway obstruction [7]. As an example, if the right mainstem bronchus is completely occluded as well as the right pulmonary artery, the patient will not benefit from regaining ventilation to their right lung and might in fact become more symptomatic as a ventilatory dead space will be created when the right mainstem bronchus obstruction is relieved. The benefit of relieving airway obstruction that is lobar or beyond is also not clear. The MAO portion of the ACQuIRE cohort, a large prospective cohort of patients undergoing interventional pulmonary procedures in North America, showed that lobar obstruction or more distal obstruction was a predictor of the absence of symptomatic response to procedures [8]. Patency of distal smaller airways can be obtained during a procedure, but MAO has a high probability of rapid recurrence if these small airways are surrounded by a tumour and are too small to be stented. No specific stent has proven its superiority in this indication.

Patients with MAO generally have limited survival and the long-term complications of stenting are less of a concern in this population, although this could change with the recent appearance on the market of medications that may significantly prolong the survival of lung cancer patients.

Benign airway stenosis

Idiopathic, post-intubation, post-tracheotomy, post-lung transplantation and surgical anastomotic airway stenosis are the most frequent causes of benign airway stenosis (BAS). Less frequent causes include papillomatosis, amyloidosis, granulomatosis with polyangiitis, sarcoidosis and tuberculosis. The clinical presentation of patients with BAS is similar to patients with MAO, but the course is generally more insidious and hence symptoms are more often long-standing.

It is important to distinguish the management of BAS from the management of MAO as patients with BAS tend to have a prolonged survival that will expose them to long-term complications of airway stenting. Stenting should not be considered as standard first-line therapy in BAS, as surgery is the treatment of choice, but as an alternative therapy when a patient is not a good surgical candidate for technical reasons or because of comorbidities. As an example, granulation tissue has more time to form and become symptomatic or metal has more time to fatigue and break in BAS than in MAO. A BAS will also tend to be stiffer and more irregular in shape, giving less of an opportunity for a stent to "anchor" in position.

Distinguishing simple and complex stenosis is also important in the approach to the endoscopic treatment of BAS. Complex stenosis is defined by the presence of cartilaginous involvement [9]. Simple or web-like stenosis, such as often seen in idiopathic tracheal stenosis, will frequently not recur after endoscopic treatment without stenting [10, 11]; hence, stenting should not be a first-intention treatment in this population, but it can be used in stenosis refractory to endoscopic treatment without stenting or complex BAS.

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Endoscopic success rates using silicone stents can reach 70% in benign tracheal stenosis (figure 2) [10] and in post-lung transplant anastomotic stenosis [12]. One must always consider surgical resection of the stenosis before stenting as this is the therapy of choice for the vast majority of BAS. Cases of BAS should be discussed with a surgeon with expertise in tracheal resection. Reports of treatment of stenoses with stents causing extension of the disease by stent-related complications that precluded future surgeries have been published [13]. One should be cautious not to cause further strictures with airway instrumentation. For this reason, partially covered SEMS are contraindicated in BAS and benign airway disease.

EDAC/tracheobronchomalacia

Patients with EDAC may present with dyspnoea, cough or recurrent infections. Stenting has resulted in mitigated results in this population in our experience. Ernst *et al.* [14] confirmed this impression in an interesting study on tracheobronchomalacia, demonstrating that respiratory symptoms can be improved in the short term, but that short- and long-term complications are frequent. Further data are required to determine the role of stenting in EDAC, but the preliminary data do not point towards airway stenting being a long-term solution. Others have used airway stenting to predict clinical response to surgical correction of EDAC [15]. Stents are left in place for a short period of time to evaluate the symptomatic response of patients and, if symptoms improve sufficiently, patients are deemed potential responders for a surgical procedure.

Fistulas

Tracheo-oesophageal fistulas (TOFs) are a cause of recurrent pulmonary infections. They can be benign (endotracheal intubation, tracheostomy or tuberculosis) or malignant (pulmonary or oesophageal cancer) in origin. The role of stenting in TOFs is mainly in malignant cases and, occasionally, in benign cases in patients unfit for surgery. Although all agree that malignant TOFs should be closed, it is unclear if this should be done with an oesophageal stent, a tracheal stent or both. When treating a malignant TOF with an oesophageal stent, clinicians should be

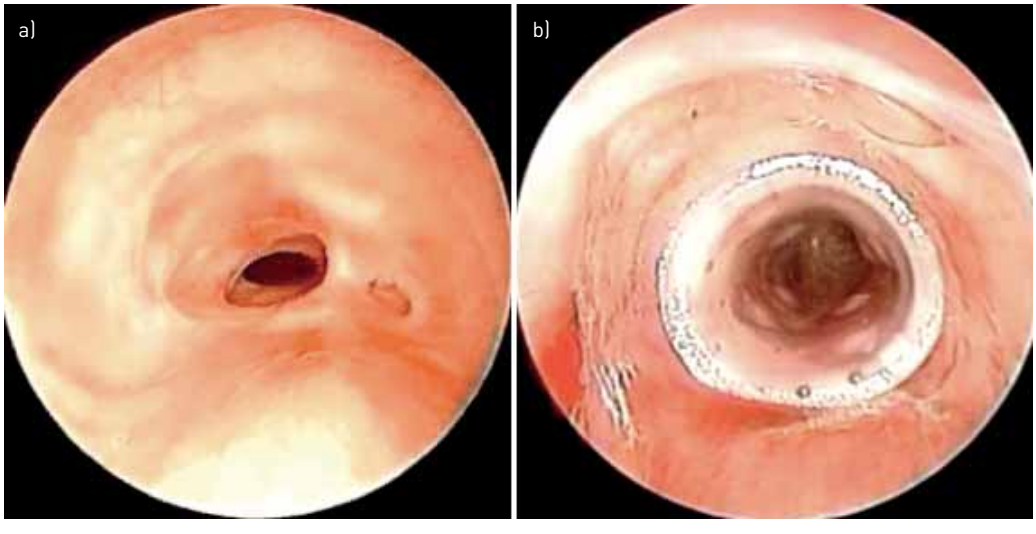

Figure 2. Benign tracheal stenosis a) before and b) after silicone stent placement.

aware of the risk of compromising the airway by pushing the tumour towards the airway lumen. For this reason, patients with symptomatic tracheal and oesophageal obstructions should all have an airway stent inserted prior to oesophageal stent insertion [16]. For patients without symptomatic airway obstruction, we prefer to start with oesophageal stenting and follow-up with the patient to see if a fistula persists and if respiratory symptoms develop. If the fistula persists despite an optimally positioned oesophageal stent or if symptomatic airway compression develops after airway stenting, an airway stent can be inserted. Fistulas are discussed in more detail elsewhere in this *Monograph* [17].

Surgical dehiscence and airway lacerations in patients unfit to undergo surgical repair may also be treated with airway stenting [18]. Airway lacerations in patients not requiring positive pressure ventilation will heal spontaneously and do not require stenting.

Type of stents

Polymer *versus* metal stents

In the early 1990s the classification of stents was simple as only Dumon silicone stents (figure 3), Montgomery silicone T-tubes and first-generation metal stents existed. Since then the first-generation metal stents (*e.g.* Gianturco (Cook Medical, Bloomington, IN, USA) and Palmaz (Johnson & Johnson, Somerville, NJ, USA) stents) have become obsolete because of their high complication rates [13, 19, 20].

To solve the problems associated with the erosion of metal stents in the airways, partially covered second-generation SEMS were developed. These stents are partially covered with polymer, but their metal frame remains bare in the distal portions to theoretically allow the stent to anchor into the mucosa and prevent migration. These dedicated airway stents provided better clinical results [5, 21, 22], although significant complications remained when they were left in place for prolonged periods of time, as became evident after several years of use in patients with BAS and prolonged survival [23, 24]. This led to a "black box warning" from the US Food and Drug Administration for the use of SEMS in BAS in 2005 [25].

Third-generation SEMS were introduced to overcome these problems. These are SEMS which are fully covered with polymer and which theoretically should not present the same

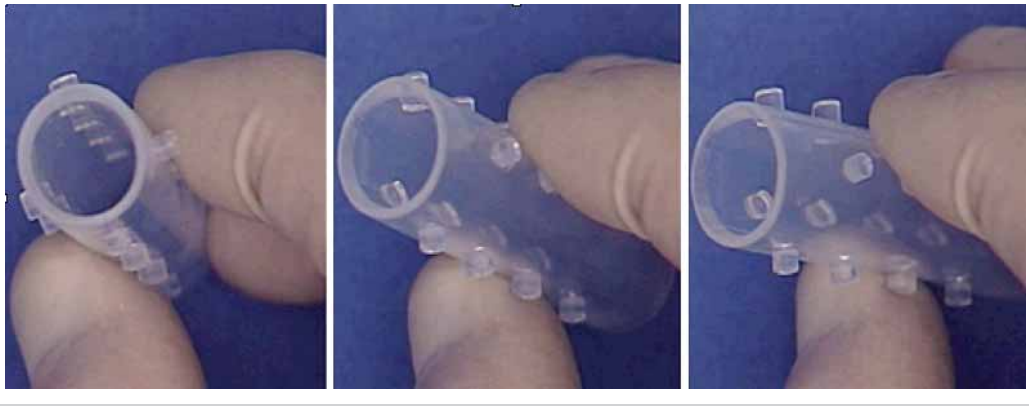

Figure 3. Dumon straight silicone stent.

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long-term complications as partially covered second-generation SEMS. Little data is available about these stents, although they have been commercialised for several years. Data about their efficacy and safety in MAO was initially published by Marchese *et al.* [26] and we recently published our experience with a third-generation SEMS in BAS, demonstrating an acceptable rate of minor complications that were all managed endoscopically with success [27]. Migration rates were high in both studies at 13.4% and 32.5%, respectively.

To the best of our knowledge, polymer stents and SEMS have never been directly compared. Efficacy and complications associated with a stent will vary depending on the indication for its use and the duration it is left in place; hence, it is difficult to compare stents by comparing the results of different studies in which the populations differ. As an example, the same stent model was used in our recent series [27] of BAS and the Marchese *et al.* [26] series of MAO, but our complication rate differed as our patients had benign disease and lived significantly longer with their stents in place. Polymer stents have the advantage of being customisable at the bedside (figure 4) [28]. As an example, if a MAO involves the proximal centimetre of the right mainstem, the distal centimetre of the trachea and the proximal centimetre of the left mainstem, a Y-stent can be customised at the bedside to fit these exact dimensions after measurements are taken endoscopically [29], whereas a one-size-fits-all stent will have to be selected if a SEMS is used, which in the end will be unnecessarily large. Customising polymer stents will also allow treatment options that are not possible with SEMS, such as creating a window in the stent to ventilate a right upper lobe. SEMS have the advantage of not requiring rigid bronchoscopy placement. In our opinion, this is not a real advantage as an individual placing an airway stent should be competent in rigid bronchoscopy, and should be able to convert to rigid bronchoscopy if a complication occurs and this technique is required.

SEMS are available in larger diameters (figure 5) than polymer stents as larger polymer stents cannot be folded to a small enough diameter to fit down a rigid bronchoscope and be positioned [30]. This difference may be of clinical interest in the treatment of tracheal disease where the largest diameter of silicone stent commercially available may be insufficient, increasing the risk of migration. Our previous work has shown a lower risk of migration with Silmet stents (Novatech, La Ciotat, France) than with Dumon silicone stents in dynamic A-shape tracheal stenosis, a situation where large tracheal stents are needed [31]. SEMS also have a thinner profile that leaves a larger residual lumen for the same outside diameter, which may facilitate mucus clearance. We will not review all stents available on the market here, as

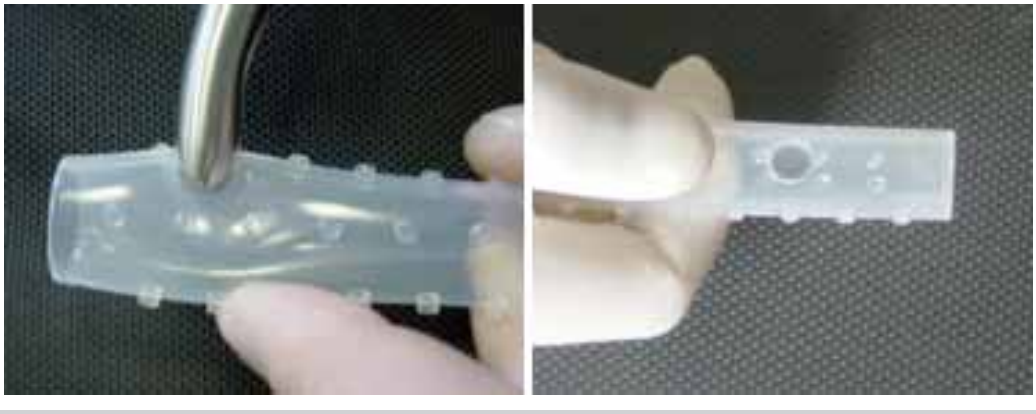

Figure 4. Onsite customisation of a Dumon stent. Reproduced and modified from [28] with permission.

this could be the topic of a full chapter in itself, but we refer the reader to previous work from Freitag [32] and our group [9] for detailed information on available airway stents.

As already noted, no clinical trial has compared different stents head to head. Only data comparing mechanical properties of different stents are available [33, 34]. Different stents have different characteristics and no stent is perfect; hence, clinical judgement should be used to choose the optimal airway stent for an individual patient. A recent survey of members of European Association for Bronchology and Interventional Pulmonology demonstrated that a wide variety of airway stents are used across Europe [35]. Dumon silicone stents and Ultraflex SEMS (Boston Scientific, Marlborough, MA, USA) (figure 6) were the most commonly used airway stents.

Biodegradable stents

Stenting in benign airway disease should be temporary in most cases and hence a second procedure during which the stent is removed will be necessary, together with the associated risks of this procedure, risks of general anaesthesia and costs. Stents that degrade and disappear after a predetermined period of time would prevent the need for this second intervention and are an appealing therapeutic option. Developing such stents is not a small feat: 1) the stent must have sufficient initial strength and flexibility, and be able maintain these properties for several months prior to its degradation; 2) the biodegradable materials used must leach nontoxic degradation products, including the metabolites of these degradation products; and 3) the stent must have comparable efficacy, complication profile and ease of use when compared with existing airway stents.

Literature regarding biodegradable stents in humans is scarce (figure 7) [36]. Only five studies including a total of 17 patients have been published to the best of our knowledge. The only adult study to date was published by Lischke *et al.* [37] and included six patients treated with 20 stents for post-lung transplant anastomotic stenosis. All stents were placed successfully and

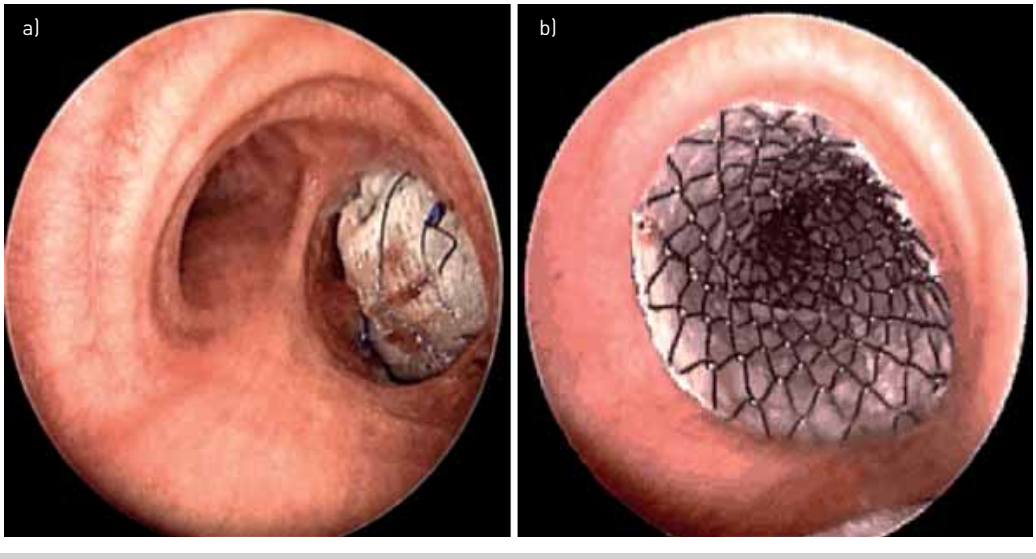

Figure 5. Complete dehiscence of the stump after right pneumonectomy a) before and b) after placement of a large conical fully covered SEMS.

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Figure 6. Ultraflex stent.

all procedures were endoscopically successful. Four of the six patients required multiple interventions with restenting for restenosis. Median (range) time to restenting was 5 (2–15) months. One patient died of a pulmonary embolus and five survived the observation period with a median (range) follow-up of 40 (7–48) months. The five surviving patients were intervention free for a median (range) of 24 (7–44) months. Vondrys *et al.* [38] also published their experience with biodegradable stents in paediatric tracheal stenosis. In total, 11 stents were implanted in four children. All stents were deployed successfully and all procedures were initial endoscopic successes. One death occurred and was unrelated to the stent. The three other patients needed repeat stenting after stent resorption. In one case, stenting allowed the patient to gain sufficient time to become a surgical candidate and undergo surgery. In the two other cases, after multiple endoscopic treatments, the initial pathology remained problematic and other endoscopic treatments were attempted. Serio *et al.* [39] published a series of 235 stents placed in 100 children over 7 years, which included three biodegradable stents. One stent failed because of insufficient radial force, one because it did not relieve symptoms and one because the underlying pathology remained after 4 months when the stent had biodegraded. Antón-Pacheco *et al.* [40] also published a case series of 14 tracheoplasties for tracheal stenosis, one of which developed a postoperative tracheal stenosis and required stenting. The underlying disease remained after 1 year and the stent had to be replaced three times over this period as the stent had biodegraded. Finally, the results of Sztanó *et al.* [41] in three patients were not as positive as stents started to degrade into large fragments after 5 weeks. This caused severe pneumonia leading to death in one patient, while another patient required urgent bronchoscopy for removal of one of the fragments. Further studies are needed to evaluate the role of biodegradable stents and to optimise their properties.

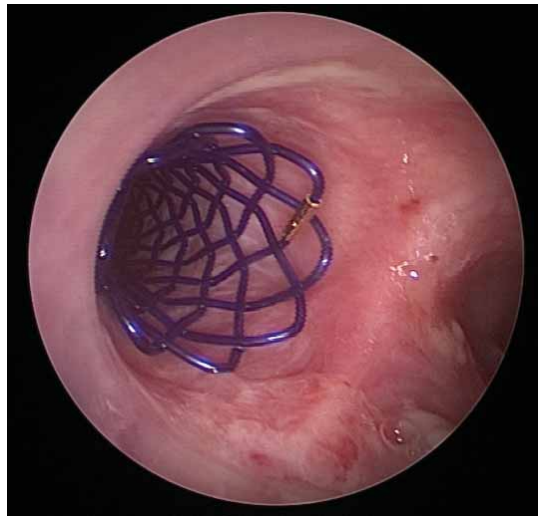

Figure 7. A biodegradable stent (Ella, Trebes, Czech Republic) in the left mainstem bronchus. Reproduced and modified from [36] with permission.

Data also need to be obtained to compare the mechanical and physical properties of biodegradable stents over time, and to compare these properties with those of existing metal and polymer stents. Materials that biodegrade over longer periods of time also need to be explored. Indeed, biodegradable stent placement could be considered for temporary splinting, as a neoadjuvant therapy before surgery or any other medical option, and with a curative intent as well. In this case, stent duration is of real importance. For instance, the success rate of endoscopic management in benign complex tracheal stenosis is close to 70% when a stent is placed for 18 months [10]. In benign anastomotic stenosis following lung transplantation, the same success rate is obtained for a stent duration of ~6 months [12]. These durations have to be obtained for biodegradable stents, without any loss of their mechanical properties.

Drug-eluting stents

Granulation tissue formation is a frequent complication of airway stents. Procedures will frequently be required to remove this tissue which can occlude stents and lessen the benefits obtained after stenting. Hence, the idea of developing stents that would release drugs over time, preventing the formation of granulation tissue. The same logic can be applied for the prevention of tumour overgrowth which can occlude stents in cases of MAO. Drug-eluting stents may also play a role in decreasing the fibrotic process in certain BAS.

Little data is available about the role of drug-eluting stents in airway stenting and mixed results were obtained in previous studies. One of the most interesting studies of drug-eluting stents for airway disease is a randomised animal study published by Zhu *et al.* [42]. 25 rabbits with benign tracheal stenosis were randomly assigned to five test groups: 1) control, 2) silicone stent, 3) biodegradable helical stent, 4) biodegradable tubular stent and 5) biodegradable tubular stent coated with mitomycin C. After 12 weeks, stenosis in group 5 was the mildest followed by group 2. Other studies of the antifibrotic properties of mitomycin C in the prevention of BAS have yielded conflicting results [43–49]. Another study of interest was published by Chao *et al.* [50] in 2013. 15 biodegradable stents coated

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with cisplatin were surgically implanted into the trachea of rabbits. A minimum blood drug level of cisplatin was sustained for >5 weeks. Interestingly, the mechanical strength of the stents was also studied and was demonstrated to be comparable to that of Ultraflex SEMS. Huvenne *et al.* [51] obtained interesting results using doxycycline-releasing stents in sinus surgery for chronic rhinosinusitis, which demonstrated lower matrix metalloproteinase-9 levels and better clinical outcomes in patients treated with drug-eluting stents *versus* patients treated with non-drug-eluting stents.

The development of drug-eluting airway stents lags far behind in interventional pulmonary medicine when compared with other fields of medicine such as interventional cardiology. Drug-eluting stents to minimise tumour overgrowth and granulation tissue formation are certainly an interesting new technology, but more efforts are needed in the design of these stents and larger trials are required to confirm their role.

Three-dimensional printed stents

The recent years have seen rapid growth in the three-dimensional (3D) printing industry, with breakthroughs in the medical field. The application of this technology in airway disease started with its use in procedural planning. In 2013, Tam *et al.* [52] printed an airway model of a patient with polychondritis and tracheobronchial chondromalacia to help in the choice of the optimal treatment for this patient with complex airway disease. After successfully using 3D printing in procedural planning, it was used in device manufacturing. In 2015, based on a digital trachea model, Cheng *et al.* [53] designed and fabricated a custom Montgomery T-tube for a patient who had undergone complex cervical tracheal resection and reconstruction for a recurrent medullary thyroid cancer. Short-term outcome was excellent, but long-term follow-up was not available. Also in 2015, Morrison *et al.* [54] published a series of three 3D printed external airway splints that were implanted in infants with severe tracheobronchomalacia with resolution of their symptoms and favourable long-term evolution. More recently, in 2017, Guibert *et al.* [55] published a case report of a 3D printed silicone stent which was used to treat a complete stenosis of the bronchus intermedius and partial dehiscence of a bronchial anastomosis after lung transplantation that would not have been treatable with any currently marketed airway stent.

The use of 3D printing is relatively simple. CT images are uploaded into 3D imaging software that is used to create a virtual 3D model. Digital modelling software is used to modify the airway model as needed. A 3D printer then prints the physical airway prosthesis model. This model can then be injected with silicone to create the stent.

Although advances in 3D printing have been rapid, there are challenges ahead. 1) Medical devices need to be approved by local authorities before use in patients. Approval of 3D printable, flexible, implantable-grade materials will be required for 3D printing to be useful clinically in airway stenting. 2) Materials used in 3D printing cannot withstand the high temperatures of autoclaves (121°C or 132°C), although other options for sterilisation such as gamma radiation can be suitable. If these challenges are overcome, one can image a day when personalised airway stents will be manufactured to address each patient's specific needs. This would allow a better fit of airway stents, which could decrease migration of loose stents and granulation tissue formation due to mechanical irritation by the end of stents that dig into the airway mucosa due to a poor fit.

Stent insertion

Polymer stents

Polymer stent insertion requires rigid bronchoscopy. Different positioning techniques exist, but they all consist of placing the folded stent in a hollow metal tube that can be inserted into the rigid bronchoscope that has previously been positioned in the desired site for stent launching. The stent is then pushed out of the distal end of the rigid bronchoscope using another metal tube which is advanced down the hollow stent launcher. Some operators attempt to launch their stent in the desired final position, but we prefer to use the "pullback technique". We launch the stent distally to its desired position, then grasp it with forceps to keep it folded and slowly pullback the rigid bronchoscope and stent until we obtain the desired position. A stent which completely deploys on its own is probably undersized. A stent should require manoeuvres with forceps or use of a dilation balloon to fully deploy.

Self-expandable metallic stents

SEMS can be positioned without the use of rigid bronchoscopy through an ETT using fluoroscopic guidance, flexible bronchoscopy and a guidewire, but this has been a subject of controversy as many argue that optimal and safe placement of all airway stents requires rigid bronchoscopy. No study has compared the safety and efficacy of both techniques. We do not see any disadvantage to the use of rigid bronchoscopy if the operator is experienced with this technique and believe that if a physician decides to position an airway stent, they should be competent in rigid bronchoscopy to manage potential complications of stent insertion such as bleeding.

Stent sizing

Stent sizing requires experience and is one of the most challenging steps in airway stent insertion. Undersizing stents will increase the risk of migration, while oversizing will increase granulation tissue formation and the risk of fracture if a metal stent is used. Different tools allow proper stent sizing. Rigid bronchoscopy allows tactile feedback. By knowing the outer diameter of the bronchoscope and feeling the resistance around it, the operator can estimate the airway diameter and choose the appropriate stent. CT images also allow measurement of airway diameters. One must keep in mind that a normal trachea has a typical diameter of 14–18 mm, while mainstem bronchi are 10–14 mm in diameter. These dimensions will vary according to height and sex. Humility is also essential in stent sizing. An initial undersized stent may help determine that the appropriate stent diameter is one size larger. Once the stent is positioned, the bronchoscopist should attempt to gently pull the stent proximal with forceps. The stent should not migrate with minimal force applied. One must also keep in mind that SEMS will keep expanding after initial positioning.

Complications

Migration

Reported stent migration rates are generally ~10% [4, 22, 26, 56], but may be significantly higher in certain situations. It is important to understand the forces holding a stent in place

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in order to understand the variations in migration rate. Stents are held in place by the friction between the outer surface of the stent and the adjacent mucosa. As an example, the larger the uncovered metallic portion of SEMS, the more friction is created, the less a stent tends to migrate. Hence, fully covered third-generation SEMS will have a greater tendency to migrate than partially covered SEMS or noncovered SEMS. For the same reason, certain silicone stents have studs to increase friction and prevent migration. Ost *et al.* [57] have shown in a retrospective review of 195 stent procedures that Dumon silicone tube stents were associated with a greater risk of migration than Ultraflex SEMS. Friction will also be affected by the pressure applied by the stent against the abnormal airway. As an example, an undersized stent will have a greater tendency to migrate. For the same reason, in certain situations, it is preferable not to completely restore the patency of an airway when debulking a MAO in order to keep a certain level of compression onto the stent. Using similar logic, stent migration may be good news in a case of MAO in a patient undergoing chemotherapy or radiation therapy: it may signify that the tumour, which was holding the stent in place, has shrunk.

A more complex aspect, which plays an important role in stent migration, is the distribution of the forces holding a stent in place along the stent itself. A common example of this situation is high hour-glass-shaped tracheal stenosis. The narrowest point of the stenosis is significantly narrower than the lumen just above the stenosis, creating, if a cylindrical stent is used, a very uneven distribution of forces along the stent. This will cause what we call a "soap bar" effect where the high pressure on the stent in the narrowest portion of stenosis combined with the absence of pressure on the proximal portion of the stent will cause the stent to migrate upwards.

Granulation tissue formation and tumour overgrowth

Tumour overgrowth may occur at the end of stents or through the metal mesh of SEMS. It is important to choose a stent slightly longer than the endobronchial portion of the tumour to be covered to prevent this complication. We suggest using a stent with a covered section 1–2 cm longer than the area that needs to be covered, especially if no adjuvant therapy is planned after stent placement. One must also keep in mind that partially covered second-generation SEMS are not covered at their distal ends.

The formation of granulation tissue can occur at the extremities of stents, and is caused by the repeated trauma between the stent and the adjacent mucosa. Reported incidence rates vary between 4% and 15% [4, 21, 22, 26, 27, 56]. It is important to understand that granulation tissue does not require any intervention unless it causes consequences such as dyspnoea or post-obstructive pneumonia. The mechanisms underlying the formation of granulation tissue have not been thoroughly explored. Kargiannidis *et al.* [58] published interesting results demonstrating high-level expression of matrix-associated transforming growth factor-β1, which is associated with enhanced fibroblastic activity in patients with stented BAS and formation of granulation tissue. Stent oversizing has also been demonstrated to be associated with granulation tissue formation [59]. Immunosuppression in certain populations, such as transplant patients, decreases the incidence of granulation tissue formation [60]. Bacterial colonisation increases the risk of granulation tissue formation [61].

Mucus plugging and bacterial colonisation

The reported incidence of airway stent mucus plugging, requiring intervention, varies between 0% and 16% [4, 21, 22, 26, 27, 56]. The longer the stent and the smaller the

diameter of the stent, the higher the chance of mucus plugging. Frail patients or patients with recurrent laryngeal nerve palsy may be unable to generate a sufficient cough flow to clear secretions from their stent, even if the stent is not particularly long or narrow. Nebulised saline solution and chest physiotherapy may help prevent mucus accumulation in airway stents. Bacterial biofilms may form on stents [62] and increase the risk of mucus plugging. Bacterial colonisation of the stent may also cause halitosis, which can be problematic and require stent removal.

Stent fracture and failure

The human airways undergo constant movement and pressure changes during the respiratory cycle. Coughing increases the pressure applied on airway stents to the extreme and deforms them [63]. After undergoing such stress the metal can fatigue and fracture. Most stent fractures will occur after the stent has been in place for a prolonged period; hence, patients with benign airway disease and prolonged survival are at higher risk of stent fracture (figure 8) [64]. Airway tortuosity is also a risk factor for stent fracture [64]. Stent fracture is a dangerous complication as broken metal wires may perforate the airway and its adjacent structures. One must also keep in mind that partially covered SEMS that have been in place for prolonged periods of time may be difficult to remove, especially if fractured. To the best of our knowledge, silicone stents have never been reported to fracture.

Surveillance

All patients should receive appropriate follow-up by an interventional pulmonologist after stent placement, and carry with them a document stating that they have an airway stent in place and providing a phone number to contact in case of emergency. What constitutes an appropriate follow-up is not well established. Matsuo and Colt [65] demonstrated that routine surveillance bronchoscopy after silicone stent placement for benign or malignant

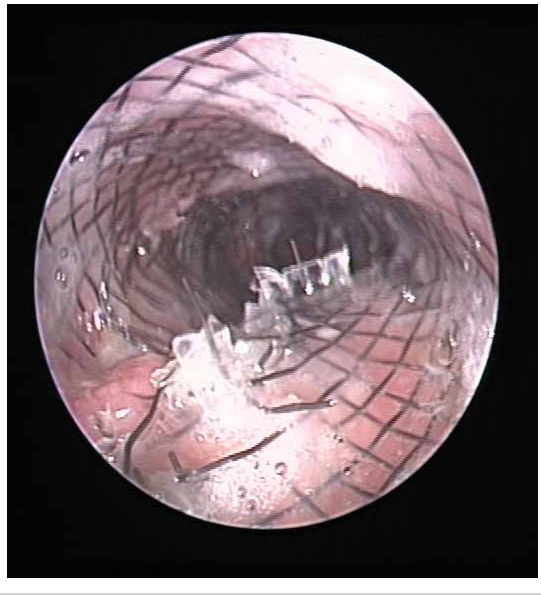

Figure 8. Fracture of the tracheal branch of a MICRO-TECH Y-stent (MICRO-TECH, Düsseldorf, Germany).

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tracheobronchial obstruction detected stent-related complications requiring intervention in only 5% of asymptomatic patients.

It is important to understand that the goal of airway stenting is palliation of symptoms; hence, if the patient remains asymptomatic, it is not necessary to take any action. Exceptions to this rule are early signs of complication that may progress further in patients with benign airway disease and an expected prolonged survival. In this situation, it is probably more appropriate to address the complications early. However, patients need to be clinically re-evaluated to ensure that they have not developed new symptoms and require bronchoscopy. The schedule according to which patients should be followed is unclear. In Quebec, Canada, patients in our institute are followed up 2–4 weeks after stent placement and then every 3 months. It is also important to follow-up with patients with MAO as their airway obstruction may decrease after treatment and their airway stent may be removed.

Conclusion

Airway stents are a relatively new treatment option for a variety of benign and malignant airway diseases. Significant progress has been made over the last 30 years in the domain of airway stenting, but much remains to be explored. Drug-eluting stents, biodegradable stents and 3D printing of stents have emerged over the last decade as potential solutions for problems associated with airway stenting. Further work is needed to improve the understanding of the existing technology and obtain a better understanding of the limitations of this technology. Large trials of airway stenting are difficult to perform as individual centres perform a limited number of procedures; hence, future studies may require the collaboration of large centres with expertise in the domain of airway stenting. Collaboration with scientists from different domains of expertise will also be crucial to the development of interventional pulmonary medicine and airway stenting.

The future of airway stenting promises to be interesting. With the advent of biodegradable, active and 3D printed stents the science of airway stenting has entered into a very promising phase of evolution. These evolutions are particularly relevant in the era of "personalised" medicine. Finally, remember that "A stent is a foreign body and nobody is perfect", so the best stent remains the one that can be avoided.

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Chapter 17

Foreign bodies

Sebastian Fernandez-Bussy[1] and Gonzalo Labarca[2,3]

Foreign body aspiration is a potentially life-threatening condition. It has a bimodal distribution, with two higher-incidence age groups clearly described: children and persons aged >75 years. The clinical presentation may be acute (dyspnoea, asphyxia, cardiac arrest, *etc.*) or chronic (recurrent pneumonia, atelectasis, chronic cough, *etc.*). Thus, a high index of suspicion is necessary. When foreign body aspiration is suspected, a multidisciplinary team should evaluate the patient and remove the foreign body as rapidly as possible. The traditional procedures for the diagnosis and treatment of foreign body aspiration are interventional methods such as rigid bronchoscopy. However, flexible bronchoscopy is a satisfactory option, particularly in centres without access to rigid bronchoscopy. Bronchoscopists may use different extraction tools such as cryoprobes, baskets, snares and forceps.

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The presence of a foreign body in the airway is potentially lethal, particularly in children [1]. All health personnel, notably emergency physicians, pulmonologists, otorhinolaryngologists, surgeons, intensivists and radiologists, should have knowledge and awareness of the signs and symptoms of this condition [2, 3]. Historically, the removal of foreign bodies was the first reference to an endoscopic airway procedure. Towards the end of the 19th century, Gustav Killian used a rigid endoscope to successfully remove a pig bone located in the right bronchus of a patient who presented with asphyxiation [1].

A high index of suspicion, an adequate temporal evaluation from the moment of aspiration to the beginning of the symptoms and timely management are all key to the effectiveness of the therapeutic measures used, the prevention of complications and the survival of these patients [2, 3].

Epidemiology

According to data reported in the literature, the presence of foreign bodies in the airway causes 17 530 hospitalisations per year, with an estimated mortality of 1.2 per 100 000

[1]Interventional Pulmonology Unit, Clinica Alemana-Universidad del Desarrollo, Santiago, Chile. [2]School of Medicine, Universidad San Sebastian, Concepcion, Chile. [3]Division of Internal Medicine, Complejo Asistencial "Dr Victor Rios Ruiz", Los Angeles, Chile.

Correspondence: Sebastian Fernandez-Bussy, Interventional Pulmonology Unit, Clinica Alemana-Universidad del Desarrollo, Manquehue Norte 1410, 7650567 Santiago, Chile. E-mail: sfernandezbussy@alemana.cl

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inhabitants [4]. According to epidemiological reports, foreign body aspiration shows a bimodal distribution, with two higher-incidence age groups clearly described [4, 5]. The first such group falls within childhood, particularly those children aged 1–3 years, and is related to the psychomotor development of children and their interest in exploring objects around them. In a diagnostic series of discharges from a paediatric clinic from 2000 to 2009, an incidence of 6.6 per 10 000 admissions per year was observed, with an associated health expenditure of up to USD486 million per year [4].

The second high-incidence group is late adulthood (particularly those adults aged >75 years) as a result of alterations in swallowing and the neurological regulation of the airway or specific pathologies such as Parkinson's disease [5, 6].

Pathophysiology

The airways feature a series of defence mechanisms against the aspiration of foreign bodies. These mechanisms include anatomical, immunological and neurological components.

The anatomical components comprise physical barriers such as the nasal passage, oropharynx, larynx and trachea. These mechanical barriers inhibit the passage of large foreign bodies, preventing them from entering the central airway. Trachea size varies, with a typical diameter of 18.5 mm (range 17.5–19.5 mm) for an adult male. At the carina, the trachea divides into two bronchi (left and right bronchi). The length of the right bronchus is ~2 cm. This bronchus is shorter than the left bronchus. Tracheobronchial angulation is another difference between the right and left bronchi. The right bronchus has an open angle to the carina. At the distal level, the airway is composed of smooth muscle surrounded by a fibrocartilage ring that confers strength and stability to the airway [6, 7].

With regard to immunological defence, the lumen has a secretory epithelium that produces abundant mucus and provides defence mechanisms against the aspiration of small particles along with the features of other sweeping mechanisms (*e.g.* cilia and flagella) and the increased production of immunoglobulin. These mechanisms are important in mucociliary clearance [7].

Several neurological reflexes of the tracheobronchial tree function to prevent foreign body aspiration, including the reflexes of normal swallowing and coughing. Normal swallowing is the result of a series of interactions between the orobuccal musculature and central mechanisms such as the swallowing reflex. This neurally controlled mechanism allows the passage of the alimentary bolus from the oral cavity towards the oesophagus, while preventing passage of the bolus into the central airway. Other centrally regulated physiological reflexes prevent the entry of foreign bodies into the central airway. For example, the cough reflex is the main component that protects against aspiration [8].

Pathologically, the occurrence of foreign body aspiration is due to an interruption of anatomical barriers. For example, a large diameter foreign body might overcome physiological and anatomical barriers, and become lodged in the central airway, most commonly in the lumen of the right bronchus [8, 9].

Other mechanisms are related to the shape and type of foreign body material, exemplified by certain vegetables or flexible foreign bodies that might migrate and affect the

tracheobronchial lumen. Some small size or organic foreign [9] bodies may occlude the lumen at a distal level and cause an asymptomatic obstruction. These cases are usually diagnosed by a complication or because of symptoms related to chronic foreign body aspiration, as discussed later in this chapter.

Despite the mechanism of obstruction, acute foreign body aspiration and luminal retention lead to decreased ventilation, which diminishes the gas exchange surface area and causes hypoxaemia. Occasionally, foreign body retention may result in a "ball valve" effect, which develops when air inflow circumvents the foreign body during inspiration but cannot exit during expiration, thereby leading to air trapping distal to the foreign body with the risk of cardiorespiratory compromise and collapse [1–4, 9].

Risk factors

The factors associated with an increased risk of foreign body aspiration in adults include alterations in the mechanisms that regulate swallowing, such as alterations in consciousness, alcoholism, loss of teeth, swallowing disorders, trauma and use of drugs (*e.g.* benzodiazepines and hypnotics) [3]. Other associated factors are related to degenerative neurological disorders, such as dementia, Parkinson's disease, mental retardation, stroke sequelae, central nervous system tumours and seizures [5, 6, 10].

Risk factors are similar for the paediatric population; however, this group is more vulnerable to foreign body aspiration because children commonly laugh, talk, cry or play with organic or inorganic objects in their mouths [2, 5].

Among the existing scenarios related to foreign body aspiration are general anaesthesia-related iatrogenic complications *via* the use of a laryngeal mask or orotracheal tube, which might displace a tooth into the distal airway, and during conscious sedation in dental procedures [3, 6, 9].

Types of foreign body

A foreign body may be classified according to its origin into organic (*e.g.* peanuts, nuts, fruits, vegetables), inorganic (*e.g.* pills, coins, plastics), mineral (*e.g.* dental pieces, bones), endogenous (*e.g.* broncholithiasis) and miscellaneous [9–13].

Clinical signs and symptoms

The clinical manifestations of foreign body aspiration are varied and may range from asymptomatic to fulminant [1]. An acute episode of foreign body aspiration (potentially a life-threatening sudden event) should be distinguished from a chronic foreign body aspiration that might lead to persistent cough, persistent or recurrent pneumonia, or atelectasis, but not to an acute life-threatening presentation [9–11].

Acute foreign body aspiration

A detailed history obtained from the patient and their relatives is important to determine the type of foreign body aspirated, the timing of the event and the severity of the condition [10].

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During the initial examination, it is crucial to identify acute episodes of aspiration with life-threatening risk secondary to obstruction of the central airway, which may provoke an episode of asphyxia and dyspnoea that could lead to acute hypoxaemic respiratory failure and cardiorespiratory arrest [3, 4].

Factors that are important to evaluate upon physical examination are haemodynamic stability, oxygenation, ventilation, state of consciousness, use of accessory muscles, thoracic asymmetry, abolition of pulmonary murmur, unilateral wheezing, auscultation of crepitus, stridor and loose teeth (table 1) [4, 9–12].

Another form of presentation, *i.e.* subacute, manifests as a result of the complications sustained from foreign body aspiration. These cases may present clinically with chest pain, dyspnoea, pneumothorax, pneumomediastinum, atelectasis or post-obstructive pneumonia [12–14].

Chronic foreign body aspiration

Familiarity with associated comorbidities such as the presence of the mental alterations that contribute to aspiration is important. The most frequently reported symptoms are cough (66%), followed by asphyxia (27%), dyspnoea (26%), fever (22%) and nonmassive haemoptysis (17%) [10, 15, 16]. For episodes of a longer duration or prolonged evolution, the presence of recurrent pneumonia or pneumonia complicated by pulmonary abscess might be reported. However, McGuirt *et al.* [15] found that up to 39% of presentations could be asymptomatic.

Paediatric foreign body aspiration

Special consideration should be given to paediatric patients because the diagnosis of foreign body aspiration is delayed in up to 25% of these patients [2]. Importantly, these patients may present with episodes of asthma, recurrent pneumonia, recurrent laryngitis or croup [2, 5]. As the clinical presentation of foreign body aspiration is less categorical in this population, clinical prediction rules have been designed to guide physicians when evaluating these patients. Janahi *et al.* [17] published a scale that included clinical presentation, physical examination, and radiological and ventilatory variables with an area under the curve of 0.76 (95% CI 0.70–0.82; $p<0.05$) (table 2). In that study, a cut-off of $\geqslant 2$ points denoted a sensitivity of 89% and a specificity of 45%, whereas a cut-off of $\geqslant 3$ points denoted a sensitivity of 75% and a specificity of 65%. In those with a score $\geqslant 2$ points, a flexible bronchoscopy should be performed to inspect the airway. For those with a score

Table 1 Signs and symptoms of foreign body aspiration

Asphyxia
Stridor
Choking episode
Cough
Wheezing
Recurrent pneumonia
Unilateral hyperinflation
Use of accessory muscles
Haemoptysis

Table 2 Scale of foreign body risk in a paediatric population

Predictor	Score
Witnessed choking	1
Noisy breathing/stridor/dysphonia	1
New-onset wheezing/recurrent/persistent wheeze	2
Abnormal chest radiograph	2
Unilateral reduced air entry	1

Information from [17].

⩾5 points, the more appropriate diagnostic and therapeutic procedure is early rigid bronchoscopy [17].

Imaging studies

Chest radiography may provide information on the foreign body location and the consequences resulting from airway obstruction. Various diagnostic performance studies have reported a sensitivity ranging from 70% to 82% and a specificity ranging from 44% to 74% [9, 10]. Chest radiography does not show adequate diagnostic performance for determining the aetiology of the foreign body. Approximately 26% of foreign bodies are radiopaque and up to 36% of radiographs are reported as normal [10, 16]. The clinician should inspect for signs of foreign body aspiration, such as pulmonary consolidation, atelectasis, pulmonary hyperinflation, pneumothorax and pneumomediastinum [18–20].

Chest CT scans allow clinicians to visualise the bronchial tree globally, enabling the detection of abnormalities and lesions located in the lumen of the airway [19–21]. However, foreign bodies (particularly long-standing bodies) may produce inflammatory or granulomatous alterations at the luminal level secondary to the inflammatory response, which makes visualisation and identification difficult. Virtual bronchoscopy uses software in which the images obtained through CT are processed to generate a visualisation of the central airway. This technique has a sensitivity of 92% and a specificity of 85.7% [19]. It also offers the advantage of being an initial guide for the planning of bronchoscopy. However, small objects may result in false-negative results; for this reason, direct inspection of the airway *via* bronchoscopy (using flexible or rigid modalities) remains the diagnostic and therapeutic method of choice [10, 22].

General management

The management of foreign bodies in airways should involve a multidisciplinary team, including close communication between pulmonologists, otolaryngologists, surgeons, radiologists and anaesthesiologists. As an initial management measure, airway inspection should be performed *via* bronchoscopy in all patients in whom foreign body aspiration is suspected [1, 3, 10].

Initial pre-hospital measures are key in life-threatening situations. One study evaluated the variables related to higher pre-hospital mortality and concluded that the presence of a witness and the use of early foreign body extraction techniques were associated with favourable outcomes [23]. The pharmacological measures reported in the literature include

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the use of glucocorticoids, bronchodilators and postural drainage. These measures have failed to demonstrate efficacy and are not currently recommended; furthermore, their use is discouraged because they can delay the endoscopic procedure and increase morbidity and mortality [9, 10, 18].

As mentioned earlier, symptom severity depends on multiple factors, such as the type, size and aspiration timing of the foreign body. The major cause of mortality is hypoxaemia [24]. A risk of imminent asphyxia exists depending on the size of the foreign body. Particular attention should be given to medications in the context of foreign bodies because upon contact with the bronchial lumen, the aspiration of a medication could cause a chemical reaction that may result in the dissolution of tablets, leading to airway erosions and burns [9, 13–16].

The use of direct laryngoscopy has been described for cases in which the foreign body is in the proximal airways. This technique allows clinicians to visualise and extract the foreign body. However, special care should be taken to avoid greater damage due to foreign body displacement and dislodgement in the more distal airways [10, 25].

Specific management

Sedation and anaesthesia

Initial management should include basic life support along with the use of oxygen and anxiolytics to reduce dyspnoea and anxiety [1, 2, 26]. The degree of sedation depends on the endoscopic procedure to be performed. For an initial approach *via* flexible bronchoscopy, conscious sedation and local anaesthesia may be used. In contrast, the performance of rigid bronchoscopy requires the use of general anaesthesia. Conscious sedation has the advantages of preserving the cough reflex and the previously described neurally controlled defence mechanisms, which might aid successful foreign body removal. Precautions for this type of sedation include protecting against the possibility of aspiration derived from the loss of foreign body control, particularly when entering the subglottis and glottis, with foreign body loss in the upper airway [8, 10, 26]. The use of rigid bronchoscopy avoids this scenario. Another potential complication is the aspiration of gastric contents during the procedure. In a review of 12 979 paediatric patients undergoing foreign body removal, no reports of gastric content aspiration were found in patients under conscious sedation or in those under general anaesthesia [27].

Rigid bronchoscopy

Rigid bronchoscopy is the method of choice for foreign body extraction, with a reported efficacy of >95% [11, 28]. This technique (discussed in more detail elsewhere in this *Monograph* [29]) allows the airway to be secured by providing oxygenation and ventilation. Through its large work channel, different rigid, large and strong forceps may be introduced. Additionally, larger baskets are available compared with flexible bronchoscopy. These baskets may be used to extract larger solid foreign bodies. Flexible bronchoscopes may be used inside the working channel of a rigid bronchoscope to first inspect and then to permit the use of other tools (cryoprobes, snares, baskets, balloon catheters, *etc.*). Rigid bronchoscopy is the treatment of choice for patients with laryngeal stridor or asphyxia symptoms, or those with a foreign body obstructing the proximal lumen. This technique

also has significantly greater suction capacity than flexible bronchoscopy. Aspiration alone can often remove the foreign body [6, 10].

A second inspection of the airway might be necessary for possible retained foreign body fragments. Moreover, foreign bodies that generate a major inflammatory reaction may result in residual cicatricial stenosis following extraction. We recommend performing a repeat bronchoscopic evaluation 1–2 weeks after foreign body removal [6].

One disadvantage of rigid bronchoscopy is the need for general anaesthesia. Complications reported with this technique include bronchial rupture, severe laryngeal oedema, bronchospasm, pneumothorax, pneumomediastinum, fractured teeth, damage to the vocal cords and bronchial laceration [18].

The combination of rigid bronchoscopy and flexible bronchoscopy provides the highest probability of foreign body removal and enables the use of a wide range of tools (figure 1), with the lowest risk of complications [28].

Flexible bronchoscopy

Flexible bronchoscopy is useful for inspecting both the upper and lower airways and extracting foreign bodies. In some centres, this procedure (discussed in more detail

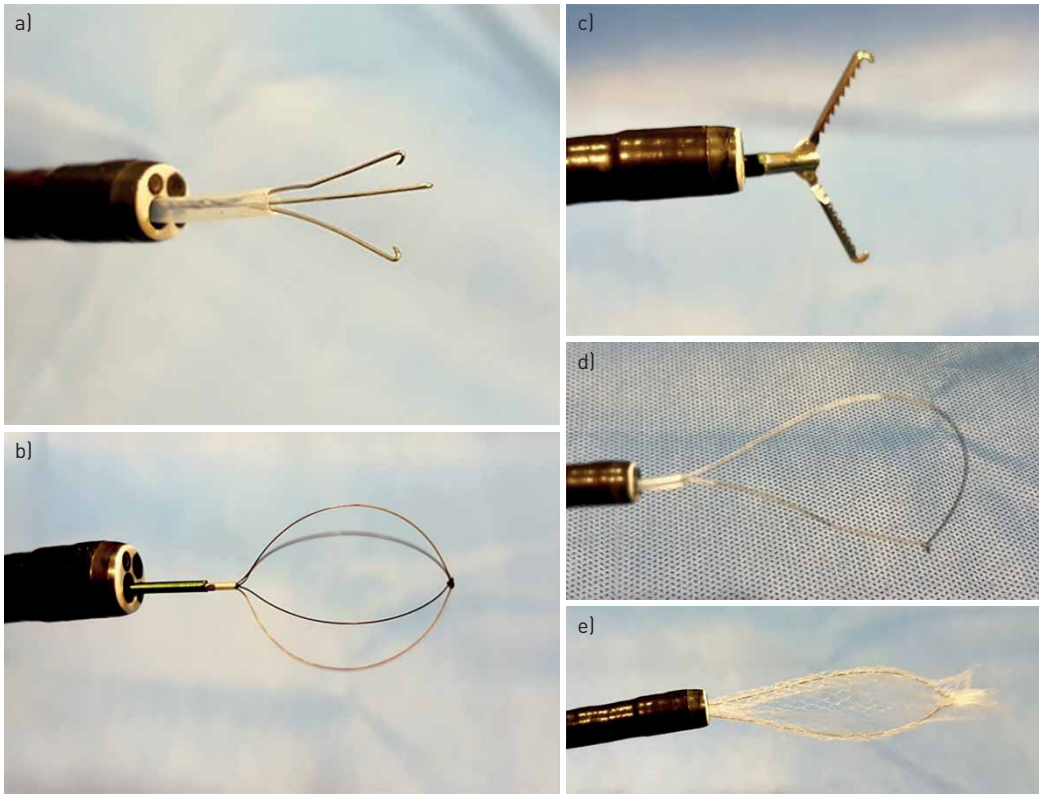

Figure 1. Bronchoscopy tools used for foreign body extraction: a) tripod forceps, b) basket, c) crocodile-grip forceps, d) snare and e) fishnet.

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elsewhere in this *Monograph* [30]) is the first option when rigid bronchoscopy is not available. The efficacy of flexible bronchoscopy was evaluated in several studies. A systematic review and meta-analysis of 1185 patients found an efficacy rate of foreign body removal of 89.6% (95% CI 86.1–93.2; p<0.001) [28]. Oral entry should be performed to provide ample space during the foreign body extraction, to avoid damage to the nasal passage and to reduce the risk of foreign body loss during its passage through the upper airway. This predicament may be avoided using rigid bronchoscopy or an orotracheal tube. However, care must be exercised because the foreign body may be released while passing through the distal end of the tube. A few reports have described flexible bronchoscopy foreign body extraction in children through a laryngeal mask with good results [26].

The inspection should be thorough because the foreign body might be covered with granulation tissue, secretions or blood. We suggest using a thin bronchoscope during inspection (*e.g.* 4.9 mm outside diameter) when a subsegmental location is suspected. In a review of foreign bodies in adults, Blanco Ramos *et al.* reported that 43% of foreign bodies were covered with granulation tissue and 28% showed inflammation of the bronchial mucosa. The most common location of foreign bodies in both adults and children is the right bronchial tree [10]. A systematic review showed that 71% of foreign bodies were in the right bronchial tree, followed by 22.8% in the left bronchial tree and 5.7% in the trachea. Within the right bronchial tree, the right lower lobe was the most frequent location (33%), followed by the intermediate bronchus (27%) [28].

Foreign body removal

Upon visualisation, the nature and type (organic, inorganic, mineral, endogenous or miscellaneous) of foreign body may be identified. According to these characteristics and the location of the foreign body, physicians must choose which tools to use for extraction. Some of the options available are flexible forceps, ragged-tooth forceps, crocodile-grip forceps, snares, baskets, cryotherapy probes, balloon catheters and magnetic extractors [9, 10, 31–34].

For cases in which the foreign body is surrounded by granulation tissue (figure 2a and b), the use of techniques that reduce this tissue to release the foreign body and that reduce bleeding during extraction should be considered. In such cases, reasonable techniques to use include electrocautery, APC, Nd-YAG (neodymium-doped yttrium aluminium garnet) laser therapy or cryotherapy [34–38].

Extraction tools

Several tools are available to remove a foreign body. Although these tools may be used alone, bronchoscopists typically must use a combination of tools [28–31].

Forceps

Forceps extraction is a widely available method and is frequently used to extract foreign bodies [9, 10]. Forceps vary in design, shape and size, as well as in technical modifications that allow for improved mobility and grasping. Some forceps may be rotated through a manipulation system at the proximal end. When selecting forceps, the shape, size, material and location of the foreign body should be considered in order to achieve effective anchorage. For a firm grip, clinicians should opt for crocodile-teeth forceps (figure 1c). For foreign bodies that require more delicate handling, clinicians should choose W-shaped or

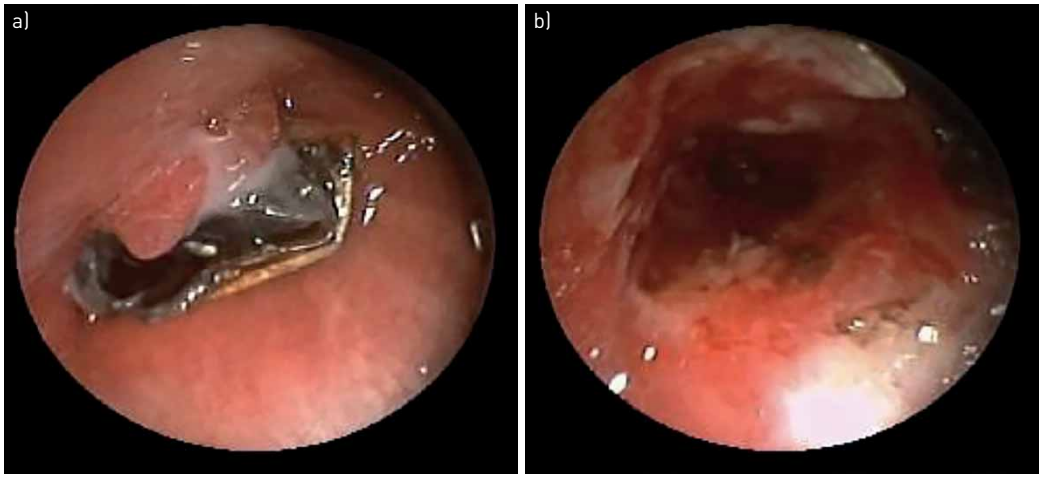

Figure 2. a) Plastic foreign body completely occluding the right upper lobe take off. b) After foreign body removal and argon plasma coagulation of granulation tissue.

covered-tip forceps. Forceps with tripod-type clamps and three semiflexible arms are available for semisolid foreign bodies (figure 1a). Importantly, a risk of losing the foreign body during passage through the subglottic zone and vocal cords exists. After grabbing the foreign body with the forceps and dislodging it, we advise bringing the distal end of the forceps towards the bronchoscope and applying continuous suction while removing everything together with the bronchoscope [34].

Baskets and snares

Baskets are variants of tools used by urologists and gastroenterologists to remove stones from the urinary or biliary tract (figure 1b). The basket has four wings that are retracted and that may be opened with proximal manipulation [11]. Baskets of different diameters exist that adapt to the size of the foreign body and its location. The technique consists of introducing the basket through the working channel of the bronchoscope, opening it inside the airway and ensnaring the foreign body. Another alternative is the fishnet, which was derived from gastroenterology and is useful for polypectomy (figure 1e). The fishnet is a fine wire mesh attached to the end of a loop. As the loop advances, it wraps around the foreign body until it is fully ensnared before final removal together with the bronchoscope. Different sizes of snares exist that may also be used, *e.g.* to grasp the head of a nail (figure 1d) [4, 11].

Balloon catheters

Many bronchoscopists underuse this tool. A balloon catheter (*e.g.* a Fogarty catheter) is introduced through the working channel of the bronchoscope and is advanced distal to the foreign body. Once the foreign body is passed, the balloon is inflated using 1–3 cm^3 of saline solution, and the catheter is moved proximally to dislodge the foreign body and move it towards the central airway. While in the central airway, it may be removed using standard tools. We recommend selecting balloons with a diameter between 4 and 7 French [10, 11].

Magnet extractors

These flexible probes have magnetic cylinders at their distal ends. The probe passes through the working channel of the bronchoscope and is useful to extract metallic bodies (*e.g.* nails, broken forceps or brushes, *etc.*) [35].

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Cryotherapy catheters

The cryoprobe uses nitrous oxide and carbon dioxide to freeze its distal end. This intervention (discussed in more detail elsewhere in this *Monograph* [39]) allows the foreign body to adhere to the distal end of the cryoprobe. Currently, two cryoprobe sizes are used: 1.9 and 2.4 mm. We suggest using the larger size to achieve a larger contact surface. Additionally, we recommend that the side of the cryoprobe tip be placed in contact with the foreign body. This method achieves a greater surface area of adhesion compared with the use of the distal end of the probe. This technique is particularly effective for extracting foreign bodies with a high liquid content (*e.g.* vegetables, fruits, insects and clots). Importantly, the cryoprobe must be removed together with the bronchoscope as a single unit. Damaging previously healthy bronchial tissue is a major complication of this procedure [32].

Nd-YAG lasers

Lasers are seldom used for foreign body extraction. One application of the Nd-YAG laser is the ability to cut metal objects (*e.g.* needles, coins, *etc.*); however, the clinician must use power settings >40–60 W and maintain close contact of the laser fibre with the object [36].

Injury caused by burning the airway is among the complications associated with the technique; thus, the inspiratory oxygen fraction should be reduced to <40%. Another potential complication is airway perforation [36].

Other alternatives

Distal impaction

The presence of a foreign body in the distal airway implies a greater challenge because the diameter of the airway decreases as it bifurcates and acquires greater angulation. When foreign body visualisation is not possible using a thin bronchoscope, fluoroscopy for radiolucent foreign bodies may be used to guide forceps or a balloon catheter and move the foreign body towards the central airway. Electromagnetic navigation may be used when attempting to reach radiopaque foreign bodies [4, 11].

Surgery

Surgical procedures should be considered as the last alternative when bronchoscopy fails to extract a foreign body. The most common cases are foreign bodies located in the distal airway at the subsegmental level that cannot be visualised with a bronchoscope. Additionally, bronchotomy extraction may be performed in patients with long-standing foreign bodies in whom the airway wall infiltrates the foreign body; however, a high risk of perforation exists during extraction [6, 8, 10].

Extracorporeal life support

This method has been reported in patients with asphyxia associated with severe respiratory failure resulting from foreign body aspiration. To date, evidence regarding this procedure is limited to a few case reports of patients with asphyxia associated with severe respiratory failure following foreign body aspiration. The use of extracorporeal life support is quite rare in cases of foreign body aspiration and does not pertain to initial management considerations [24].

Conclusion

A patient with foreign body aspiration may present with an acute episode of asphyxia with mild symptoms such as cough or with long-term consequences such as post-obstructive pneumonia, or the patient may be asymptomatic. A high index of suspicion must always be maintained. Bronchoscopy remains the most useful diagnostic and therapeutic tool. Rigid bronchoscopy is the preferred method for foreign body removal, particularly in children.

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Disclosures: None declared.

Chapter 18

Airway fistulas

Christophe Dooms and Jonas Yserbyt

Airway fistulas are categorised by their localisation (tracheo-oesophageal, bronchopleural or alveolopleural) and by aetiology (spontaneous or as the result of an intervention). The mainstay in the treatment of nonmalignant fistulas is surgical repair, although endoscopic treatment plays a potential role when surgery is considered to be morbid or technically unfeasible. In general, the grade of evidence for endoscopic interventions is low, with expert opinion guiding clinical practice, with the exception of the use of unidirectional valves to treat alveolopleural fistulas. The latter have been subject of several cohort studies. Spontaneous airway fistulas most often originate from neoplastic disorders, infection, or macro- or microscopic deformities of the subpleural region. In neoplastic disorders, the role of surgical repair is limited, since the occurrence of the airway fistula is often a consequence of locoregional advanced disease in which endoscopic treatment plays an important role in palliation.

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Airway fistulas are relatively uncommon but are associated with significant morbidity and mortality. Clinical signs or symptoms are related to the anatomical localisation. Tracheo-oesophageal fistulas (TOFs) present predominantly with respiratory symptoms, such as cough while swallowing. Broncho- or alveolopleural fistulas can be assessed whenever a chest tube is present, for example a continuous air leak in large bronchopleural fistulas or in patients on mechanical ventilation, or a (forced) expiratory air leak in alveolopleural fistulas.

Tracheo-oesophageal fistulas

An acquired TOF might be caused by either a malignancy or a nonmalignant entity. Regardless of aetiology, the symptoms and clinical signs are similar and predominantly respiratory, such as cough while swallowing, increased secretions, recurrent respiratory infection and inadequate nutrition with weight loss. In order to achieve a successful outcome, one must take into account the aetiology, accurate anatomical assessment and potential definitive treatment modalities. A complete evaluation consists of a clinical

Dept of Respiratory Diseases, University Hospitals KU Leuven, Leuven, Belgium.

Correspondence: Christophe Dooms, Dept of Respiratory Diseases, University Hospitals KU Leuven, 3000 Leuven, Belgium. E-mail: christophe.dooms@uzleuven.be

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examination, contrast-enhanced chest CT, bronchoscopy with or without methylene blue through the oesophagoscope in order to facilitate the identification of a very small TOF (figure 1a), and oesophagogastroscopy.

Most malignant TOFs occur spontaneously due to tumour invasion or as a complication during or after radiochemotherapy for oesophageal, lung or tracheal cancer. The choice of the appropriate treatment depends on the characteristics of the fistula, the patient's clinical state and the prognosis of the underlying disease. Most of these patients have an incurable cancer with limited life expectancy and mostly benefit from palliation by inserting either a fully covered oesophageal SEMS, or a tracheal silicone stent or fully covered SEMS. Stenting of TOFs in the oesophagus is preferred whenever a stenosis is present to secure the position of the stent, seal the fistula and also palliate dysphagia. In the absence of dysphagia or in the presence of a tracheal stenosis, the endoscopic placement of a tracheal stent (silicone or fully covered metallic stent depending on tracheal diameter and shape) is preferred. Ideally, the chosen stent diameter should guarantee a firm sitting, and the coated

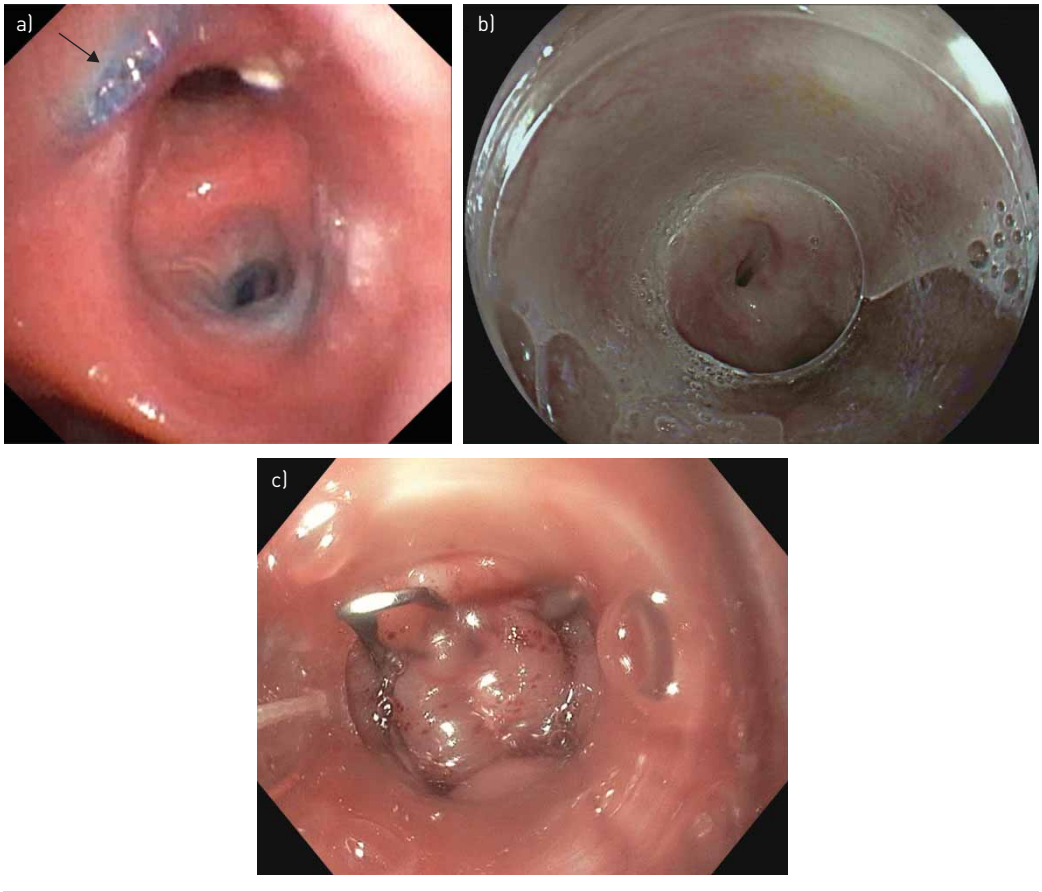

Figure 1. a) Bronchoscopy after methylene blue injection into the oesophagus with identification of a small 1 mm fistula at the posterior wall of the left upper-lobe bronchus (indicated by an arrow); b) upper gastrointestinal endoscopy with a transparent plastic cap attached to the distal tip showing a fistula of 3–4 mm with clean edges located at 30 cm from incisors at 9 am; c) successful closure of a small chronic broncho-oesophageal fistula with an over-the-scope clip system.

part of the stent should cover at least 1.5–2 cm of healthy wall proximal and distal to the fistula margins. The use of double (oesophageal and tracheal) stents is discouraged as this might cause pressure necrosis to the walls of both the oesophagus and the trachea between the two stents, which results in an enlargement of the TOF. Whenever the TOF is close to the main carina, a silicone or self-expandable Y-stent should be considered.

The aetiology of an acquired nonmalignant TOF can be a tracheal post-intubation injury, or prior oesophageal or tracheal surgery. Spontaneous closure in these cases is rare. Surgical correction is considered the gold standard for a nonmalignant TOF and typically requires fistula division with oesophageal repair, and tracheal repair or tracheal resection with airway reconstruction for small or large TOFs, respectively [1]. Surgery comes with an operative mortality of 3–5% and a recurrence rate as high as 11%, even in high-volume centres [2, 3]. Technically, an endoluminal stent, either in the oesophageal or the endotracheal position, might seal a nonmalignant TOF, but a mature TOF cannot heal with a stent in place. As a result, stenting is not regarded as a long-term solution. A stent can be considered temporarily as a bridge to surgical repair for very selected cases in which an improvement of the patient's pulmonary and/or metabolic status is deemed necessary prior to surgery (figure 2). A recently introduced alternative to small TOFs is an endoscopic over-the-scope clipping. The fistula and surrounding oesophageal tissue are suctioned into a cap fitted on to the tip of the endoscope (figure 1b) and a clip is deployed (figure 1c). This clip provides circumferential approximation by encircling the defect, folding and compressing the gathered tissue towards the centre with all of the tissue edges approximated within the clip perimeter [4, 5].

Bronchopleural fistulas

Dehiscence of an end-to-end surgical anastomosis

Lobar resection with bronchial reconstruction and bronchial resection without lobar resection are often performed as lung-sparing surgical procedures, having in common the performance of bronchoplasty with bronchial re-anastomosis or reconstruction [6]. Overall, bronchial sleeve resections can be performed with a low risk of bronchial anastomotic complications, but a bronchopleural fistula might occur as a result of ischaemia or excessive tension. A recent review on the subject showed that the prevalence of bronchopleural fistulas or dehiscence after sleeve lobectomy ranges from 1.1% to 9.3% [7]. In the early postoperative period, the clinical suspicion of bronchopleural fistula is raised whenever a postoperative air leak persists or subcutaneous emphysema is increasing. When respiration or haemodynamics are compromised, this can potentially be life-threatening. Less often, bronchopleural fistulas can occur in the long term, most frequently presenting as a pleural infection.

The management of anastomotic problems after sleeve resections is often very challenging. Some authors recommend a surveillance bronchoscopy early after such bronchoplasty in order to identify potential threats. Surgical revision of the anastomosis is considered the standard treatment [7]. Endobronchial treatment strategies are considered less frequently applicable, as stenting of the anastomotic area after sleeve lobectomy is often technically challenging due to a short remaining main bronchus and/or segmental bronchi located very close below the anastomosis. A recently developed silicone OKI-stent (Novatech GSS) or small-sized silicone Y-stent (Novatech GSS) might be a solution in selected cases [8].

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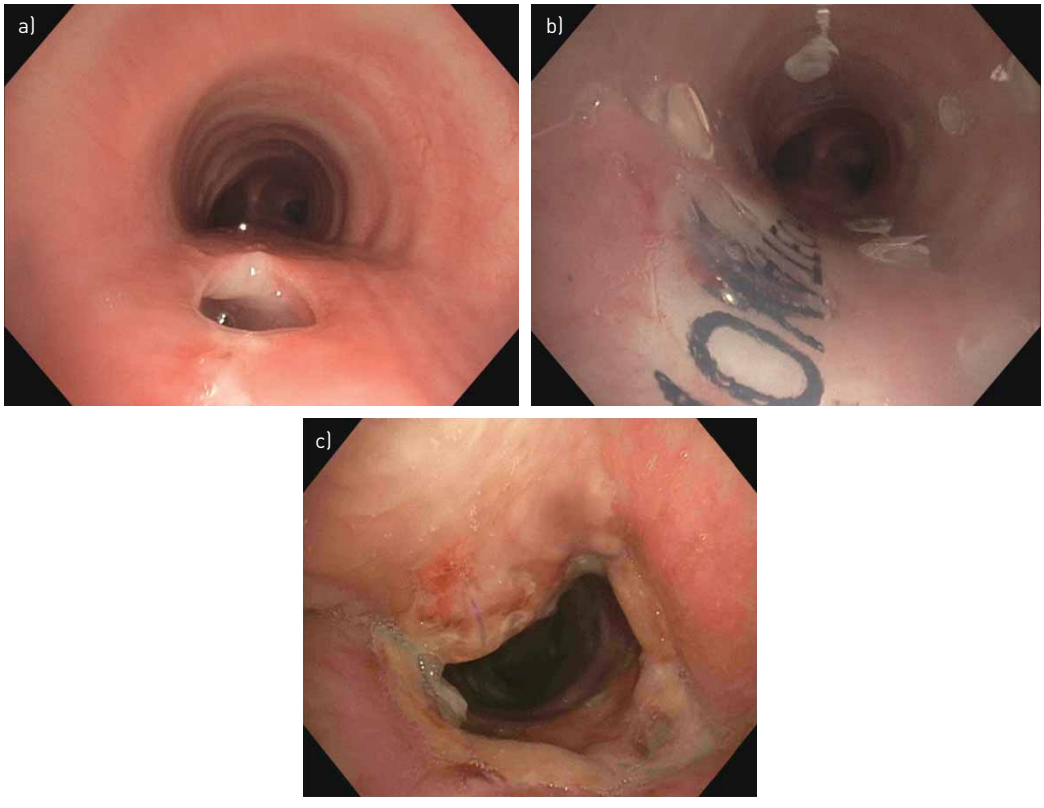

Figure 2. a) Bronchosocpy performed 2.5 years after minimally invasive oesophagectomy for oesophageal cancer showing a trachea-neogastric fistula with clean edges of size 8 mm and located at the pars membranacea 5 cm proximal to the main carina; b) a temporary tracheal silicone stent of 50×18 mm inserted successfully to cover the fistula; c) after a 6-month interval, the stent has been removed, and a one-stage tracheal transection and resection of the fistula with gastric and tracheal repair has been performed.

A retrospective series of 218 patients subjected to sleeve lobectomy for nonsmall cell lung cancer reported a bronchial anastomotic complication in 14 patients: seven patients required re-operation, three required airway stenting, two were managed conservatively and two were fatal [9]. Another retrospective series of 108 patients who underwent a bronchial sleeve resection reported dehiscence in seven patients of whom all but one healed conservatively, and bronchopleural fistulas in three patients of whom two were covered by a silicone bronchial stent and one healed conservatively [10].

Since its introduction in the early 1960s, lung transplantation has evolved from an experimental surgical intervention with excess morbidity and mortality to the treatment of reference for end-stage respiratory diseases. As the transplantation volume increases, anastomotic complications and more specifically dehiscence or (less frequently) bronchopleural fistulas are important determinants of morbidity and even mortality [11–13]. Anastomotic complications have classically been described in the Shennib and Massard classification, a classification of stages of healing taking into account the macroscopy of ischaemia/necrosis and the phenomena of healing (granulation, stricture, malacia), without taking into account the fact that different stages can coexist [14]. The Groupe d'Endoscopie de Langue Française proposed the MDS classification (currently under prospective

validation), which overcomes this limitation, taking into account the macroscopic aspect, the diameter of the anastomosis and potential suture dehiscence [15]. In general, most cases of limited disruption of the anastomosis may evolve favourably without any intervention [13]. There is a role for protective ventilator strategies, early extubation and anti-infective/antifungal treatment, since anastomotic defects may be rapidly covered with fibrin or granulation tissue. Severe dehiscence is often life-threatening, and urgent surgical re-intervention is mandatory, although the risk of transplantectomy is considerable [11]. In all other cases of dehiscence after lung transplantation, a thorough clinical and multidisciplinary assessment is important before deciding to intervene. The use of bronchial stents to treat dehiscence after lung transplantation is less obvious than their use in the case of anastomotic stenosis or malacia [16]. The introduction of a rigid bronchoscope in the anastomotic region comprises a risk for increasing dehiscence, especially when the region is ischaemic or infected. Concerning the use of airway stents, silicone stents are preferred over a partially covered SEMS for all benign bronchial complications, although the insertion of a SEMS in the case of anastomotic dehiscence is technically easier than the insertion of a silicone stent [17–20]. The use of a fully covered SEMS might combine the technical feasibility of a partially covered SEMS with the full covering feature of silicone stents, but sufficient data on their use in lung transplantation are currently lacking. In our own experience, only four cases of a bronchopleural fistula after lung transplantation were treated with stent insertion over an 8-year time period. In two cases, a silicone stent was successfully removed after 1 and 3 years, respectively [8]. In one case, further dehiscence occurred after SEMS insertion necessitating transplantectomy, and in the other case, two attempts to extract the SEMS led to re-insertion of a third covered SEMS that was left in place permanently. Specific treatments for bronchopleural fistulas have been described in case series and consist of bronchoscopic treatment or surgery, whereas other reports only consider surgical re-interventions in the case of anastomotic dehiscence [21–23].

Dehiscence of a surgical stump

A bronchopleural fistula is a serious complication after lung resection, with an incidence of <1% after lobectomy and 5% after pneumonectomy [24]. The treatment should focus on both the fistula itself and the health status of the patient. The management of a bronchopleural fistula includes conservative treatment and various bronchoscopic or surgical procedures. As randomised or controlled studies comparing these options are lacking, the best treatment to be adopted depends largely on the size, site and morphology of the bronchopleural fistula in combination with expert opinion and knowledge of retrospective case series. Conservative treatment allows a spontaneous closure, which is obtained during chest-tube drainage, and should certainly be considered in very small fistulas, while some series have reported on success with this conservative treatment in larger bronchopleural fistulas [25–27]. Bronchoscopic treatment can be added to this conservative approach and can consist of the closure of a 1–3 mm fistula using biological (*e.g.* fibrin) or synthetic (*e.g.* cyanoacrylate) glues with adhesive and sealer properties, with the highest success rate in fistulas of 1 mm [28]. For the definitive bronchoscopic treatment of bronchopleural fistulas ranging from 3 to 6 mm, the use of spongy calf bone or polyvinyl alcohol sponge and glue are available strategies [29, 30]. In bronchopleural fistulas, temporary or definitive fistula coverage has been reported with placement of endoscopic devices such as silicone or a fully covered SEMS or atrial septal occluder devices such as the Amplatzer septal occluder (St Jude Medical, Minneapolis, MN, USA) (figure 3) [28, 31–33]. Definitive closure of a bronchopleural fistula of ⩾6 mm by a bronchoscopic

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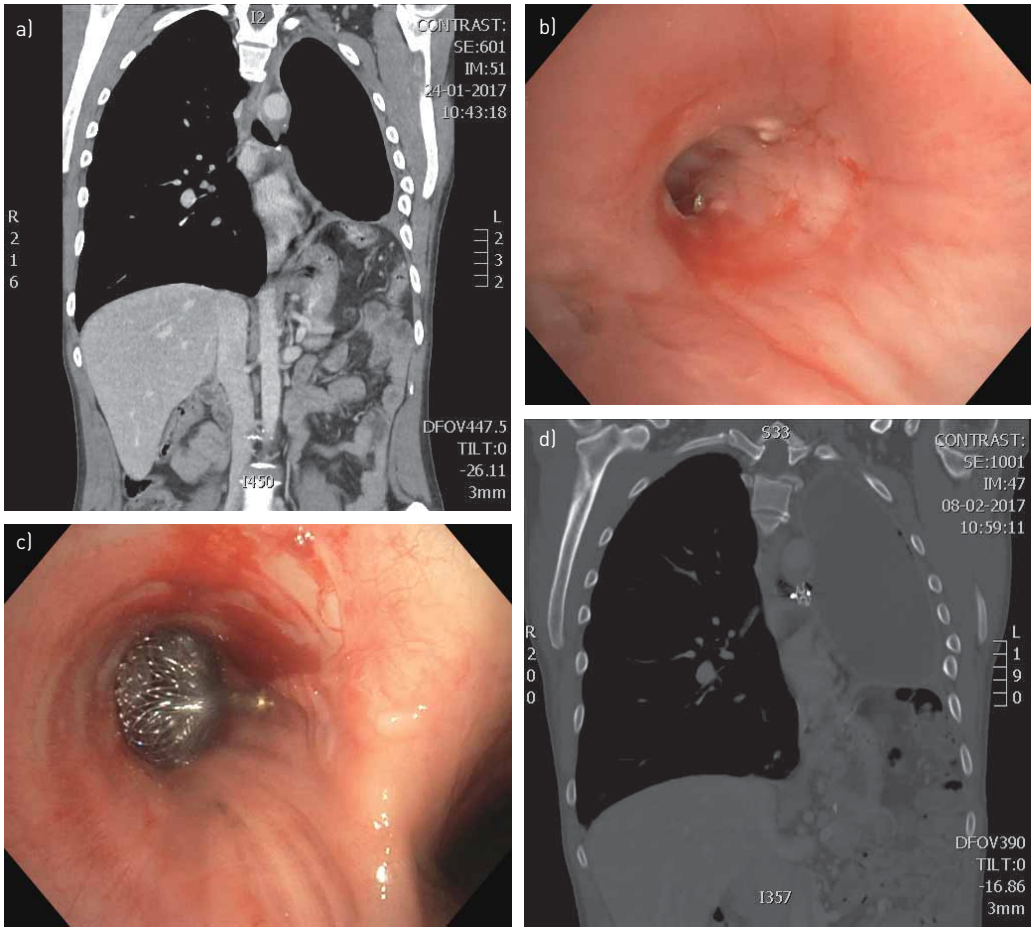

Figure 3. a) Chest CT showing bronchopleural fistula at the left bronchial stump; b) video bronchoscopy showing a partial bronchopleural fistula; c) video bronchoscopy showing an Amplatzer septal occluder (St Jude Medical, Minneapolis, MN, USA) immediately after its placement; d) chest CT showing an Amplatzer septal occluder 2 months after its placement.

intervention represents a rarity, and surgical repair is therefore the preferred approach whenever feasible.

Alveolopleural fistulas

Alveolopleural fistula as a complication after thoracic surgery

Thoracic surgery to the lung, such as pleural decortication for pleural mesothelioma, lung volume reduction surgery (LVRS) for severe emphysema, diagnostic wedge resection for a suspected pulmonary nodule, and anatomical segmentectomy or lobectomy for lung cancer, may be complicated by an alveolopleural fistula. The reasons for a postoperative pulmonary air leak are mechanical injury of the visceral pleural surface, stapler line disruption or tension tears near the stapler line, or tears from divided adhesions. The treatment of choice for a postoperative pulmonary air leak is watchful waiting with drainage through a chest

tube under reduced suction or an early water seal, as >90% of air leaks stop spontaneously, while an aggressive re-intervention is needed in <2% of cases [34]. There is no standard definition for a persistent pulmonary air leak, but most literature data define a persistent pulmonary air leak as an air leak that is still present on day 5 after any surgical intervention. Persistent pulmonary air leaks lead to increased length of hospital stay, decreased patient satisfaction, and increased morbidity and cost. Multiple treatment options are available for persistent pulmonary air leaks, such as discharge with a Heimlich valve, talc pleurodesis, and endobronchial techniques and devices. However, no clear statements and little evidence-based guidance for interventions have been published. Endobronchial techniques include endobronchial silicone plugs (Novatech SA, La Ciotat, France), an endobronchial autologous blood patch, and endobronchial valves such as the Spiration Valve System (Spiration Inc., Redmond, WA, USA) and Zephyr endobronchial valve (Pulmonx Corp., Redwood City, CA, USA) [35–37]. Silicone plugs can significantly reduce the air leak, but migration and retro-obstructive infections have been reported, resulting in an overall limited success rate [38]. Autologous blood-patch pleurodesis remains controversial due to a lack of robust data regarding its efficacy, the technique of application and its role in clinical practice [39]. Endobronchial valves are unidirectional valves that may reduce air flow through the leaking visceral pleura, facilitating local tissue healing and consequent closure of an alveolopleural fistula [38]. In 2008, the Humanitarian Device Exemption of the US Food and Drug Administration approved the use of an intrabronchial valve for a persistent post-surgical (after partial or complete lobectomy, or LVRS) pulmonary air leak, unless it is observed only during forced exhalation or cough (figure 4). Since then, additional data have been published on surgical and nonsurgical persistent air leaks (table 1). The success rate of valve treatment can be measured from the length of hospital stay, the time to chest-tube removal or the time to air-leak cessation (table 1). The use of endobronchial valves in persistent post-surgical pulmonary air leaks results in air-leak cessation 2–4 days after valve insertion and successful chest-tube removal in 85–90% of patients [42, 44]. An important limitation to valve treatment is that current

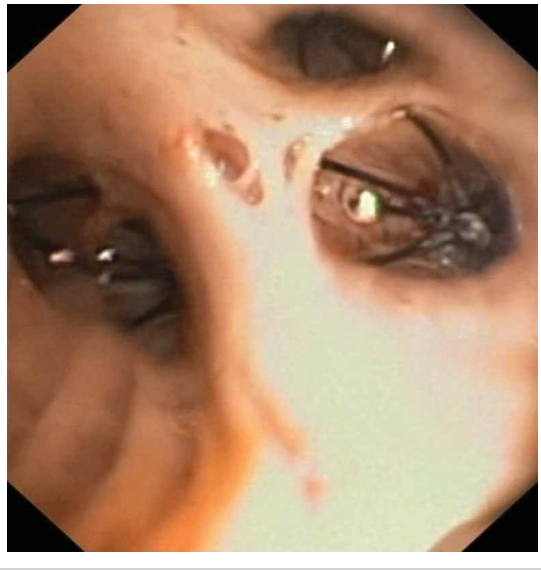

Figure 4. Video bronchoscopy showing four endobronchial Spiration valves (Spiration Inc., Redmond, WA, USA) placed within the right upper-lobe bronchi for a persistent postoperative air leak.

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Table 1 Overview of published cohort series evaluating the efficacy and safety of endobronchial valves for persistent alveolopleural air leaks

First author [ref.]	Study	ITT n	Treated n (%)	Aetiology[#]	Air leak days	Assessment	Air-leak stop days[¶]	Hospital days[¶]	Success rate in ITT %
Gillespie [40]	R	9	7 (78)	7/2	7.5	Visual (bubbles)	1	3	75
Firlinger [41]	R	16	13 (81)	9/4	17	Digital	NR	NR	63
Dooms [42]	P	10	9 (90)	10/0	7	Digital	2	NR	90
Hance [36]	R	NR	14	8/6	7.5	Visual	NR	4	57
Reed [37]	R	NR	22	8/14	11	Visual	NR	5	86
Bakhos [43]	R	15	11 (73)	8/3	11	Visual (digital)	10	7	66
Gilbert [44]	R	94	75 (80)	26/68	9	Visual	4	NR	67

ITT: intention-to-treat; R: retrospective; NR: not reported; P: prospective. [#]: ratio of surgical/nonsurgical; [¶]: numbers are expressed as the median.

evaluation of an air leak remains largely physician dependent, but the advent of digital drainage systems might enable a more objective assessment [38]. The assessment to guide valve placement should include a pre-test with balloon occlusion of the targeted airways using a digital thoracic drainage system in order to evaluate whether the air leak can be significantly reduced or stopped, and whether the patient clinically tolerates airway occlusion [42, 45]. The most important reasons for valve failure are valve dislocation or the presence of collateral ventilation. Complications related to endobronchial valves are uncommon and consist of a 1.5% reported incidence of empyema and a 10% need for additional procedures due to valve failure. Potential advantages for endobronchial valves clearly exist, despite the absence of comparative outcome data. Valves are less invasive than surgical re-interventions, have proven efficacy and are relatively easy to place with a low risk of procedural complications.

Spontaneous nonsurgical alveolopleural fistula

Pneumothorax is defined as the presence of air within the pleural cavity. The term "spontaneous pneumothorax" is used to contrast with provoked pneumothoraces (*e.g.* iatrogenic or traumatic). A spontaneous pneumothorax can occur in the absence of clinically apparent lung disease and is referred to as a primary spontaneous pneumothorax (PSP). A secondary pneumothorax occurs spontaneously in patients with lung disorders such as COPD, cystic fibrosis, pulmonary fibrosis, tuberculosis, cystic metastatic cancer and lung cancer. The discrimination between "primary" and "secondary" has been contested, since it could suggest the absence of any underlying cause provoking the air leak at the surface of the visceral pleura, a suggestion that is, of course, outdated since several papers have addressed the pathophysiology in these cases [46–50].

Although a spontaneous pneumothorax is not the most complex clinical topic in thoracic endoscopy, the practical management is subject to heterogeneity. This is in part related to the lack of uniformity among the different evidence-based guidelines [51]. However, the 2015 European Respiratory Society (ERS) task force statement on PSP was established to partially overcome these objections [52]. The emphasis in the strategy on facing a first

episode of PSP is on outpatient management, contrasting with earlier British Thoracic Society (BTS) and American Chest College Physicians (ACCP) guidelines [53, 54]. The treatment modalities are determined by the presence or absence of symptoms, rather than on the extent or volume of the pneumothorax. Following these principles, there are three appropriate options for the outpatient management of PSP, each with a different level of evidence. A conservative management of PSP might be indicated whenever dyspnoea is absent, aiming at the spontaneous resorption of air (anticipated at a resorption rate of 2% day^{-1}) [52]. Whether a conservative approach is efficient and safe in PSP is the subject of an ongoing Australian multicentric randomised trial for either conservative treatment or intervention [55]. In the presence of dyspnoea, manual aspiration in order to enable lung re-expansion is the mainstay of treatment, since it is supported by robust scientific evidence with an instant success rate of ~60% [56, 57]. A third option often referred to, but with only a low level of evidence, is the use of a small-bore catheter connected to a Heimlich valve, allowing outpatient management of the PSP. As a result of these emerging semi-invasive management options for PSP, most clinical algorithms nowadays state that insertion of a chest tube should be avoided in first episodes of PSP and is only appropriate when conservative management or manual aspiration fails. A pneumothorax in patients with underlying lung disease is often symptomatic, due to a reduction in respiratory capacity. This situation is potentially life-threatening and should be managed with chest-tube insertion. In cases of a persistent air leak or nonexpanding lung, evaluation and referral for endobronchial valve insertion or surgical intervention are recommended [53, 54]. For persistent air leaks due to pneumothorax, the BTS and ACCP guidelines recommend pleurodesis as the treatment of choice to prevent future recurrence [53, 54]. The pleural porosity pathophysiology of a spontaneous pneumothorax warrants chemical or mechanical pleurodesis as treatment, with a long-term success rate of >90% [58]. Some studies did evaluate the efficacy of endobronchial valves in spontaneous pneumothorax and reported a short-term success rate of ~60% [44]. This treatment option could be considered in patients with failed pleurodesis or in patients unable to undergo medical or surgical pleurodesis.

Severe pulmonary infections can cause parenchymal damage and formation of an alveolopleural fistula in continuity with the pleural space. The most commonly known causes are tuberculosis and bacterial pneumonia [59]. Some case reports suggest that endobronchial silicone plugs can control chronic tuberculous empyema with an alveolopleural fistula [60]. Recently, an association between HIV infection and pneumothorax with a persistent air leak has been mentioned as a result of *Pneumocystis jirovecii* infection leading to necrotising alveolitis with necrotic thin-walled cysts and emphysema-like bullae [53]. A spontaneous air leak can also occur in patients with a necrotic or cystic malignant pulmonary lesion [61]. An alveolopleural air leak can be the first sign of a malignant pleural mass due to direct invasion, or it can present as a complication of a tumour response to a successful cytotoxic treatment. Spontaneous resolution has been described, as well as chest-tube drainage with or without chemical pleurodesis [62–65]. Cases of endobronchial treatment with silicone plugs or endobronchial valves have been reported [66, 67].

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Chapter 19

Bronchoscopic lung volume reduction

Dirk-Jan Slebos, Karin Klooster and Nick H.T. Ten Hacken

Bronchoscopic lung volume reduction (BLVR) is becoming the last-resort treatment option for patients with severe emphysema where current pharmaceutical treatments are not sufficient and surgical treatments are contraindicated. Over the past decade a number of devices and techniques have been developed to accommodate the very different emphysema phenotypes. The treatment options can be divided into "blocking" and "nonblocking" techniques. Blocking techniques use unidirectional valves to induce the collapse of a single lobe. This treatment is currently the most effective and fully reversible option, although it is only possible in emphysema patients with absence of interlobar collateral ventilation. In patients who do not qualify for a blocking technique, nonblocking techniques using nitinol coils or "sclerosing" techniques, such as vapour ablation or sealants, can be used as an alternative. Due to the complexity of the disease, patient selection, treatment logistics and dealing with complications in these very diseased patients, BLVR should only be performed in centres of excellence where multiple options are available and using a multidisciplinary team approach.

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Bronchoscopic lung volume reduction (BLVR) is "the new kid on the block" in interventional pulmonology, and is becoming the last-resort treatment option for patients with severe emphysema where current pharmaceutical treatments are not sufficient and surgical treatments are contraindicated [1, 2]. During the past decade a number of bronchoscopic interventions have been developed to accommodate the very different emphysema phenotypes that exist [3]. By means of elegant and robust trial designs and repetitive solid outcomes, the use of BLVR as a treatment option for emphysema has also been acknowledged in the 2017 Global Initiative for Chronic Obstructive Lung Disease (GOLD) COPD recommendations (grading level B evidence) [4, 5]. Although lung volume reduction surgery (LVRS) still has a solid scientific and guideline position in the treatment of patients with severe emphysema, the actual use of the surgical approach is rather limited [6]. This is driven by limited surgical expertise worldwide, morbidity, the narrow indication window as defined by the National Emphysema Treatment Trial results [7] and current

Dept of Pulmonary Diseases, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands.

Correspondence: Dirk-Jan Slebos, Dept of Pulmonary Diseases/Interventional Bronchoscopy AA11, University Medical Center Groningen, PO Box 30001, 9700 RB Groningen, The Netherlands. E-mail: d.j.slebos@umcg.nl

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lack of confidence by referring physicians. The need for advanced treatments in severe emphysema and the small patient group that might benefit from LVRS drove the development of bronchoscopic alternatives. The current innovative bronchoscopic approaches are much less invasive compared with surgical treatments and are applicable in a greater population of patients with very severe COPD, thereby potentially serving a large need. Currently, BLVR is resulting in large patient referral numbers, thereby potentially also contributing to revisiting and reviving the use of LVRS [2, 8].

Hyperinflation in emphysema

Emphysema as part of the umbrella term "COPD" is characterised by a continuous loss of lung tissue. Chronic inflammation develops due to cigarette smoking or inhalation of toxic agents, leading to destruction of elastin and a weakened lung parenchyma. This loss of lung tissue is visualised in the flow–volume diagram by the well-known sudden drop in the first part of expiration, indicating an increased valve mechanism during forced expiration. In emphysema, reduced elastic recoil decreases the alveolar pressure, whereas loss of radial traction on airways decreases airway patency, both components contributing to a low FEV_1. The cardinal sign of emphysema is breathlessness during exertion, a phenomenon poorly associated with low FEV_1 and closely associated with hyperinflation. Breathlessness may introduce a vicious circle of avoidance of activities, leading to deconditioning, reduced exercise capacity and increased breathlessness. In particular, the work of Cooper and O'Donnell indicated that hyperinflation plays a key role in the feelings of dyspnoea and reduced exercise capacity in emphysema [9, 10].

Static hyperinflation in emphysema develops over many years (decades), and is due to the continuous loss of lung tissue and destruction of elastin. In contrast, dynamic hyperinflation is an acute process (minutes) due to the higher breathing frequency and reduced time to exhale completely during exercise. During exercise the dynamic hyperinflation on top of static hyperinflation leads to a reduced inspiratory capacity, which induces feelings of dyspnoea. These feelings result from the higher, yet less effective efforts of the inspiratory muscles to reward the increasing ventilatory needs. Inspiratory muscles in a hyperinflated state operate at a shortened resting length in an unfavourable position on the length–tension curve, thus the force generation capacity of the muscles is decreased. Additionally, the load against which the inspiratory muscles must operate is increased due to hyperinflation. In particular, when the inspiratory capacity approaches 0.5 L, this imbalance translates to high-intensity feelings of dyspnoea [9].

Different interventions are available that may improve hyperinflation and dyspnoea during exercise. Bronchodilators have been shown to reduce hyperinflation during exercise and improve exercise tolerance, yet the effect sizes are small [11, 12]. Their method of action is to decrease expiratory airflow resistance, leading to a better emptying of the lung at shorter expiration times. Supplemental oxygen during exercise improves exercise capacity in another way. Due to a lower ventilator drive the breathing frequency is lowered, also allowing more time to exhale between breaths and thus reducing dynamic hyperinflation. Pulmonary rehabilitation may decrease the ventilatory drive during exercise and slow down the respiration rate. Additionally, emphysema patients may learn to use "pursed lip breathing", which results in a longer expiration time, as well as improved airway patency [9, 10].

The most direct way to reduce hyperinflation is to deflate the lungs by bronchoscopic or surgical techniques. LVRS improves lung function primarily by better matching the size of the lungs to the thorax [13]. This increases the vital capacity, *i.e.* the major determinant of FEV_1, and consequently improves static and dynamic hyperinflation [13, 14]. BLVR techniques also attempt to improve static and dynamic hyperinflation, yet without the need for invasive surgery. Different bronchoscopic techniques have been developed, *e.g.* airway bypass stents, valve implants, coil implants, bronchial thermal vapour ablation and biological lung volume reduction, to accommodate different emphysema phenotypes. All these techniques aim to deflate the lung, but the mechanisms of action show important differences. Airway stents bypass the obstructed airways, one-way valves deflate target lobes during expiration (not allowing inspiration), coils lead to torqueing of the bronchi and increase the radial tension of the adjacent airway network, and thermal vapour ablation and biological lung volume reduction induce a local inflammatory and fibrotic reaction. The efficacy and adverse reactions of these techniques also show important differences, and depend on the different mechanisms of actions [2, 3].

BLVR techniques

Blocking techniques ("valves")

Endobronchial valve treatment

One-way endobronchial valve treatment is a bronchoscopic procedure designed to collapse an entire lobe to induce lung volume reduction in severe emphysema patients. These valves mimic the effects observed with surgical lung volume reduction by excluding the most diseased lobe of the lung and the result is potentially reversible. The endobronchial valves (Zephyr endobronchial valves; PulmonX, Redwood, CA, USA) are small self-expandable nitinol (shape memory wire) stents with a silicone coating and a unidirectional Heimlich valve incorporated in the body of the device (figure 1). The valves are available in different

Figure 1. Endobronchial one-way valve (Zephyr endobronchial valve; PulmonX, Redwood, CA, USA). Reproduced with kind permission from PulmonX.

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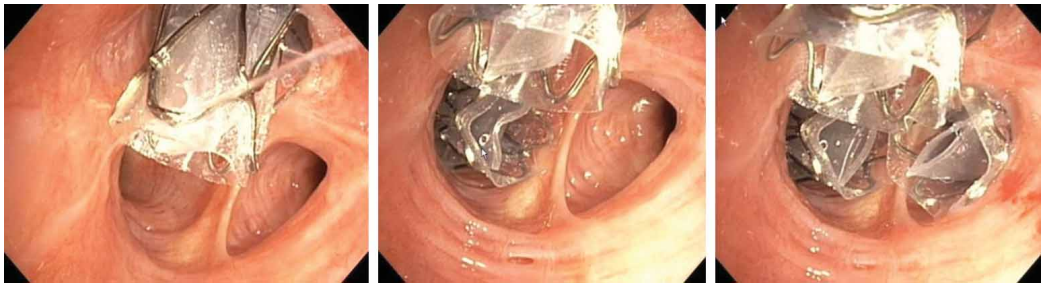

Figure 2. Bronchoscopic image of Zephyr endobronchial valve (PulmonX, Redwood, CA, USA) treatment of the right upper lobe, showing sequential placement of the valves in RB1, RB3 and RB2 to completely close the entire lobe ("lobar occlusion").

sizes to accommodate different airway dimensions. Endobronchial valves are delivered using a dedicated delivery catheter and should be placed in all segmental bronchi of the target lobe (figure 2). It is crucial that all valves are perfectly placed in order to allow the lobe to fully empty. Furthermore, the valve treatment will not be effective in situations where interlobar collateral ventilation is present between the target lobe and the adjacent lobe. Interlobar collateral ventilation can be detected by using the Chartis system (PulmonX) (figure 3). Pre-selection of potential treatment candidates can be done using chest CT fissure integrity analysis [15].

After the first efforts using one-way endobronchial valves [16] and the first feasibility trials showing promise [17, 18], the international multicentre (2:1) randomised controlled VENT trial was performed, investigating the safety and efficacy of endobronchial valve treatment in patients with heterogeneous emphysema. This study was undertaken in the USA (321 patients in 31 sites) as well as in Europe (171 patients in 23 sites), with the results being

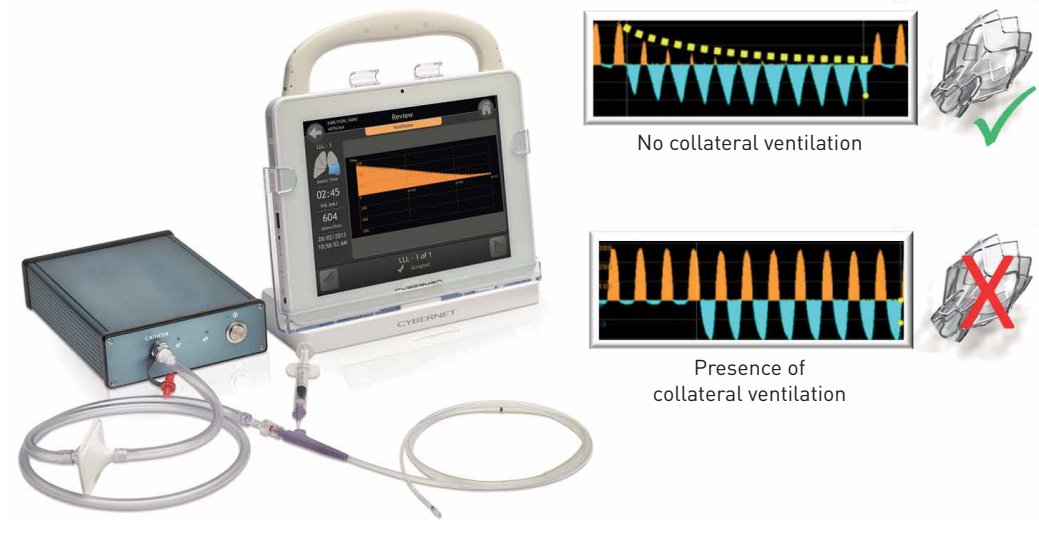

Figure 3. Chartis system (PulmonX, Redwood, CA, USA) to measure interlobar collateral ventilation. Absence of collateral ventilation qualifies a patient for valve treatment, whereas presence of collateral ventilation makes a patient unsuitable for this treatment [24, 26]. Reproduced with kind permission from PulmonX.

published separately for the two continents [19, 20]. The main inclusion criteria were COPD with a FEV1 15–45% predicted, residual volume (RV) >150% predicted and heterogeneous emphysema on a chest CT scan. In the US trial, FEV1 improved by +6.8%, 6-min walk distance (6MWD) by +19.1 m and the St George's Respiratory Questionnaire (SGRQ) score by −3.4 points (all $p<0.05$) [19].

In the European part of the trial, mean FEV1 improved by +6.5% and 6MWD by +5 m (both nonsignificant), with a change of −4.7 points in the SGRQ score ($p<0.05$) [20]. Although the overall trial results might have just reached statistical significance, the clinical responder rate was rather disappointing. However, a small group of patients did benefit very significantly from this treatment and *post hoc* analyses showed that a complete fissure (being a surrogate for absence of interlobar collateral ventilation) and a correct valve placement (meaning a full lobar occlusion with valves) resulted in a clinically significant improvement in outcome [19–21].

These *post hoc* insights of the VENT trial contributed to the understanding of the importance of having no interlobar collateral flow between the treated lobe and adjacent nontreated lobe. A (near-)complete interlobar fissure on chest CT scan might indicate such a situation, but it is still a surrogate for the real-life situation. Therefore, the development of the Chartis system to actually measure functional collateral ventilation created a breakthrough in patient selection for endobronchial valve treatment [22]. With the introduction of Chartis, responder rates in target lung volume reduction improved to 75% and set the standard for future trials [23, 24].

The first trials (both single-centre trials) prospectively using best-responder criteria for endobronchial valve treatment were the BeLieVeR-HIFi study (using CT fissure analysis to select patients) [25] and STELVIO trial (using Chartis to select patients) [26], and were the benchmark for subsequent larger randomised controlled studies. The BeLieVeR-HIFi study was a (1:1) randomised, full sham bronchoscopy controlled study in patients (n=50) with heterogeneous emphysema and a fissure completeness of >90% on CT [25]. Chartis was performed in all patients, but only used for *post hoc* analysis. At 3-month follow-up, FEV1 improved by mean +24.8% in the endobronchial valve group *versus* +3.9% in the sham control group. Median results showed an improvement in FEV1 of 8.8% in the treatment group *versus* 2.9% in the controls ($p=0.0326$), +25 m in 6MWD *versus* 3 m for the controls ($p=0.0119$) and −4.4 points in the SGRQ score *versus* −3.6 points for the controls (nonsignificant). However, when using the Chartis data, four patients in the treatment group had presence of collateral ventilation and thus no clinical benefit. Excluding these patients with collateral ventilation improved all clinical outcomes of this study [25].

In the STELVIO trial [26], 68 patients were (1:1) randomised to treatment with endobronchial valves or usual care, with a 6-month follow-up period. A re-bronchoscopy was allowed in this trial to adjust the initial valve placement in case of lack of target lobar volume reduction. Endobronchial valve treatment demonstrated a +20.9% improvement in FEV1 for the treatment group *versus* +3.1% for the controls, an improvement in 6MWD of +60 m for the treatment group *versus* −14 m for the controls and a SGRQ score difference of −14.7 points in favour of the treated *versus* the control patients (all $p<0.001$) [26]. This trial furthermore demonstrated the advantage of endobronchial valve treatment, as the valves can be removed or replaced to optimise outcomes and manage pneumothoraces, which was necessary in a third of all patients. The impact of endobronchial valve treatment in well-selected patients was furthermore shown by a significant and clinically very relevant

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improvement in physical activity as measured in steps per day, which showed a difference of 1340 steps per day between treatment and controls [27]. More recently, the 1-year follow-up results of STELVIO have been reported, including the data of the crossover to treatment results of the initial control patients [28]. The data show persistence of benefit of the treated patients, with significant improvements at 1 year in FEV1 (+17%), RV (−687 mL), 6MWD (+61 m) and SGRQ score (−11 points) (all p<0.001). All these improvements in a disease as severe as end-stage emphysema can contribute to a potential survival benefit. Although never scientifically proven, *post hoc* data and open-label single-centre experiences show strong signals that support this statement [29, 30].

All trials thus far have primarily focused on treating patients with a heterogeneous emphysema distribution. However, *post hoc* analysis using quantitative CT (QCT) analysis also showed solid significant results for pulmonary function, exercise and quality of life in patients with a homogeneous emphysema distribution [20, 26]. These findings were prospectively tested in the multicentre (1:1) randomised controlled IMPACT trial, where endobronchial valve treatment was evaluated in patients (n=93) with homogeneous emphysema in the absence of collateral ventilation (using Chartis). At 3 months after treatment, FEV1 improved by +13.7% from baseline in the valve treatment group *versus* −3.2% in the controls, 6MWD to 22.6 m *versus* −17 m and quality of life measured by the SGRQ score to −8.6 *versus* 1.0 points (all p<0.001) [31]. This trial clearly demonstrated the validity of endobronchial valve treatment in patients with a predominant homogeneous emphysema phenotype without collateral ventilation. This is an important finding, especially since the majority of these patients do not qualify for LVRS.

Recently, the data from the TRANSFORM trial, the first multicentre (2:1) randomised controlled trial in patients (n=97) with heterogeneous emphysema and absence of collateral ventilation (using Chartis), were presented [32]. At 6-month follow-up after endobronchial valve therapy, FEV1 improved +20.7% in the treatment group *versus* −8.6% for controls, with a between-group difference in RV of 700 mL, 6MWD of 78.7 m and SGRQ score of −6.5 points (all p<0.001). These findings confirm the earlier single-centre trial data experience from STELVIO [26] using best-responder criteria for endobronchial valve treatment [32].

Intrabronchial valve treatment

The Spiration intrabronchial valve (Spiration/Olympus, Redmond, WA, USA) is also a unidirectional valve mechanism with the same proposed mechanism of action as the endobronchial valves. The intrabronchial valve, however, has an umbrella-shaped design, which is compressed against the airway, thus acting as a valve mechanism. The intrabronchial valve is bronchoscopically placed by a special delivery catheter and comes in different sizes. Very precise airway sizing (using a special balloon sizing catheter kit) is crucial to obtain full lobar occlusion.

After an early pilot study with bilateral total occlusion of both upper lobes, showing a serious safety issue [33], the use of intrabronchial valves was promoted to be used bilaterally, but nonfully occluding by leaving one segment of a lobe untreated, and thus avoiding pneumothoraces. In a (1:1) randomised sham controlled multicentre study, patients (n=73) with upper lobe predominant heterogeneous emphysema were evaluated using this approach [34]. As anticipated, no pneumothoraces occurred. However, there were also no significant improvements in mean SGRQ, FEV1, RV and 6MWD. A second randomised controlled trial using the same treatment approach also failed to demonstrate significant clinical outcomes [35]. The bilateral nonoccluding approach was abandoned

after these trials. Driven by the results of the endobronchial valve trials and clinical expertise, intrabronchial valve treatment was thereafter only used in the same way as for endobronchial valves, *i.e.* complete lobar occlusion. In order to prove this concept, a very elegant trial was performed by EBERHARDT *et al.* [36], who in a single-centre (1:1) randomised controlled trial compared unilateral complete lobar occlusion with intrabronchial valves with the bilateral nonoccluding approach in upper lobe heterogeneous patients (n=22). As expected, the unilateral treatment group showed significant improvements in all clinical outcomes, whereas the bilateral nonoccluding approach resulted in no benefit [36].

Recently, the results of the very first (2:1) randomised controlled trial using intrabronchial valves as a unilateral full occluding treatment were reported in abstract form [37]. In this Chinese study (REACH study), heterogeneous emphysema patients (n=101) selected on the basis of having a complete fissure on CT as a surrogate for having no collateral ventilation (no measurement of collateral ventilation was performed) were evaluated. At 6 months after treatment, 67% of the patients showed a significant target lobar volume reduction on CT, with a mean reduction of 779 mL. Also at 6 months, mean FEV_1 improved to +12.9% for the treatment group *versus* −1.7% for controls ($p<0.001$) and the SGRQ score to −9.1 *versus* +3.5 points ($p=0.0023$). The pneumothorax rate was ∼8%. This trial clearly shows that the intrabronchial valve design also works in this patient group. Comparable to the BeLieVeR-HIFi results where endobronchial valves were used, also using CT fissure analysis only as the determinator to select patients for valve treatment, the outcome of valve treatment seems even more pronounced when adding Chartis as a physiological measure of collateral flow to the treatment algorithm. The two approaches have not been evaluated head to head, but comparing the results of the trials using Chartis *versus* the REACH study clearly shows the additional value of selecting-out patients with presence of collateral flow despite having a complete fissure on CT. To illustrate this, in the STELVIO trial [26] the target lobar volume reduction on CT was mean 1.3 L with a 88% response rate and in the TRANSFORM trial [32] the target lobar volume reduction was 1.1 L with a response rate of 89%. Retrospective analysis shows a quite similar predictive value of both dedicated CT fissure analysis and Chartis [38, 39], with an even higher predictive value when combining both techniques [40].

Choosing between the two commercially available valve designs will depend on local practice and expertise, ease of use, and product availability and marketing strategies. In the more experienced centres they are sometimes even used together in one patient, because each of them has its unique features. Whereas the endobronchial valve will more easily accommodate the different airway dimensions with less sizing issues and due to the design being compliant to the changes in airway diameter in COPD airways, the intrabronchial valve is more suitable for very difficult airway anatomical situations (especially the B6 segments).

Pneumothorax after valve therapy

A post-procedural pneumothorax is the most common complication after valve treatment, but should actually be regarded as being part of the procedure. This is because of the likelihood that it will happen, the experience needed to deal with the different types of pneumothoraces that arise and the fact that patients who developed a pneumothorax have a similar outcome compared with those who do not [15, 41, 42]. The sudden change in lung volume due to the valve-induced atelectasis causes a further decrease of the negative intrapleural pressure, and with subpleural bullae and adhesions being present can cause a pneumothorax. These pneumothoraces can be asymptomatic in the case of "*ex vacuo*"

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situations when the treated lobe is affected or highly symptomatic, requiring chest tube insertion when arising from the nontreated lobe. In the early endobronchial valve studies the pneumothorax ratio was ~4%, although in the most recent studies this increased to 20–25% due to optimal patient selection and more experienced treating physicians. This higher pneumothorax rate correlates perfectly with a much better outcome compared with previous low-rate pneumothorax studies [42].

A few attempts have been made to identify patients at risk for developing a pneumothorax, with high baseline RV, target lobar volume and presence of significant pleural adhesions associated with a higher pneumothorax rate [43, 44].

This knowledge can be used to discuss the risk of pneumothorax with the individual patient.

The treatment of a valve-induced pneumothorax is described in detail in an expert statement on this topic [42]. As the majority of pneumothoraces occur within the first days, it is recommended to keep these patients for observation in the hospital for 3–5 days with access to emergency chest tube placement after treatment. Dealing with these pneumothoraces is one of the reasons to organise high-volume centres of excellence, in order to be able to make this special pneumothorax management routine practice [15].

Nonblocking techniques

Coils

Lung volume reduction using endobronchial coils is another technique developed to treat patients bronchoscopically with advanced emphysema. The RePneu lung volume reduction coil (PneumRx Inc., Santa Clara, CA, USA) is a nitinol device (figure 4) that is delivered bronchoscopically using a special delivery system into subsegmental airways. About 10–12 coils, available in three sizes (100, 125 and 150 mm, to accommodate different airway lengths), are placed in the desired lobes under fluoroscopy to visualise positioning (figure 5). The procedure is preferably performed under general anaesthesia and patients generally stay in hospital for 1 night of observation after the procedure. The lung volume reduction coil procedure is a sequential treatment, with one lobe per procedure treated; the contralateral lobe is treated 4–8 weeks later. Bilateral treatment is needed to obtain optimal results. The coils have to be regarded as an implant and treatment is permanent. However, they are adjustable periprocedurally; long after the procedure, at most one or two coils can be removed when causing local problems, but only in experienced hands [45, 46].

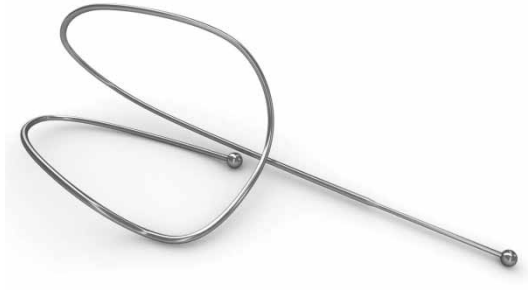

Figure 4. Endobronchial lung volume reduction coil (RePneu lung volume reduction coil; PneumRx Inc., Santa Clara, CA, USA). Reproduced with kind permission from PneumRx Inc.

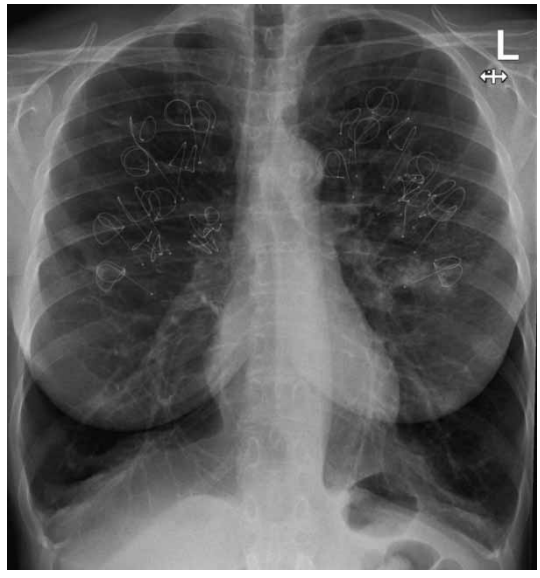

Figure 5. Bilateral endobronchial lung volume reduction coil treatment (RePneu lung volume reduction coils; PneumRx/BTG, Santa Clara, CA, USA) in a severe emphysema patient with 12 coils in the right upper lobe and 11 coils in the left upper lobe.

This treatment was first performed in a small safety study in 2008 in Heidelberg, Germany, in which up to six coils were placed per lobe [47]. After this, the coil treatment was further developed in Groningen, the Netherlands, using a new-generation coil and optimised by implanting 10–12 coils per lobe. This approach was tested in several feasibility trials in both heterogeneous as well as homogeneous emphysema patients [48–50]. These trials all showed a consistent outcome with significant improvements in pulmonary function, exercise capacity and quality of life. The mechanism of action of these coils seems multiple and more complex than with LVRS or valves. The coils do indeed induce lung volume reduction, restore the lung tissue elastic recoil, reduce airway resistance and work independent of collateral flow [45, 49, 51].

The first (1:1) randomised controlled trial using coils was the RESET trial [52], where patients (n=45) with both homogeneous and heterogeneous severe emphysema were treated bilaterally. In this trial, mean SGRQ score improved −8.4 points at 3 months post-treatment when compared with the control group (p=0.01). For the treated patients, FEV_1 improved by +10.6%, RV by −0.31 L and 6MWD by +64 m when compared with controls [52].

Subsequently, two larger randomised controlled studies investigating bilateral coil treatment *versus* usual care were performed. In the first trial, the French REVOLENS study [53], patients (n=100) with severe emphysema were (1:1) randomised. The primary 6MWD end-point was met, with 18 patients (36%) achieving the predefined 54 m improvement compared with nine patients (18%) for controls (p=0.03). Mean 6MWD difference at 12 months was 21 m (p=0.12), FEV_1 +11% (p=0.03), RV −0.36 L (p=0.004) and SGRQ score −10.6 points (p<0.001) [53].

The second trial, the international (USA, Canada and the European Union), multicentre (n=26) (1:1) randomised controlled RENEW trial, also evaluated the effect of coil treatment

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versus usual care in 315 patients with both severe homogeneous (77% of the included patients) and heterogeneous emphysema [54]. At 1-year follow-up, 6MWD for the treated patients improved +14.6 m (p=0.02), FEV1 +7.0% (p<0.001) and SGRQ score −8.9 points when compared with controls (p<0.001). *Post hoc* analysis showed more pronounced results, both statistically significant and clinically relevant, at 1 year after treatment for FEV1, RV, 6MWD and SGRQ score in patients with severe hyperinflation at baseline (RV >225% predicted) [54].

All trials performed with coils show a consistently higher number of patients having COPD exacerbations, pneumonias and noninfectious coil-associated opacities when compared with the control group patients, which tend to normalise longer after the initial treatment [52–54]. Remarkably, the occurrence of coil-associated opacities predicted a positive treatment response, this by inducing a larger lung volume reduction effect [54].

Small open-label studies show a gradual decline of the initial benefit from coil treatment 1–3 years after treatment, but with a significant group of patients still having a clinically meaningful benefit at 3 years [55, 56].

BLVR using endobronchial coils can be used independently of collateral ventilation and so can be used in patients who do not qualify for valve treatment. Furthermore, emphysema patients with a homogeneous or heterogeneous phenotype can be considered for treatment. Selecting patients with severe hyperinflation, severe emphysema and avoiding significant airway disease (asthma, chronic bronchitis, bronchiectasis) is key to success [15, 45].

Bronchoscopic thermal vapour ablation

BLVR using steam is called bronchoscopic thermal vapour ablation (InterVapor; Uptake Medical Technology, Seattle, WA, USA). This therapy uses bronchoscopically applied heated water vapour delivered *via* a dedicated system and catheter (figure 6) to induce a localised inflammatory reaction and tissue damage, followed by permanent fibrosis and local atelectasis resulting in the desired lung volume reduction [57, 58]. As a result,

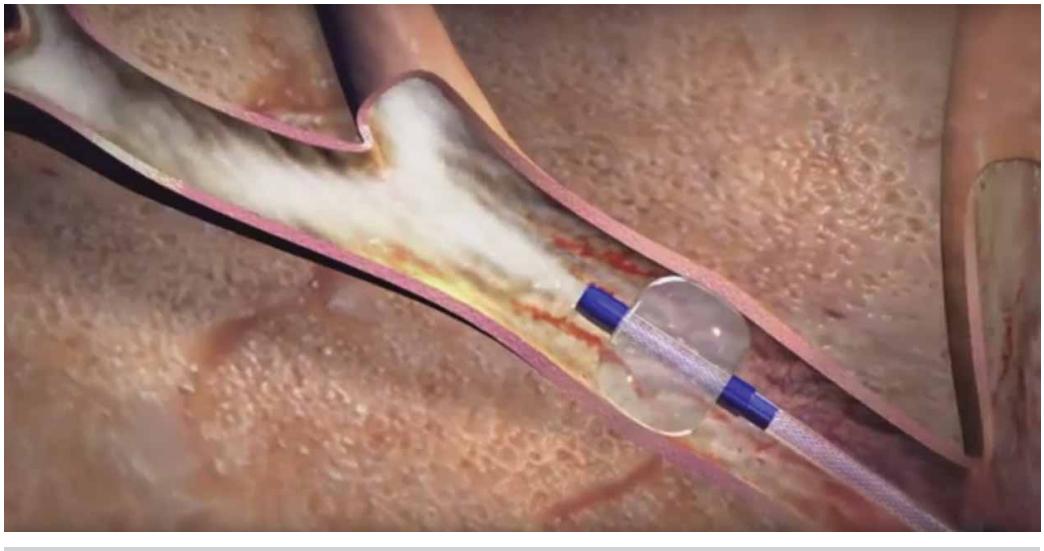

Figure 6. Bronchoscopic thermal vapour ablation (InterVapor; Uptake Medical Technology, Seattle, WA, USA). Cartoon showing actual segmental bronchoscopic treatment.

bronchoscopic thermal vapour ablation can be used independent of inter- or intralobar collateral flow. For safety reasons, bronchoscopic thermal vapour ablation is best performed using sequential bronchoscopies in a staged manner, by selecting the most damaged emphysematous segments. The induced fibrosis and scarring is permanent, and the treatment can be repeated over time [59, 60]. The main complication is caused by the inflammatory response to the energy delivered in the treated segments. Patients can be asymptomatic or develop pneumonia-like symptoms, starting after the first week after treatment and resolving within 2–3 months [60].

The first clinical trials performed showed a significant clinical benefit of the treatment in patients with severe heterogeneous emphysema. However, because of the high dose of energy delivered and the lung segments being treated in one procedure, the safety of this approach was of concern [61, 62]. As a result of these safety issues, the approach of using vapour ablation was changed to using lower energy and distributing the treatment over two sessions. This approach was successfully tested in the STEP-UP study, a multicentre (2:1) randomised controlled study evaluating the outcome of bronchoscopic thermal vapour ablation (using two sequential bronchoscopic procedures with a 3-month interval) in patients (n=70) with upper lobe predominant heterogeneous emphysema [60]. At 6-month follow-up, mean difference between the active treatment group and controls for FEV_1 was +14.7% ($p<0.001$), 6MWD +30.5 m ($p=0.06$), RV −0.30 L ($p=0.015$) and SGRQ score −9.7 points ($p=0.0021$) [60]. Recently, the 12-month follow-up data [63] from this trial showed a between-group difference for FEV_1 of +12.8% ($p=0.0039$), −237 mL for RV ($p=0.075$), +3.6 m for 6MWD ($p=0.844$) and −12.1 points for SGRQ score ($p=0.0021$), thereby indicating persistent benefit in quality of life, but a slow decline in functional parameters over time, which is comparable to the results of all nonblocking techniques available to date [53, 54, 60].

Lung sealant

BLVR using AeriSeal emphysematous lung sealant (PulmonX), sometimes also referred to as biological lung volume reduction, is the second sclerosing lung volume reduction

Figure 7. AeriSeal emphysematous lung sealant (PulmonX, Redwood, CA, USA). Image showing the two components that make the AeriSeal foam: vial A containing aminated polyvinyl alcohol and vial B containing glutaraldehyde. Reproduced with permission from PulmonX.

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therapy, next to the vapour ablation. The lung sealant is a cross-linking compound and is made from aminated polyvinyl alcohol (4.5 mL, 2.1% w/v) and glutaraldehyde (0.5 mL, 1.25% w/v) (figure 7). These two compounds are mixed with air to a foam and then delivered immediately using a dedicated catheter *via* a bronchoscope to the desired segments. The lung sealant closes off smaller airways and alveoli, and locally blocks collateral channels, preventing gas from entering the region and leading to absorption atelectasis. Secondarily, the sealant causes an inflammatory response producing a healing fibrotic reaction, inducing the desired lung volume reduction effect. Thus, as with all nonblocking techniques, its efficacy is not influenced by collateral ventilation [64]. Due to the abundant inflammatory response, which can start within 24 h after treatment, patients will have to be treated prophylactically with antibiotics and corticosteroids.

Since 2009, AeriSeal has been evaluated in several clinical trials showing very promising efficacy results. However, in the first trials larger dosages of AeriSeal, sometimes even in bilateral single procedures, were used, causing serious safety issues because of the inflammatory reaction [65, 66]. This approach was also evaluated in the ASPIRE study, a multicentre (2:1) randomised controlled trial in patients (n=57 patients evaluable at 3-month follow-up) with advanced upper lobe predominant emphysema [67]. Unfortunately, the study was terminated after 95 out of 300 planned patients were randomised due to financial problems with the sponsor. Fortunately, the available 3-month data were published and showed a median FEV_1 improvement of +11.4% for the AeriSeal treatment *versus* −2.1% in the controls (p=0.0037). The SGRQ score improved −11 points for the treatment *versus* −4 points in the controls (p=0.026). Six-month follow-up data were also available for fewer patients, but still showing a statistically and clinically significant benefit for the treated patients. Comparable to the earlier bronchoscopic thermal vapour safety issues, there was also a high number of adverse events.

As a result of the lack of financing and the inflammation-induced adverse events, this technology has also been redesigned to a sequential procedure using only 20–25% of the previous AeriSeal dosages. This approach is currently being tested in a new clinical trial (STAGE trial; ClinicalTrials.gov: identifier NCT02877459).

Airway bypass

BLVR using an airway bypass is an entirely different approach to treating severe emphysema patients. The airway bypass technique uses the presence of inter- and intralobar collateral ventilation to empty the lung on exhalation by creating a direct access between the lung and main bronchi. This is performed by bronchoscopically making extra-anatomical passages (the "airway bypass") and supporting these with drug-eluting stents to promote patency (figure 8). This concept was tested in the multicentre (1:1) randomised, full sham bronchoscopy controlled EASE trial [68]. This trial showed proof of concept of the airway bypass by a significant improvement in pulmonary function 1 day after the procedure. However, the effects disappeared within a few months, caused by loss of patency of the airway bypass. Alternatively, a surgical approach of creating a transthoracic airway bypass to deflate the emphysematous lung has been developed and investigated. This creative approach also proved the efficacy of the airway bypass concept [69, 70]. However, this approach also failed due to lack of solid financing and passage patency issues. Due to the striking immediate effects seen in these severely diseased emphysema patients, the airway bypass is still a concept to investigate and develop further in the future [71].

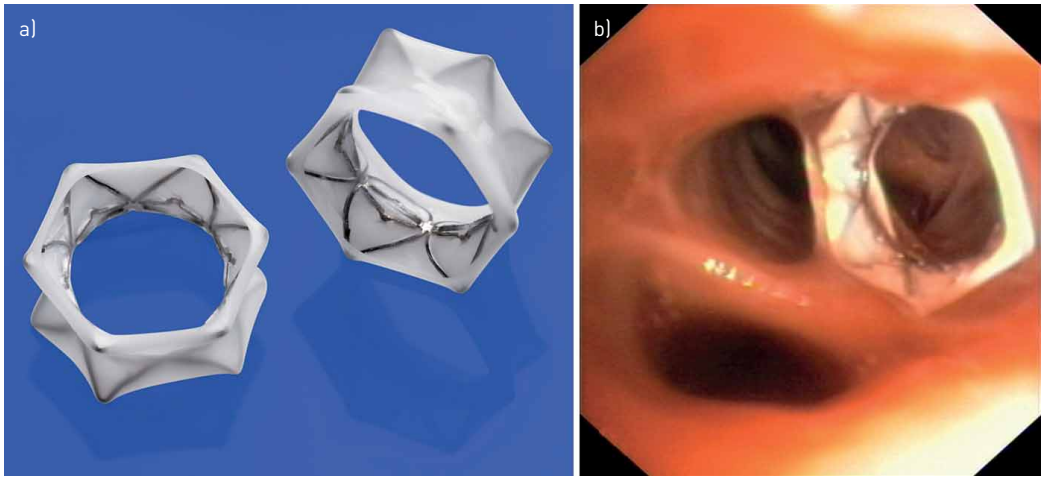

Figure 8. a) Airway bypass paclitaxel drug-eluting stents (Exhale stent; former Bronchus Technologies, San Jose, CA, USA). b) Example image of a newly created passage to the lung tissue using an airway bypass supported by an Exhale stent.

Patient selection

Selecting the right emphysema phenotype for the right treatment is crucial for a successful outcome. Due to its complexity, this should be performed in a multidisciplinary team setting with knowledge of COPD, rehabilitation, radiology, interventional pulmonology and surgery. The important selection criteria key words are: "emphysema", "symptomatic", "hyperinflation", avoidance of "comorbidity" and "infectious lung disease".

Assessment of the patient's chest CT scan is crucial for selection. To evaluate patients for BLVR, a thin slice (1 mm) volume CT scan should be acquired, ideally in both inspiration and expiration. This is to allow reconstruction in all three planes, screening for nodules, precise emphysema phenotyping and fissure analysis. Ruling out severe underlying pathology incompliant with lung volume reduction, *e.g.* severe airways disease, bronchiectasis, suspected lung cancer or ILDs, can be done by eyeballing by a radiologist. However, QCT analysis will have to be used to assess the severity of emphysema destruction and distribution, lobar volumes, amount of lobar air trapping, and fissure

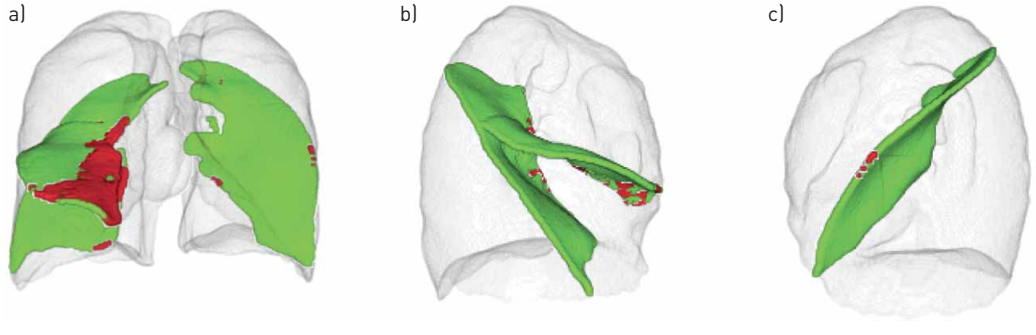

Figure 9. Three-dimensional rendering of the interlobar fissures using quantitative CT analysis (Thirona, Nijmegen, The Netherlands) to assess fissure integrity: a) coronal, b) sagittal right lung and c) sagittal left lung.

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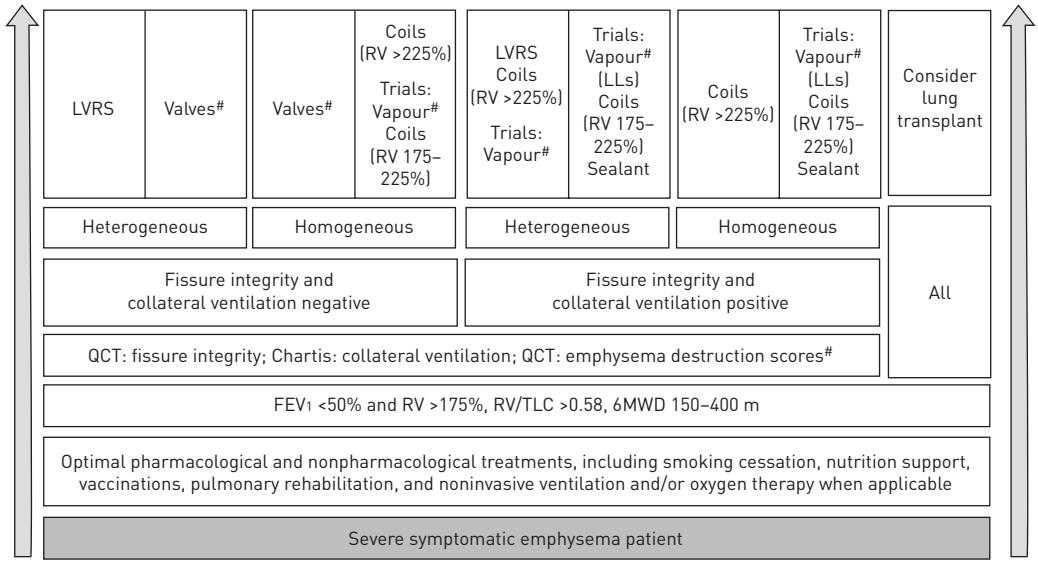

Figure 10. Flowchart of selection for bronchoscopic lung volume reduction in patients with severe emphysema. This scheme should be read from bottom to top and starts with selecting emphysema as the predominant COPD phenotype. All these patients should be on optimal medical treatment before considering advanced treatment options. The next criteria involve hyperinflation defined by having at least a residual volume (RV) of >175% predicted and RV/total lung capacity (TLC) >0.58, both measured by body plethysmography (note: these are minimal criteria). 6-min walk distance (6MWD) is advised to be 150–400 m, with the lower threshold being crucial for safety. Assessing emphysema severity and fissure integrity should be performed using quantitative CT (QCT) analysis to check for lobar destruction, lobar volumes and the presence of a potential complete fissure. If the interlobar fissure is >80% complete on QCT, a Chartis measurement is performed to check for absence of collateral ventilation. Depending on the emphysema distribution and absence of collateral ventilation, the available treatment options can be discussed with the patient. It should also be remembered that patients also have valid surgical alternatives such as lung volume reduction surgery (LVRS) and lung transplantation. #: only to be used in patients with higher emphysema destruction scores. Reproduced and modified from [6] with permission. LL: lower lobe.

analysis (figure 9) [40, 72]. Emphysema heterogeneity in lung volume reduction terms is the difference in the emphysema scores between ipsilateral lobes. There is no definition of heterogeneity, but >25% between-lobe difference in destruction at −910 Hounsfield units or >15% difference at −950 Hounsfield units are commonly used thresholds. Although the presence of emphysema heterogeneity becomes less important to select patients for both valve and coil treatment, it is still very important to select the most diseased lobe(s) to target. This can be done by combining the QCT parameters (destruction, volume, air trapping) with perfusion data (using nuclear scanning) [6].

Guidance on selecting patients has been published by an expert panel [6], and will be updated frequently based on new trials published and novel insights and techniques. It is crucial to only treat symptomatic emphysema patients without any serious comorbidity that can affect the procedure, anaesthesia or limit the ability to survive adverse events. The flowchart in figure 10 shows how to select the treatment option fitting the patient's phenotype.

Conclusion

BLVR is a minor invasive treatment option for patients with severe emphysema. Various devices have been developed to accommodate the very different emphysema phenotypes that

Table 1. Summary of results of randomised clinical trials on bronchoscopic lung volume reduction techniques for emphysema

	Patients n	Follow-up months	ΔFEV1 %#	ΔRV L#	Δ6MWD m#	ΔSGRQ score#
Endobronchial valves						
BeLieVeR-HIFi [25]	50	3	+20.9	−0.37	+33	−5.1§
STELVIO [26]	68	6	+17.8	−0.83	+74	−14.7
IMPACT [31]	93	3	+17.0	−0.48	+40	−9.6
TRANSFORM [32]¶	97	6	+29.3	−0.70	+79	−6.5
Intrabronchial valves						
REACH [37]	101	6	+14.6		+42	−12.6
Endobronchial coils						
RESET [52]	45	3	+10.6	−0.31	+64	−8.4
REVOLENS [53]	100	12	+11.0	−0.36	+21	−10.6
RENEW [54]	315	12	+7.0	−0.31	+15	−8.9
Vapour ablation						
STEP-UP [62]¶	70	12	+12.8	−0.24	+4§	−12.1
AeriSeal						
ASPIRE [67]¶	57	3	+13.5			−7.0

RV: residual volume; 6MWD: 6-min walk distance; SGRQ: St George's Respiratory Questionnaire. #: between-group differences. ¶: 2:1 randomisation (treatment:control); §: nonsignificant.

exist and the field is still very active in developing the highly necessary new treatment strategies. The level of evidence for each of them is very variable, from still very early stage (the sclerosing techniques) to adoption in the 2017 GOLD COPD recommendations (endobronchial valves and coils) (table 1). One-way endobronchial valve treatment is currently the most effective and also reversible option; however, it is only possible in patients with complete absence of interlobar collateral ventilation. In patients who do not qualify for a blocking technique, a wide range of "nonblocking" techniques can be used. Due to the complexity of the disease, patient selection, treatment logistics and dealing with complications in these very diseased patients, BLVR should only be performed in centres of excellence where multiple options are available and using a multidisciplinary team approach.

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Chapter 20

Bronchial thermoplasty

Michel Aubier[1,2,3,4], Marie-Christine Dombret[1], Marie-Pierre Debray[5] and Marina Pretolani[2,3,4]

Bronchial thermoplasty is an endoscopic procedure for use in patients with severe asthma who remain uncontrolled despite optimal medical treatment. Through the delivery of local radiofrequency energy to the airways, bronchial thermoplasty generates improvements in different clinical outcomes, such as asthma control and exacerbations. In 2010, bronchial thermoplasty was approved by the US Food and Drug Administration for the treatment of severe persistent asthma in patients ⩾18 years of age whose asthma cannot be not well controlled with inhaled corticosteroids and long-acting β_2-agonists; in 2011, it was CE marked and has been available in Europe since that time.

Bronchial thermoplasty aims to reduce the airway smooth muscle mass, a key feature of airway remodelling. The mechanism of action, however, is likely to be much more complex and is still incompletely understood. In the clinical setting, bronchial thermoplasty represents an attractive alternative management strategy in patients with severe asthma that is difficult to control with the available pharmacological treatments, including the new biologics. However, larger studies are still needed to investigate the mechanism of action of bronchial thermoplasty, and to search for clinical and biomarkers that differentiate responder from the non-responder patients.

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Asthma affects >235 million people worldwide. Treatment focuses on monitoring asthma severity, assessing symptom control and eliminating or reducing exacerbations [1]. Most asthmatics can be well controlled using currently available inhaler therapy with controller medications such as inhaled cortocosteroids (ICS), short-acting β_2-agonists and long-acting β_2-agonists (LABAs). However, the daily lives of a small percentage (5–10%) of severely symptomatic patients are limited by their chronic condition [2].

Severe asthma is still defined as uncontrolled despite the use of high doses of ICS alongside a second controller medication (an anticholinergic inhaler or anti-leukotriene receptor

[1]Dept of Pneumology A, Bichat-Claude Bernard University Hospital, Paris, France. [2]Faculty of Medicine, Paris Diderot University, Paris, France. [3]Laboratory of Excellence, INFLAMEX, Université Sorbonne Paris Cité and DHU FIRE, Paris, France. [4]INSERM UMR1152, Physiopathology and Epidemiology of Respiratory Diseases, Paris, France.. [5]Dept of Radiology, Bichat-Claude Bernard University Hospital, Paris, France.

Correspondence: Michel Aubier, INSERM UMR1152, Paris Diderot University, Faculty of Medicine, Bichat campus, 16 rue Henri Huchard, 75018 Paris, France. E-mail: michel.aubier@inserm.fr

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antagonist) and/or systemic oral corticosteroids (OCS) [2]. These severe asthmatics have a high burden of disease with frequent asthma exacerbations and/or progressive lung function decline resulting in excessive use of healthcare resources [3].

Management of severe asthmatics is complicated by heterogeneity in the physiological, pathological and molecular airway abnormalities. Some specific asthma phenotypes have been identified on the basis of demographic, functional, pathological, inflammatory and clinical characteristics [4, 5]. Therapeutic options for these patients are limited and when asthma control is not achieved, add-on treatments with anti-immunoglobulin (Ig)E or anti-interleukin-5 (anti-IL-5) monoclonal antibodies driven by selected phenotypes are recommended [1]. However, the use of anti-IgE therapy remains restricted to patients with allergic sensitisation and an elevated serum IgE level [6, 7], and the use of anti-IL-5 agents is limited to patients with a predominant eosinophilic phenotype [8]. Several new biological therapies targeting specific mediators of the underlying immune response have yielded promising preliminary results, but they remain experimental and only appear effective in patients with severe asthma with a high type 2 T-helper cell phenotype [9, 10].

Persistent airway inflammation and remodelling are fundamental features of severe asthma [11, 12]. However, all treatments available thus far target inflammatory/immune airway abnormalities but not the remodelling component. Airway remodelling refers to the long-term microscopic structural changes observed in the bronchial wall. Remodelling in asthma typically manifests as epithelial cell hyperplasia, goblet cell metaplasia, sub-epithelial fibrosis, angiogenesis and an increase in airway smooth muscle (ASM) mass [13, 14]. These changes correlate with asthma severity, and with the degree or the reversibility of airflow obstruction [13, 14]. Several reports have highlighted the effect of increased ASM mass in severe asthma, particularly on airway hyperresponsiveness and permanent airflow limitation [12, 15].

Bronchial thermoplasty is based on the premise that ablation of the ASM will minimise brochoconstriction and will reduce asthma symptoms and exacerbations. As such, bronchial thermoplasty is the first asthma treatment that targets airway remodelling instead of modulating airway inflammation and bronchomotor tone. Therefore, bronchial thermoplasty represents an attractive alternative management strategy in patients with severe difficult-to-control asthma, using the available pharmacological treatments including the new biologics.

Bronchial thermoplasty is a device-based therapy that delivers controlled thermal energy to the airway wall as part of a series of three bronchoscopic procedures. In 2010, it was approved by the US Food and Drug Administration (FDA) for the treatment of severe persistent asthma in patients ⩾18 years of age whose asthma is not well controlled with ICS and LABAs; in 2011, it was CE marked and has been available in Europe since that time. Bronchial thermoplasty is the subject of an important clinical development programme as well as a large body of published clinical work; however, many unresolved questions remain about the therapy.

In this chapter, we will begin by describing the procedure and presenting the results of the major clinical trials that have been published. We will then move on to consider the recent data on mechanisms of action. Finally, unresolved questions, such as patient selection in clinical practice, will be discussed.

The procedure

Bronchial thermoplasty is an endoscopic minimally invasive procedure that is based on local, radiofrequeny energy. Treatment requires a bronchoscope that is compatible with a radiofrequency catheter, and has an insertion diameter of 4.9–5.2 mm and a working channel of ⩾2 mm. Larger bronchoscopes are less suitable as they reduce access to the distal airways. The catheter is placed in the distal aspect of the airway that is being treated and is advanced using visual guidance. The electrode's array is then expanded to make contact with the airway wall, and a footswitch is activated to deliver radiofrequency energy *via* the Alair system (Boston Scientific, Natick, MA, USA) (figure 1). Each radiofrequency energy delivery or activation takes 10 s and heats the airway to 65°C. It is recommended that patients undergo three treatment sessions at ∼3-week intervals; it is essential that the patient recovers fully between treatments in order to proceed. The sequence of treatments is as follows: right lower lobe (first session), left lower lobe (second session), both upper lobes (third session). The right middle lobe is not treated as the guidelines for bronchial thermoplasty excluded this area based on the theoretical possibility of obstruction and right middle lobe syndrome [16]. Each bronchial thermoplasty session takes ∼30–45 min. Each bronchus is treated along its entire visible length, with each activation targeting a 5-mm section of bronchus 3–10 mm in diameter beginning at the periphery and moving proximally. Areas should not be retreated. Full treatment consists of ∼30–70 activations per lobe (depending on the specific anatomy); on average, 44 for the right lower lobe, 47 for

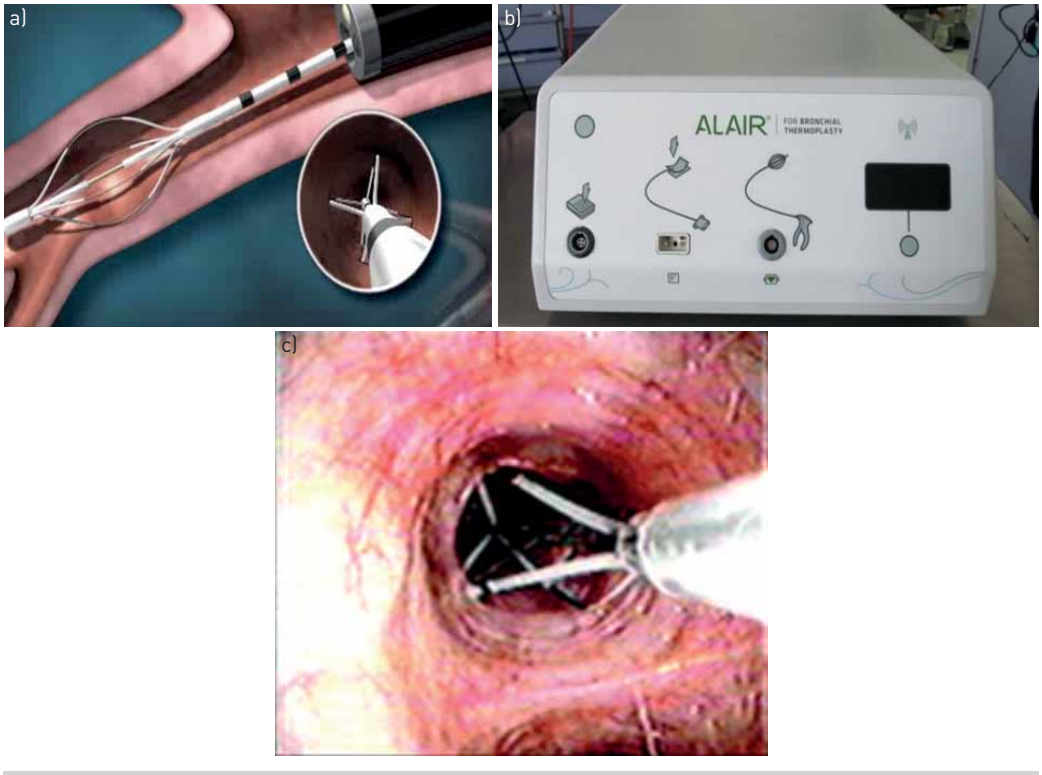

Figure 1. a) Schematic representation of the Alair catheter (Boston Scientific, Natick, MA, USA). b) The Alair radiofrequency generator (Boston Scientific). c) The Alair catheter during an activation of radiofrequency energy delivery to the airways.

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the left lower lobe and 60 for the upper lobes [16]. The effectiveness of the treatment depends on how thoroughly the procedure is performed. An untreated segment may theoretically continue to constrict when stimulated, which may counteract treatment benefits. A meticulous technique and airway mapping are therefore very important. Activation of the bronchial thermoplasty catheter does not have a macroscopic effect on the bronchial mucosa but may cause transient blanching, which is represented by a whitening of the mucosa. This makes identification of the treated bronchi difficult; close attention is therefore required on the part of the bronchoscopist. Immediately following the procedure, close clinical monitoring is required as asthma symptoms are more common in the hours immediately following treatment. Patients receive oral prednisolone (50 mg per day) for 3 days before the day of and 1 day after the procedure. The procedure can be carried out under sedation or using general anaesthesia, depending on the resources available and the preferences of the physician/institution. Although carrying out bronchial thermoplasty may seem straightforward, it requires expertise in asthma management and interventional bronchoscopy. A multidisciplinary team that combines physicians with a specific interest in interventional endoscopy and those with an expertise in chronic airway disorders will ensure the best possible care for and that is most appropriate to the patient. Appropriate patient assessment and monitoring before, during and after the procedure has been well described elsewhere and can be performed in an inpatient or outpatient setting [17].

Bronchial thermoplasty can only be considered for use in patients whose asthma is well-documented. Current warnings, precautions and exclusions include COPD, bronchiectasis, recurrent respiratory infections and any other uncontrolled significant respiratory disease. The treating facility (as well as the asthma specialist and the interventional bronchoscopist) should be familiar with the clinical course of their patients in order to ensure appropriate patient selection and to optimise asthma control, both prior to bronchial thermoplasty and throughout the treatment period. Bronchial thermoplasty treatment can temporarily worsen asthma symptoms, and the intensity of this can be proportional to the patient's asthma severity [18]. The clinical benefits should be reassessed at the end of the treatment period (6 weeks after the final bronchoscopy). Pharmacological treatments should be adjusted to their lowest possible dosages, beginning with a reduction in OCS followed by a decrease in ICS and/or LABA if the asthma remains well-controlled [19].

Clinical evidence of bronchial thermoplasty in asthma patients

Efficacy

In 2006, Cox *et al.* [16] reported the findings of an observational pilot study that explored the safety and clinical effects of bronchial thermoplasty. 16 patients with mild-to-moderate asthma reported improvements in: symptom-free days; morning peak expiratory flow 3 months afters bronchial thermoplasty treatment; and a reduction in airway hyperresponsiveness to methacholine. These improvements persisted for ⩽3 years (this finding was not significant as a high number of patients were lost to follow-up, especially in the untreated group).

Following this initial study, three randomised clinical trials were carried out in patients with moderate-to-severe asthma [18, 20, 21].

The Asthma Intervention Research (AIR) Trial [20] was a randomised, controlled study performed in 112 asthma patients, all of whom required treatment with ICS and LABA.

56 of the patients received bronchial thermoplasty and 56 received standard care. The trial measured the average frequency of mild exacerbations during LABA withdrawal periods. The group treated with bronchial thermoplasty presented fewer average mild exacerbations than the control group during the LABA withdrawal period at 1 year. Asthma control improved after bronchial thermoplasty, patients had more symptom-free days and quality of life was significantly better compared with the control group. Subjects treated with bronchial thermoplasty also used fewer rescue medications, equating to approximately two fewer canisters of short-acting bronchodilators per year. Morning peak flow measurements were better than in the control group, but no differences were noted in prebronchodilator FEV_1 % predicted airway hyperresposiveness between patients receiving bronchial thermoplasty and control patients.

The smaller Research in Severe Asthma (RISA) Trial [18], performed following the results of the AIR Trial [20], was designed to evaluate bronchial thermoplasty in patients with severe, symptomatic asthma. RISA was a randomised, controlled safety study in performed 32 severe patients whose asthma was uncontrolled despite high doses of ICS. In the study, 15 patients received bronchial thermoplasty and 17 continued with usual care. After the initial evaluation, forced steroid withdrawal took place between weeks 22 and 36 in an attempt to wean patients off ICS and OCS. Although subjects who underwent bronchial thermoplasty were on reduced maintenance therapy following the steroid-wean phase, they showed improved quality of life compared with control subjects. The group treated with bronchial thermoplasty also showed improved asthma control and a reduction in the use of rescue medications prior to the forced-steroid withdrawal period. Despite a decrease in medication use following the steroid-wean phase, the bronchial thermoplasty group continued to show a reduction in the use of short-acting bronchodilators, more symptom-free days and maintenance of an improved Asthma Control Questionnaire (ACQ) score. In bronchial thermoplasty subjects, the use of OCS and ICS fell by 63.5% and 28.6%, respectively, compared with 26.2% and 20% in the control group. In spite of the decrease in maintenance therapy, significant improvements were seen in quality of life and asthma symptom scores 4 months after the steroid-wean phase.

Although the findings of the AIR and RISA trials showed improvements in some clinical outcomes, the unblinded nature of these studies raised questions regarding a possible pacebo effect rather than real efficacy of bronchial thermoplasty. The AIR2 trial [21] was designed specifically to address this limitation [18, 20].

The AIR2 Trial, the largest pivotal study, was double-blinded, randomised, sham-controlled and enrolled patients who had uncontrolled asthma despite high doses of ICS and LABAs [21]. The Trial assigned 288 patients with severe asthma 2:1 to bronchial thermoplasty (190 patients) or sham bronchoscopy (98 patients). The sham thermoplasty treatment reproduced all the audio and visual signals of bronchial thermoplasty but the catheter did not deliver any radiofrequency energy. The treatment was administered by an unblinded bronchoscopy team and all the assessments and follow-up visits were conducted by a blinded team. The primary outcome measure of the study was the change from baseline in the average group mean Asthma-related Quality of Life (AQLQ) score. The bronchial thermoplasty group demonstrated superior AQLQ scores compared with the sham-control group, as well as a greater proportion with a clinically meaningful improvement in AQLQ ($\geqslant$0.5) in the intent-to-treat and per-protocol groups (79% *versus* 64% and 81% *versus* 63%; posterior probability of superiority (PPS) 99.6% and 99.9%, respectively). A significant reduction was noted in the number of bronchial thermoplasty subjects with worsening

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asthma compared with sham-control subjects in the post-treatment period (27.3% *versus* 42.9%, respectively; PPS 99.7%). No difference was noted in the number of symptom-free days, the use of rescue medications or the total asthma symptom score. In comparison with the sham-control group, the bronchial thermoplasty group demonstrated fewer: severe exacerbations (−32%; PPS 95.5%); visits to emergency care (−84%; PPS 99.9%); and days absent from work or school (−66%; PPS 99.3%). There was no change in respiratory function at 1 year post-treatment.

The three trials showed improvements in different outcomes, such as AQLQ, asthma control and exacerbations following bronchial thermoplasty. These improvements were noted 1 year after the last thermoplasty session. Of the patients enrolled in the AIR2 Trial [21] and randomly assigned to bronchial thermoplasty, 162 (85%) underwent a 5-year follow-up evaluation [22]. There were persistent reductions in severe exacerbations and emergency department visits over 5 years compared with the year prior to BT. However, it should be noted that the patients enrolled in the control group were not followed-up because it was deemed unethical and impossible to withhold potential new therapies for this long-duration follow-up. The findings of the AIR2 Trial led to approval by the FDA as a treatment option in patients with moderate-to-severe uncontrolled asthma.

Safety profile

Adverse events in the initial treatment period

In comparison with controls, subjects treated with bronchial thermoplasty have been shown to present with more symptoms that are typical of asthma (*e.g.* cough, wheeze, expectoration, dyspnoea, nocturnal awakening), as well as occasional general symptoms such as fever, in the hours following treatment [18, 21]. These symptoms usually resolve after 7 days but have lead to hospital admission in 3.4% of bronchoscopies in moderate-to-severe asthma [21] and 15.4% of severe asthma cases [18]. This underlines the importance of optimising asthma control prior to the first bronchial thermoplasty treatment and ensuring close monitoring in the days following treatment. In AIR2, one patient presented with significant haemoptysis in the right upper lobe 1 month after the last session and required bronchial artery embolisation. Slight bleeding had been observed during the treatment of this lobe and it was felt that this complication was related to the treatment [21]. Acute bronchospasm can occur during the intervention and may require termination of the procedure.

Long-term safety

Asthma is associated with structural and inflammatory abnormalities of the bronchial mucosa [11, 12], and the application of controlled thermal energy (65°C) raises the question as to whether bronchial thermoplasty induces further injury to the bronchial wall. After long term follow-up in the four clinical trials, no evidence of treatment-related airway stenosis or bronchiectasis was found. After 1 year of follow-up, none of the trials documented any bronchial damage.

In two studies of patients with moderate-to-severe asthma, pre-bronchodilator FEV_1 remained stable during a 5-year follow-up period [22, 23]. In the AIR Trial, follow-up at 5 years was performed in a small group with the most severe asthma (45 patients receiving bronchial thermoplasty and 24 controls) [24]. All patients underwent annual evaluation, including spirometry, static lung volumes, diffusing capacity, bronchoprovocation testing and chest radiography. There were no decrements in spirometry, lung volume or diffusion

capacity test results, and no significant changes in chest radiographs. Follow-up of patients enrolled in the RISA Trial [18] was limited to subjects who underwent bronchial thermoplasty, with 14 of the 15 consenting to 4 years of follow-up after the first year [23]. As in the AIR Trial, no deterioration of pulmonary function was noted over the 5-year study.

Mechanisms underlying the effect of bronchial thermoplasty

There are a number of possible mechanisms of action that alone, or in combination, might explain the beneficial effects of bronchial thermoplasty. To date no unique mechanism has been formally identified.

As ASM mass is one of the major characteristics of airway remodelling in severe asthma patients [12, 15], the first and best documented mechanism of action is a reduction in the bronchial wall smooth muscle. A number of reports have emphasised the effects of increased ASM mass in severe asthma, particularly on airway hyperresponsiveness and permanent airflow limitation [12, 15].

Preclinical studies have shown that bronchial thermoplasty reduces ASM mass in a canine model of asthma, which was associated with a long-term reduction in airway hyperresponsivness. The effectiveness of bronchial thermoplasty on reducing the ASM in patients with severe asthma patients was first demonstrated by Pretolani *et al.* [25]. The study analysed the ASM mass percentage (ASM area as a percentage of the total biopsy aerea) in airway biopsies 15 days before the first bronchial thermoplasty session and 3 months after three bronchial thermoplasty sessions performed in 10 severe asthma patients. A reduction in ASM mass from 20.25% before bronchial thermoplasty to 7.28% (60%) was found. Following the study by Pretolani *et al.* [25], Denner *et al.* [26] observed an ASM reduction from 38% before the first bronchial thermoplasty session to 16% (58%) 6 weeks after the first bronchial thermoplasty session (taken during the third thermoplasty session) in 11 patients. This was confirmed with an ASM reduction from 12.9% before the first bronchial thermoplasty session to 4.6% (64%) 3 weeks after the first thermoplasty (taken during the second session) in another 17 severe asthma patients [27]. Most recently, Pretolani *et al.* [28] confirmed an ASM mass reduction (ASM area as a percentage of the submucosal tissue area) from 19.7% to 5.2% (73%) in 15 severe patients who were selected on a baseline ASM mass of ⩽15%. This reduction in ASM area correlated with several clinical outcomes at 3 months: improved asthma control and quality of life; a decrease in severe exacerbations, hospitalisation and visits to the emergency department for asthma. Importantly, all correlations were maintained at 1 year after bronchial thermoplasty (table 1).

As heat energy produced during bronchial thermoplasty can potentially alter airway structural components other than the ASM, it is possible that additional mechanisms contribute to the observed clinical efficacy. Pretolani *et al.* [28] found that nerve fibres (in the bronchial sub-mucosa and ASM bundles) as well as the neuroendocrine epithelial cells drastically decreased 3 months after bronchial thermoplasty. This reduction was significantly associated with a decline severe exacerbations, suggesting that damage of autonomic-innervated structures induced by bronchial thermoplasty downregulated airway excitability and thus improved asthma control (table 1).

Interestingly, a reduction in ASM [25] and a downregulation of the neuroepithelial cells [28] in the non-treated right middle lobe was previously reported. Recently, Debray *et al.*

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Table 1. Correlation analyses between histopathological changes and the clinical benefits of bronchial thermoplasty

Parameter	ACT	Hospitalisation	Exacerbations
ASM area	**0.003**	**0.03**	**<0.001**
SBM thickening	**0.02**	0.18	0.08
Submucosal nerves	0.08	0.06	**<0.001**
ASM-associated nerves	0.39	0.32	**0.05**
Epithelium neuroendocrine cells	**0.02**	**0.02**	**0.01**

Data are presented as p-values. Bold indicates statistical significance. ACT: asthma control test; ASM: airway smooth muscle; SBM: sub-epithelial basal membrane.

[29] reported the presence of peribronchial consolidations and ground-glass opacities in the treated lobes of 13 severe asthmatics (38 treated lobes) the day after bronchial thermoplasty (figure 2); the involvement of an adjacent untreated lobe was observed in 12 (32%) out of 38 cases. All opacities decreased after 8 days and disappeared at 1 month. This suggests that the effects of bronchial thermoplasty are spread out to distal untreated airways, even though the heat is delivered to the larger airways (airway diameter of ⩾2–3 mm).

As ASM produces pro-inflammatory cytokines and chemokines [15], a reduction in ASM may lead to a potential effect of bronchial thermoplasty on airway inflammation, another mechanism that could contribute to its benefits. Denner *et al.* [26] investigated cytokines associated with airway inflammation in BAL and found a significant reduction in transforming growth factor-β and RANTES (regulated on activation, normal T-cell expressed and secreted) but no change in asthma key cytokines such as eotaxin, IL-4, IL-5, IL-13 and IL-17. In airway biopsies taken 3 months after bronchial thermoplasty, Pretolani *et al.* [28] found no change in mucosal eosinophil and neutrophils. Therefore, the question of whether there is a bronchial thermoplasty-induced effect on airway inflammation remains unanswered.

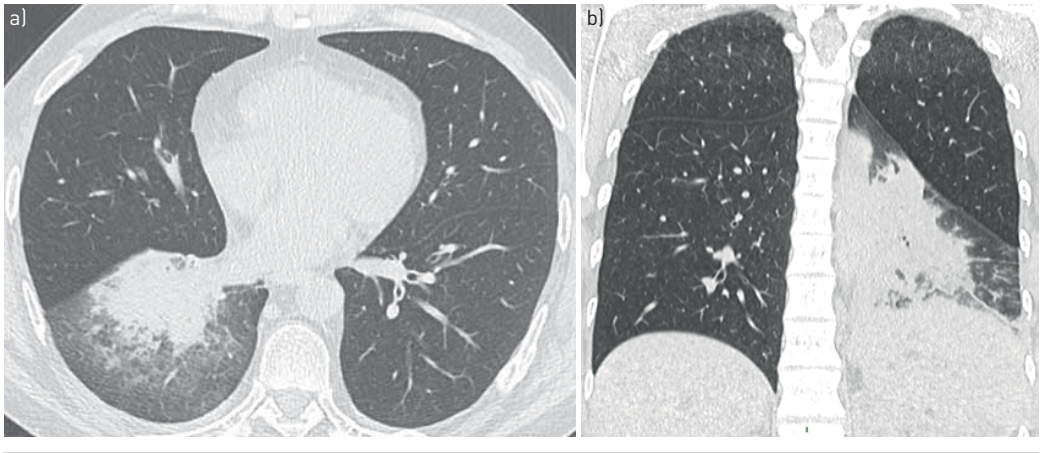

Figure 2. a) Chest CT scan of the coronal plane performed the day after bronchial thermoplasty. The right lower lobe shows peribronchial consolidations. b) Chest CT scan in the axial plane performed the day after bronchial thermoplasty. The left lower lobe shows peribronchial consolidations surrounded by ground-glass opacities, filling of bronchial lumen and mild volume loss of the treated lobe. Reproduced and modified from [29].

Currently, the mechanism of action of bronchial thermoplasty is incompletely understood and is likely to be much more than solely ASM mass reduction. More work is needed in order to clarify the mechanisms of action of bronchial thermoplasty. This understanding is necessary in order to determine the asthma phenotype that will benefit most of this treatment modality.

The unanswered questions

Is bronchial thermoplasty only for severe refractory asthma?

Clinical studies of bronchial thermoplasty in adults with asthma have addressed a broad range of asthma patient severity, from mild to severe. In the AIR Trial [20], the majority of patients had moderate asthma. The patients in the AIR2 trial [21] were more severe; although they were excluded if they required >10 $mg \cdot day^{-1}$ of OCS, had four or more exacerbations requiring bursts of OCS and had three or more hospitalisations for asthma. Therefore, very few patients (seven in the bronchial thermoplasty group, one in the sham group) required systemic corticosteroids, and only five patients (two in the bronchial thermoplasty group, three in the sham group) received omalizumab.

Most of the morbidity and mortality related to asthma occurs in patients with severe, poorly controlled disease [30, 31]. Patients with very severe asthma, experiencing multiple exacerbations and hospitalisations, and refractory to the available treatments (such as anti-IgE or anti-IL-5) would be the target population for bronchial thermoplasty rather than those enrolled in the AIR and AIR2 trials. This is supported by a recent study that reported the important clinical benefits of BT in a small group of 15 patients with severe refractory asthma [28]. Patients in the study [28]were more symptomatic than those enrolled in earlier trials [18, 20, 21], with mean numbers of exacerbations during the year before entry of 9.7, instead of 0.7, mean AQLQ scores of 2.6, instead of 4.7 and greater prevalence of maintenance use of OCS. In these ultra-severe asthmatic patients, the clinical improvement at 12 months was of a higher magnitude than that previously shown, with a 92% decrease in the number of exacerbations, a 90% lower number of visits to the emergency room, 88% less hospitalisations and admittance to intensive care for asthma, and improvements of 93% and 62% in asthma control test (ACT) and AQLQ scores, respectively. These effects were accompanied by a significant reduction in maintenance doses and the number of bursts of OCS. This sub-population of very severe asthmatics in whom the available pharmacological therapies are either not effective or are less effective may be the ideal candidates for bronchial thermoplasty. Larger clinical trials specifically targeting these ultra-severe asthmatics are needed to confirm the results obtained in the small group of patients studied by Pretolani *et al.* [28].

Is bronchial thermoplasty effective in all patients with severe refractory asthma?

Clinical studies have demonstrated that 12 months after bronchial thermoplasty, significant improvements are seen in patients symptom scores, reliever medication usage and asthma exacerbations requiring OCS [20, 21]. However, there is very little data regarding those who failed to respond, nor the contributing reasons for this lack of response.

In a sub-analysis, Pretolani *et al.* [28] observed that the favourable clinical outcome following bronchial thermoplasty was inconsistent in the 15 patients studied. Indeed, after

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12 months, four of the 15 patients continued to experience poor asthma control, as shown by the ACT values and the AQLQ scores, which were similar to those measured before bronchial thermoplasty. This finding may be explained by the distinct intrinsic sensitivities of severe asthmatics to bronchial thermoplasty, despite apparent clinical similarities, or by an incomplete effectiveness of the procedure on the different airway structures. Indeed, a poor response to bronchial thermoplasty was accompanied by an impaired reduction in ASM area and in the number of neuroendocrine epithelial cells, suggesting a causal relationship between the ablation of these bronchial structural elements and clinical benefit.

The lack of response in some patients could be caused by a variation in the number of activations delivered to the airways during bronchial thermoplasty. A lower number of activations may lead to a reduction in treatment of ASM and decreased effectiveness. In a recent study of 24 uncontrolled severe asthmatics, Langton *et al.* [32] specifically examined the relationship between radiofrequency activations and clinical response. An improvement in ACQ-5 of > 0.5 units (the minimal clinically significant difference) [33] was observed in 21 (88%) of the 24 participants. The three nonresponders were compared with their counterparts across a range of clinical variables, including: age, sex, baseline FEV1%, baseline bronchodilator response, medication usage and exacerbation frequency. The only significant difference noted between the two groups was the number of radiofrequency activations. In nonresponders, the mean±SD activations were 139±45 compared with 221±45 in responders. However, two studies showing a reduction in ASM following bronchial thermoplasty were unable to correlate the degree of reduction in ASM with the number of activations applied [25, 27].

Debray *et al.* [29], who reported the presence of peri-bronchial consolidations the day after bronchial thermoplasty in all treated lobes, found that their extent was proportional to the number of radiofrequency activations. As previously discussed, this suggests that the effectiveness of bronchial thermoplasty is not solely linked to a reduction in ASM, but involves other airway structures at different levels of the bronchial tree, proximal and distal. Whatever the impact of bronchial thermoplasty on airway structures, this highlights the need for a future study of predictors of response to bronchial thermoplasty in a large cohort of patients.

How should patients be selected for bronchial thermoplasty?

Although patients with very severe asthma, multiple exacerbations and numerous hospitalisations are an attractive population for bronchial thermoplasty, identifying asthma phenotypes with the greatest response to the procedure is likely to mean better patient selection and, ultimately, better patient outcome.

Considering the reduction in ASM found after bronchial thermoplasty in patients with severe asthma, we might imagine that the patients who will benefit the most from bronchial thermoplasty would be those who have a greater ASM mass, leading to increased airway hyperreactivity and frequent exacerbations. This is supported by a study in which patients with severe asthma were selected for bronchial thermoplasty on the basis of a high ASM mass on the bronchial biopsies (ASM mass >15% over the surface of the total biopsy) [28]. These patients had a better clinical outcome following bronchial thermoplasty compared with those who were not selected on the basis of ASM mass [20, 21]. However, no or very little improvement in lung function following bronchial thermoplasty has been reported

[16, 20, 28]. This is surprising as there is a very good inverse correletion between ASM mass and FEV1 [12]. The lack of effect of bronchial thermoplasty on lung function and the absence of a control group of patients with a lower ASM mass [28] do not permit the use of ASM as a biomarker of the efficacy of bronchial thermoplasty.

Evaluation of ASM mass on bronchial biopsies is invasive and difficult to perform routinely in clinical practice in all severe uncontrolled asthma patients. Noninvasive imaging techniques might be interesting tools to select patients for bronchial thermoplasty. A recent study performed in healthy subjects and 10 patients with severe asthma, quantified regional lung ventilation before and after BT by using a combination of helium-3 magnetic resonance imaging and CT [34]. Patients with asthma demonstrated larger segmental defect percentages than healthy volunteers. Ventilation defects increased for earlier post-treatment times but decreased for later post-treatment times. This quantitative measure indicating the relative ventilation of differing segments may allow us to make judicious decisions regarding the areas to treat with bronchial thermoplasty, the time between treatment sessions and whether all treatment sessions are necessary.

OCT is a minimally invasive imaging technique that is used to visualise airway wall structures with a near-histological resolution [35]. Using OCT, a pilot study evaluated two severe asthmatics immediately prior to and longitudinally following bronchial [36]. A similar FEV1 (50% pred) was reported in both patients, as well as comparable doses of ICS, with both requiring OCS on a long-term basis. OCT images were obtained pre-bronchial thermoplasty, immediately post-bronchial thermoplasty, and 3 weeks, 6 weeks, 6 months and 2 years post bronchial thermoplasty. Following bronchial thermoplasty, OCT imaging showed no reduction in airway wall thickness in one of the patients (patient A), and their symptoms returned 4 months post-treatment. In contrast, the second patient (patient B) showed progressive improvements in FEV1 for ⩾6 months and reductions in OCT airway wall thickness; they also demonstrated improvements in respiratory symptoms and a decrease in medication use for 2 years post-bronchial thermoplasty. Before bronchial thermoplasty, patient A had a thickened and inflamed epithelium, irregular basement membrane and prominent ASM. At 3 and 6 weeks post-bronchial thermoplasty, the epithelium appeared thinner and ASM was less promnent. At 6 months and 2 years post-BT, recurrence of the inflammatory changes in the epithelium was shown on OCT. In contrast to patient A, the epithelial layer of patient B was not inflamed before bronchial thermoplasty and the ASM layer was also less prominent 6 weeks post-bronchial thermoplasty and remained the same at 6 months and 2 years. At 6 months and 2 years post- bronchial thermoplasty, patient B had a normal bronchial epithelium. Although patient A was a clear nonresponder to bronchial thermoplasty, patient B demonstrated improvements following the procedure that could not have been predicted based on baseline spirometry or clinical features. A larger study is required to establish whether OCT can identify characteristics in the airway wall that predict response to bronchial thermoplasty, such as an inflammation component.

Conclusion

Bronchial thermoplasty is a novel, innovative treatment for patients with severe asthma. The clinical efficacy and safety of the procedure are now beginning to be better understood. It is the only therapy that targets airway remodelling and as such, is complementary to most available therapies that target the underlying inflammatory response. In addition to the

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FDA's approval of the procedure for the treatment of severe asthma that cannot be controlled with ICS and LABA, the guidelines of the British Thoracic Society (BTS) and the Global Initiative for Asthma (GINA) recommend bronchial thermoplasty as a possible treatment option in selected patients with severe asthma who are already on maximal therapy [1]. Patient selection should be performed in a team with asthma specialists and interventional pulmonologists in order to select the appropriate treatment for the right patient.

Larger studies are still needed to investigate the mechanism of action of bronchial thermoplasty and try to determine the clinical parmeters and biomarkers that differentiate the responders from the nonresponders.

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Advanced techniques in local anaesthetic thoracoscopy

Rahul Bhatnagar[1,2], Rachel Jones[3] and Nick Maskell[1,2]

Interventional pulmonologists are increasingly using local anaesthetic thoracoscopy to diagnose and treat pleural diseases. Within this technique, there are a range of applications that may be considered more advanced and are thus usually performed by those practitioners with additional experience or a research interest. This chapter discusses the evidence and practicalities behind advanced thoracoscopic procedures, including cryoprobe biopsy, the use of diathermy, talc pleurodesis, and the management of pneumothorax and pleural infection.

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Endoscopic examination of the thoracic cavity was once the sole domain of those with formal surgical training. The last few decades, however, have seen the increasingly widespread introduction of local anaesthetic thoracoscopy (LAT), typically undertaken by pulmonologists with an interest in intervention or pleural disease. Interchangeably referred to as medical thoracoscopy or medical pleuroscopy, LAT is becoming available to an ever-growing proportion of the world's medical professionals and patients [1, 2], and now forms a vital part of many services' pleural effusion pathways. The reasons for LAT becoming more popular are numerous and vary from region to region, but are likely to include lower costs and reduced waiting times (when compared with thoracic surgery), and less strict exclusion criteria due to general anaesthetic not being required. In general, however, centres with ready access to thoracic surgical colleagues are perhaps less likely to need to develop LAT services.

As skills, experience and confidence have progressed in some of those centres that have adopted LAT, the line between traditionally "surgical" procedures and those undertaken by physicians has become blurred. Similarly, a spectrum within LAT appears to be emerging, with a greater distinction between "basic" LAT, performed by the majority, and "advanced" LAT, which is usually confined to tertiary or research-focused centres.

The British Thoracic Society (BTS) guidelines divide thoracoscopy practitioners into levels I, II and III, with level III referring to VATS techniques beyond the remit of most physicians

[1]Academic Respiratory Unit, University of Bristol, Southmead Hospital, Bristol, UK. [2]North Bristol Lung Centre, Southmead Hospital, Bristol, UK. [3]Intensive Care Unit, Musgrove Park Hospital, Taunton, UK.

Correspondence: Rahul Bhatnagar, Academic Respiratory Unit, University of Bristol, Learning and Research Building, Southmead Hospital, Southmead Road, Bristol, BS10 5NB, UK. E-mail: Rahul.Bhatnagar@Bristol.ac.uk

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and the scope of this chapter (table 1) [3]. The definitions of "basic" and "advanced" LAT are not universal, however, and may vary according to the procedure(s) performed and/or the indication for which LAT is being attempted. For those who perform LAT infrequently, anything beyond routine (stripping) biopsies in a patient with a moderate to large effusion is likely to be considered "advanced", whereas those with relatively more experience may develop competence to attempt more invasive or less straightforward procedures.

For the purposes of this chapter, we have chosen to largely define advanced LAT in line with the BTS level II standard, relating to procedures carried out by physicians on patients under sedation. We also discuss thoracoscopic poudrage, what we consider to be rarer or more technically challenging biopsy techniques and those interventions that remain confined to the experimental or research arenas. Such techniques, save perhaps talc poudrage, are not required by the majority of LAT practitioners and are usually only adopted following many years of practice at a basic level. Many of these diagnostic and therapeutic procedures are discussed in other chapters throughout this *Monograph* [4].

Finally, in general, the evidence base in this area is lacking, as most research relating to LAT comes in the form of expert opinion, case series or retrospective analyses of practice. That being said, literature quoted in this chapter emanates from across Europe (where LAT was first developed) and the rest of the world, and as such we believe what follows will be of value to a wide audience.

Pre-procedure

Hospital environment

A major appeal of LAT is that it may be performed safely in hospital environments outside of the operating theatre, such as an endoscopy suite. Indeed, data would suggest that the

Table 1. Summary of the British Thoracic Society thoracoscopy expertise levels I, II and III

	Level I (basic)	Level II (advanced)	Level III (thoracic surgeon)
Sedation	Light, physician controlled	Deep, either physician or anaesthetist controlled (general anaesthetic in select centres)	General anaesthetic
Effusion	Intervention in large, simple effusions	Intervention in small effusions/no effusion if induced pneumothorax possible or those with early fluid complexity	Any
Biopsy	Basic pleural stripping or nodule sampling	Cryobiopsy (parietal), diathermy (parietal, visceral or pinch lung biopsy)	Any
Intervention	Simple adhesiolysis, talc poudrage for effusion	Mature adhesiolysis using diathermy (*e.g.* pleural infection), talc poudrage for pneumothorax, nerve chain lysis in very select centres	Any, including lung resection

Information from [3].

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Table 2. Local anaesthetic thoracoscopy complications and mortality reported in large retrospective series within the last 25 years

First author [ref.]	Year	Total patients N	Mortality %	Major complication rate n/N (%)[#]
Maturu [6]	2015	264	0.4	16/264 (6.1)
Agarwal [7]	2014	128	0	2/128 (1.6)
Gao [8]	2014	215	0	0/215 (0)
Metintas [9]	2013	355	0.3	50/355 (14.1)
Metintas [10]	2010	124	0	3/124 (2.4)
Medford [11]	2009	124	0.8	5/124 (4.0)
Sakuraba [12]	2006	138	0	0/138 (0)
Hansen [13]	1998	146	0	3/146 (2.1)
Macha [14]	1993	687	0	4/687 (0.6)
Boutin [15]	1993	188	0	4/188 (2.1)

[#]: major complications include pneumonia, empyema, extensive surgical emphysema, prolonged air leak, bleeding, venous thromboembolic events, cardiovascular insufficiency, respiratory failure and re-expansion pulmonary oedema. Reproduced and modified from [5] with permission.

incidence of complication, major or otherwise, is extremely low and this is demonstrated in table 2 [3, 5]. However, as a practitioner begins to perform increasingly invasive, and thus theoretically riskier, thoracoscopic procedures, it becomes more important that these risks are appropriately mitigated. To accomplish this, several factors should be considered and first among these is the more general hospital environment. We would advocate ready emergency access to either onsite thoracic surgical cover or experienced interventional radiology (ideally both) to intervene in the event of significant vascular or visceral damage. To complement these, there should also be appropriate anaesthetic and intensive care support available.

The procedural environment must also be optimised. An appropriate number of support staff must be available, adequately trained and versed in the procedures being undertaken, as well as the potential risks and the protocols to be followed in the event of emergency. Although LAT can often be performed with a single operator, it may also be prudent to provide for additional medical support. However, whether this extends to include direct anaesthetic involvement is somewhat contentious.

Sedation and analgesia

LAT can typically be accomplished with relatively light intravenous sedation and analgesia, using benzodiazepine and opiate medications that are familiar to the pulmonologist (*e.g.* midazolam and fentanyl) [3]. With these drugs, it is common practice for the primary operator to oversee the patient's conscious level alongside the intervention itself. In some centres, however, the role of monitoring this aspect of the procedure is delegated to an anaesthetist. Although such arrangements may liberate the operator to focus on more invasive procedures and have been used to excellent effect by surgeons [16], an attraction of LAT to many is the reduced resources required compared with VATS. Nonetheless, the use of certain anaesthetic agents, especially propofol, is attractive to pulmonologists due to an encouraging evidence base in bronchoscopy [17, 18] and their rapidity of onset and offset, with a feasibility study suggesting this may be a reasonable approach for LAT [19].

The question of whether physician-led propofol could replace standard sedation was addressed in a randomised trial of 90 patients in 2014. Grendelmeier *et al.* [20] concluded that, although no procedure had to be abandoned and no patients required treatment escalation, the use of propofol was associated with a significantly higher rate of hypoxaemia. This led Grendelmeier *et al.* [20] to conclude that this regimen should not be considered first line and triggered the early cessation of a similar study in South Africa [21]. This approach is still advocated by some, however, who argue that, with intensive, anaesthetist-led training for all involved in LAT (something that was not used in the Grendelmeier *et al.* [20] study), high standards and safety can be achieved routinely [19, 22].

Accessing the small pleural space

One of the primary differentiators between a basic and advanced LAT practitioner is the size of the effusion or pleural space that they might consider safe for intervention. Even with thoracic ultrasound guidance, a small collection may present a significantly higher risk of visceral or diaphragmatic damage compared with a moderate or large effusion.

Reducing the size of instrumentation may help to alleviate some of this risk. So-called "mini-thoracoscopy" (figure 1) uses instruments with diameters of up to 5–6 mm to try to achieve this, with diagnostic yield in one small series being comparable to that seen with larger devices [23]. Modern mini-thoracoscopes offer a wide range of interventional options and are seen by some authors as an ideal way to expand the reach of LAT [24].

Perhaps the more usual method for approaching the small pleural space, however, is the induction of an artificial pneumothorax. This technique had a place in pulmonology for many decades [25], but became less familiar to most modern practitioners with the success of antituberculous medications. Due to the negative pressure within the pleural cavity, creating an open connection to the atmosphere will result in a pneumothorax. Doing so will cause the lung to "fall away" from the internal chest wall and thus create a space that can be dissected into at LAT. This effect is enhanced further by placing the patient in the typical lateral decubitus position. An artificial pneumothorax is usually induced in a controlled fashion by inserting a blunt, wide-bore needle into the small pleural effusion.

Figure 1. Example of a mini-thoracoscope designed for single port use (Richard Wolf, Knittlingen, Germany).

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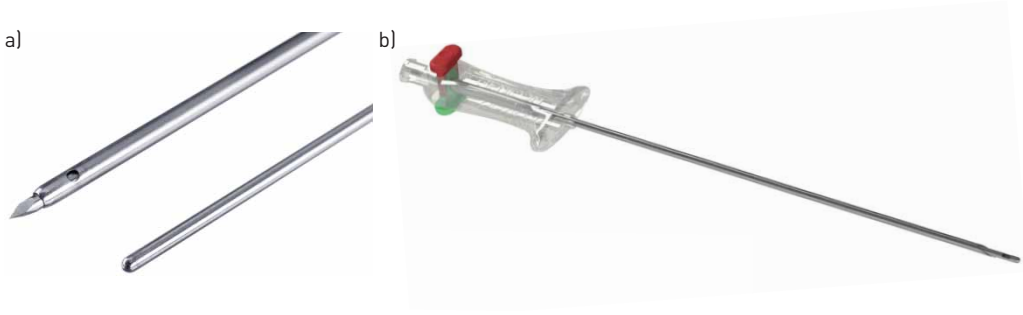

Figure 2. a) Boutin trochar needle. Reproduced with kind permission of Novatech (La Ciotat, France) ©Novatech S.A. France. b) Veress insufflator needle. Reproduced with kind permission of Genicon (Winter Park, FL, USA).

Although this is often achieved with a Boutin trochar system, it may just as easily be performed using the Veress needle (with its spring-loaded safety device) more commonly used to induce a pneumoperitoneum prior to abdominal surgery (figure 2). Following insertion of the needle, the patient should be encouraged to take 15–20 slow deep breaths to facilitate lung collapse. Regardless of the device, direct ultrasound guidance should be considered for all such procedures.

Some centres choose to attempt induction of a pneumothorax "on the table", immediately prior to the procedure. While this runs the risk of having to abandon a LAT if the lung is excessively adhered, evidence would suggest that an assessment of pleural "sliding" on ultrasound can reliably predict those lungs that will collapse as intended [26]. This means that, even in patients with the smallest of pleural effusions, careful blunt dissection may be sufficient to allow LAT to take place (figure 3). An alternative approach is to induce a pneumothorax ~2 h before a LAT and to confirm its size using a lateral decubitus chest radiograph. This approach minimises the likelihood of encountering a lung that has been unable to reduce in volume due to the presence of unseen, mature, parietovisceral

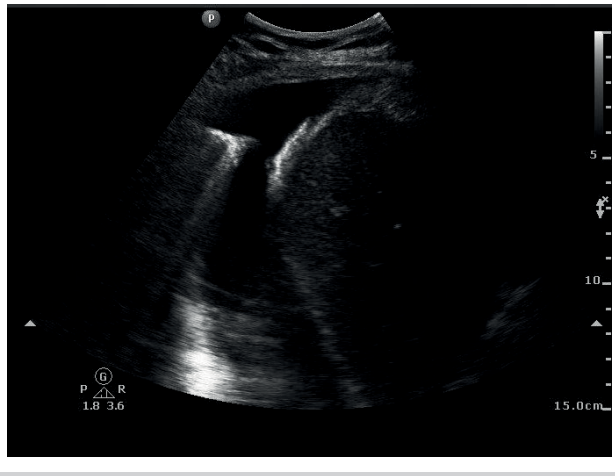

Figure 3. Ultrasound image of a small pleural effusion for which induced pneumothorax prior to thoracoscopy would be appropriate.

adhesions. However, in the scenario of a "failed" LAT such as this, switching immediately to an ultrasound-guided cutting needle biopsy may be enough to achieve sufficient tissue in the large majority of cases, thus obviating the need for more invasive intervention [27].

Induced pneumothorax has been shown to be safe when performed by expert centres. One group described 77 consecutive ultrasound-guided pneumothorax inductions, which comprised just over a third of the total number of LAT cases undertaken over a 3-year period. Encouragingly, no significant complications were reported [26].

Advanced diagnostic techniques

Cryoprobe biopsy

Obtaining sufficient tissue during pleural biopsy is of paramount importance. In cases of clear malignant infiltration, it is usually sufficient to sample a selection of nodules to obtain a definitive histological diagnosis. Certain diseases, however, tend to be more challenging to sample, especially if they cause diffuse parietal pleural thickening rather than nodular change. Among these may be malignant mesothelioma, which also often requires histological evidence of fat invasion to be definitively diagnosed [28]. Standard pleural biopsy techniques, which involve the indentation and subsequent progressive stripping of sections of tissue layers, may fail more readily in such cases due to difficulty in achieving adequate sampling depth, difficulty gaining purchase on a hardened smooth surface or the presence of crush artefacts degrading sample quality [29, 30].

Parietal pleural cryobiopsy has the potential to alleviate some or all of these issues but, despite being first described in 1989 (and its increasing importance in diagnosing ILD at bronchoscopy), it still remains a relatively infrequently used technique at thoracoscopy [31, 32]. The apparatus usually consists of a freezing unit connected to a flexible cryoprobe, which is passed down the channel of a thoracoscope with a dedicated working channel. Practically, this usually means either a rigid mini-thoracoscope or, more commonly, a semirigid thoracoscope. The tip of the cryoprobe is rapidly cooled for ~5 s, which flash-freezes any adjacent tissue and causes it to stick to the tip of the probe. By then removing the scope and probe together, the biopsy sample is separated from the sampling area and can be prepared for analysis (figure 4). Cryobiopsy techniques are discussed in more detail elsewhere in this *Monograph* [34].

Several authors have reported success using pleural cryobiopsy, often comparing the size and quality of biopsy samples to those taken using standard flexible forceps during the same procedure [29, 30, 33, 35–37]. In general, these series reported significantly larger biopsy sizes and a dramatic reduction in crush artefacts [29, 30] when using the cryoprobe, with no apparent increase in the rate of procedural complications [29, 30, 35–37]. In one case report, a patient with challenging sarcomatoid mesothelioma was able to be diagnosed using cryobiopsy after failure of the more conventional approach [33]. Only one series has compared rigid biopsies with both flexible and cryoprobe biopsies. The authors concluded that, although rigid sampling remains the gold standard for tissue volume and improving depth (being significantly better than either of the other approaches), cryoprobe biopsies are themselves significantly better than standard flexible biopsies [35].

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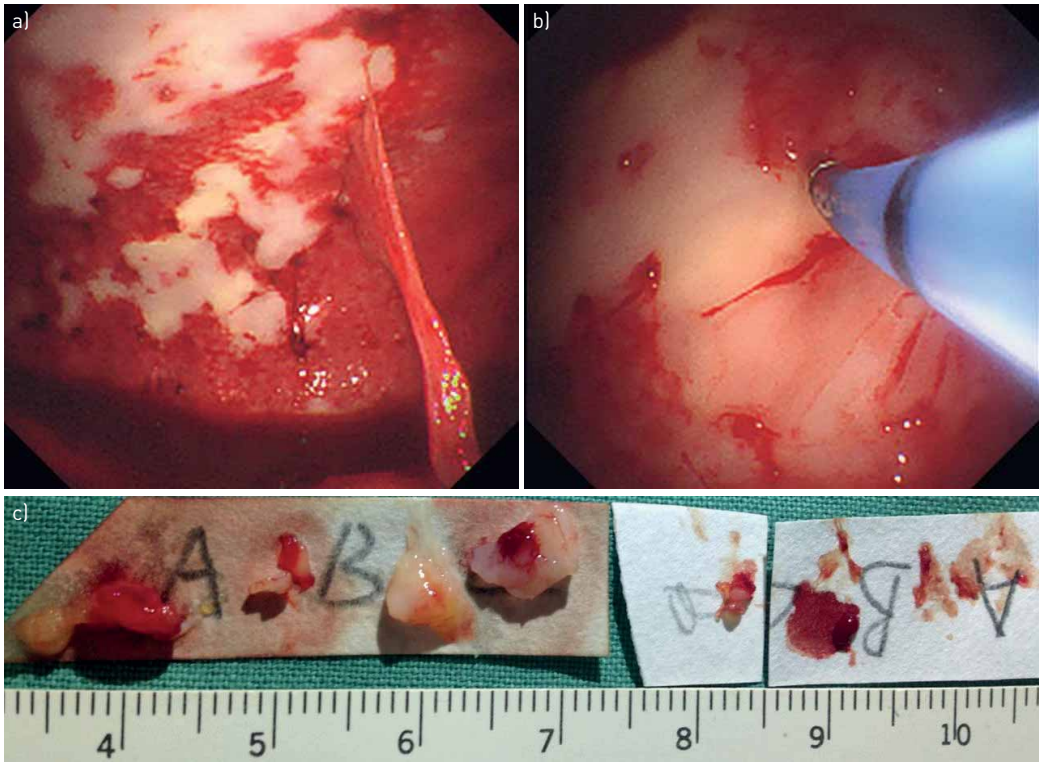

Figure 4. Use of pleural cryobiopsy to diagnose mesothelioma. a) Candle wax parietal pleural abnormalities; b) cryoprobe biopsy of target area; c) size of pleural biopsies (left: cryoprobe; right: forceps). Reproduced and modified from [33] with permission.

Improving videoscopic appearance

The typical thoracoscopy, much like bronchoscopy or endoscopy, involves the use of "white" light, giving the operator a visual representation of the pleural landscape akin to using their own eyes in natural light. In some circumstances, however, differentiating between normal, inflammatory and malignant tissue areas can be extremely challenging using this method.

A number of attempts have been made to try and overcome this by altering the images sent back to the LAT operator. Broadly speaking, this involves adapting the wavelengths of light detected by the thoracoscopy camera system based on the behaviours of different types of tissue under varying conditions. The different techniques may be broken down into photosensitiser-enhanced fluorescence, autofluorescence and NBI. The first relies on both the prior administration of a fluorescing agent and a suitably stimulating light generator, the second on just the light generator, and the third on the use of specific light wavelengths that are known to be well absorbed by vascular structures. Myers and Lam [38] provide a more detailed description of some of these specific techniques in the context of early lung cancer detection.

Following small animal studies, the first description of such an approach was published in 2004 [39] and was followed up in 2006 by a small series from the same centre [40]. Noppen *et al.* [40] asked 12 patients with primary spontaneous pneumothoraces (and 17 controls) to inhale a solution of 10% fluorescein prior to LAT. Under "blue" light, areas of subpleural photosensitiser accumulation were seen in areas that were not otherwise picked up with

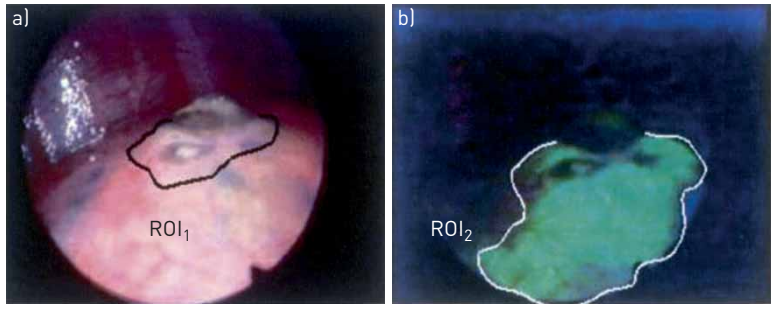

Figure 5. Fluorescein-enhanced imaging in a patient with pneumothorax. a) White light thoracoscopic view of an abnormal region of the lung (visceral pleural irregularity, covered with foam). The approximate surface of the outlined region of interest $(ROI)_1$ is ~2×3 cm. b) Blue light image of the same region shows a much larger area of subpleural fluorescein accumulation; the outlined ROI_2 covers ~5×7 cm. Reproduced and modified from [39] with permission.

conventional white light, suggesting that there may be a role for improving targets for visceral intervention (figure 5). Some groups have used 5-aminolaevulinic acid as the photosensitiser, this time pre-administered orally, and concluded that there was a subjective improvement in being able to identify areas for pleural biopsy as areas of suspected malignancy were highlighted as bright red. The effect was particularly useful in cases of mesothelioma as up to 57% of patients could be upstaged due to the identification of additional lesions [41, 42].

Autofluorescence relies on the intrinsic response of certain tissues to particular light types, most commonly that in the range 390–460 nm. Chrysanthidis and Janssen [43] used this technique in 24 patients with undiagnosed pleural effusions, describing a 100% sensitivity for malignancy (with dramatic colour change and sharp tissue demarcation under blue light) (figure 6) and a 75% specificity (due to chronic pleuritis giving similar appearances in two cases). Although similarly encouraging results have been described by some authors [44], others have noted lower utility, which was driven largely by the challenges associated with identifying mesothelioma [45].

NBI is readily available on most bronchoscopic systems. It utilises very specific wavelengths of light, with different penetration abilities, to image blood vessels at different levels in

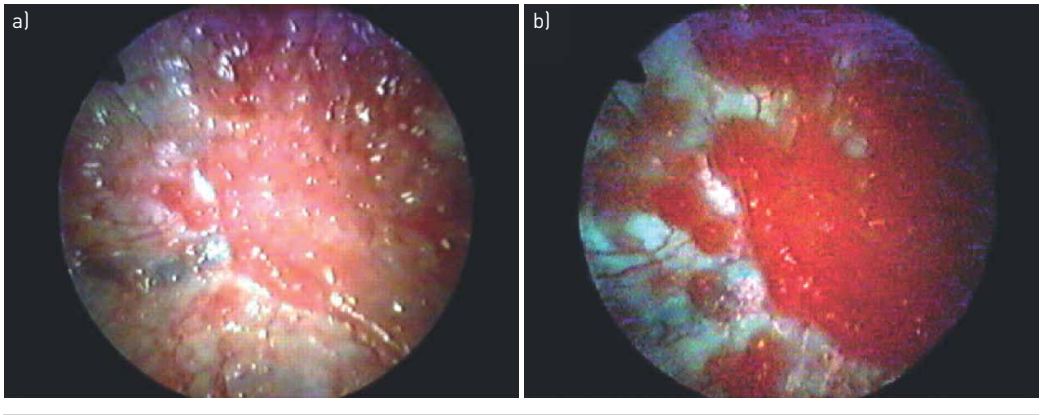

Figure 6. Autofluorescence thoracoscopy showing clear demarcation of malignant tissue. a) White light thoracoscopy. b) Autofluorescence thoracoscopy. Reproduced and modified from [43] with permission.

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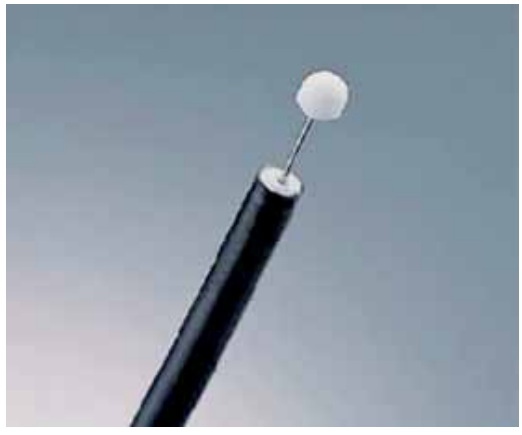

Figure 7. Example of an insulated-tip diathermy knife (Olympus Medical Systems, Tokyo, Japan). Reproduced and modified from [49] with permission.

mucosal tissues, aiming to highlight particularly vascular (and potentially malignant) areas for biopsy. Two case series have looked at the utility of NBI at LAT. Both sets of authors were more clearly able to visualise blood vessels compared with conventional white light [46, 47], but only one group found enough of an improvement to reliably identify malignant lesions, an effect which was even more pronounced in flat lesions [46].

All of the image enhancement techniques described are promising, but none have, as yet, found a role beyond the research environment. This is most likely due to the already high diagnostic rates of standard LAT [48], which suggest that, if image enhancement is to become mainstream, it will be with the promise of incremental gains in diagnostic yield only.

Diathermy-enhanced biopsy techniques

Diathermy involves the creation of very-high-frequency alternating current and its subsequent passage through the body. The electricity generates high localised heat that is targeted to coagulate bleeding vessels or cut through tissues. Having become a staple in all kinds of surgery, recent years have seen the development of devices that are primarily intended for endoluminal use, especially at gastroendoscopy, and that have begun to find application at LAT. These "insulated-tip" (IT) electrosurgical knives utilise a blunt ceramic pad at the end of a flexible probe, the distal portion of which has a short, exposed diathermy region (figure 7). Diathermic biopsies may theoretically be used to break down more vascular intrapleural adhesions, to obtain samples from either the parietal or visceral pleural surfaces, or indeed to biopsy the lung parenchyma itself.

The first reports of IT knives being used to improve parietal biopsy at LAT appeared in 2008, with probes being passed *via* semirigid devices [50, 51]. Following a subpleural injection of epinephrine and local anaesthetic to raise the pleural surface, a small hole was made in the pleural surface before the IT knife was used to excise a large, circular biopsy specimen [50]. The same group then described a series of 20 patients biopsied using a combination of an IT knife and standard forceps. The data describe no significant complications and a higher diagnostic yield with the diathermy technique (85% *versus* 60%). In 40% of cases the IT knife biopsy was diagnostic when the standard technique was

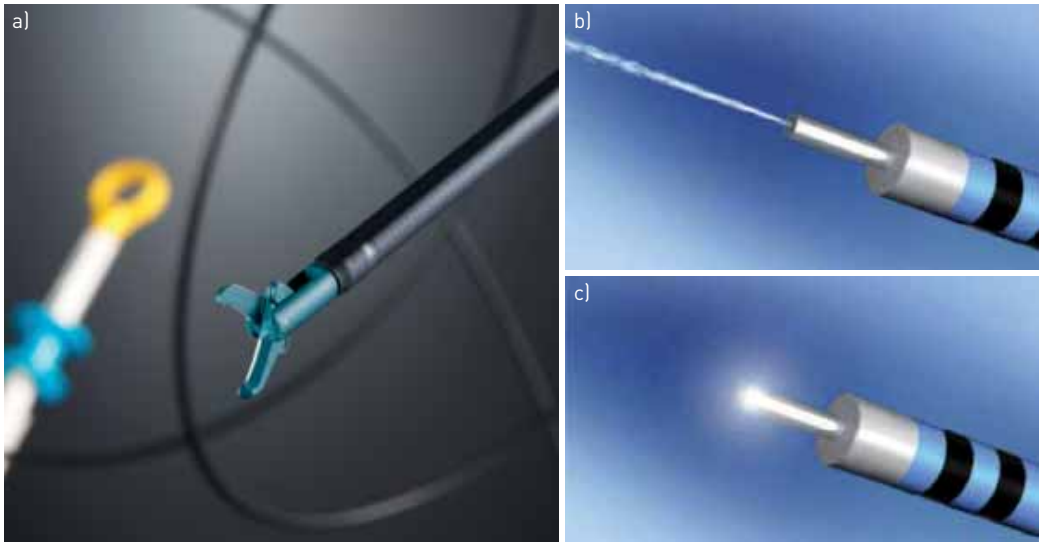

Figure 8. a) SB Knife Jr. Reproduced with kind permission of BVM Medical (Hinkley, UK). b, c) Hybridknife (Erbe Medical, Leeds, UK).

not [49]. Subsequent, recent publications have focused on improved technology to enhance the ease and effectiveness of the biopsy process. Wang *et al.* [52] describe the use of the SB Knife Jr, an insulated scissor-like probe, in two patients, and Yin *et al.* [53] used a water-jet/diathermy hybrid probe, both with documented success (figure 8).

Peripheral lung biopsy at rigid thoracoscopy for the diagnosis of parenchymal disease was described as early at 1982 [54], with this technique perhaps representing the closest encroachment by physicians on what is typically considered uniquely surgical ground. The usual approach is to use diathermy cup forceps to sample the lung either peripherally (for visceral pleura) or slightly deeper (for subpleural parenchymal tissue) [55, 56]. Studies have been targeted at those patients who have undergone unsuccessful standard workup for ILD but in whom general anaesthetic VATS is not felt to be appropriate. A few retrospective studies, predominantly from Egypt, have found the procedure to be safe and feasible for LAT operators, albeit with a tendency to require intercostal tubes to remain in place for slightly longer than is usual after standard LAT [57–59]. Complications were rare, the largest series (of 55 patients) describing cases of prolonged air leak (four patients), residual pneumothorax (one patient) and subcutaneous emphysema (two patients). No deaths were reported and a definitive diagnosis was achieved in >98% of cases [58].

Despite these reports, visceral intervention at LAT is rare and, in our opinion, should be approached and used with extreme caution only by those with sufficient training and support.

Advanced therapeutic techniques

Thoracoscopic pleurodesis

Following parietal pleural biopsy, an attempt at inducing pleurodesis is perhaps the most common intervention undertaken at LAT. For many, the ability to perform a "one-stop"

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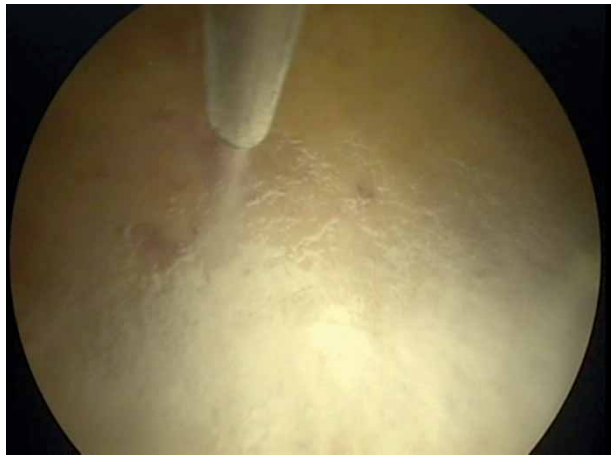

Figure 9. Image of thoracoscopic talc pleurodesis. Reproduced with kind permission of N. Rahman (University of Oxford, Oxford, UK).

diagnostic, therapeutic and theoretically preventative procedure for undiagnosed pleural effusion is the primary attraction of the technique. Indeed, the BTS now considers pleurodesis to be part of the core skill set for those setting up a thoracoscopy service and define it as a level I competency [3]. In those with recurrent malignant pleural effusion (MPE), LAT may also be used with the sole intent of relieving symptoms and administering a pleurodesis agent. A great number of different agents have been used to try to induce a reliable chemical pleurodesis [60]. Of these, talcum powder has been shown repeatedly to be the most efficacious and easy to use, and it is now regarded as the gold standard agent by national guidelines [61]. It should be noted, however, that talc being the preferred pleurodesis agent is not synonymous with pleurodesis itself being the preferred treatment for all patients with MPE. Recent opinion (and certainly our own practice) has begun to swing towards offering a treatment strategy more attuned to the wishes and life expectancy of the patient, including the first-line use of indwelling pleural catheters if appropriate [62–64].

Talc may be applied to the pleural cavity either in slurry form, *via* an already-inserted chest tube, or *via* "poudrage", at thoracoscopy, whereby atomised talc powder is coated over the whole of the pleural surfaces (figure 9). Both methods are performed with a view to stimulating a generalised inflammatory reaction and visceroparietal adhesion, but the appeal of the latter is being able to have a greater degree of control over the talc application and distribution, theoretically producing a more even inflammatory response. This may have merit as previous studies have shown a tendency for talc slurry to accumulate basally in the costophrenic recesses [65].

The technique of talc poudrage varies slightly depending on the LAT equipment being used. With the more common, and larger, rigid scopes, a hand-held pump atomiser apparatus is used to drive a typical dose of 4 g of talc through a fine nozzle and into the pleural cavity *via* the thoracoscopy port (figure 10). The operator is easily able to vary the speed and direction of the jet of talc, and if a dual-port approach is used, can do so under direct vision. If a semirigid thoracoscope or mini-thoracoscope is used instead, either hand-atomised or an aerosol-driven talc dose may be given *via* a narrower, longer nozzle which is passed down either scope's working channel.

Figure 10. Examples of devices available for poudrage. Reproduced with kind permission of Novatech (La Ciotat, France) ©Novatech S.A. France.

The effectiveness of talc poudrage in MPE, especially in comparison with talc slurry, has been the subject of several randomised studies [66–68]. The largest of these, by Dresler *et al.* [66] in 2005, was unable to demonstrate any significant difference between the two methods, although secondary outcomes suggested that there may be a signal for benefit in certain subgroups. This study was included in a recent, comprehensive network meta-analysis that collated data from 62 randomised controlled trials of pleurodesis agents, encompassing almost 3500 participants. Significant heterogeneity between studies was noted, but with this caveat, talc poudrage was felt likely to be the most efficacious agent in comparison with others, without any evidence to suggest its use leads to more pain, fever or death [60]. Although likely to be the "best" agent, quantifying the exact success (or failure) rate for talc poudrage is more challenging, not least because of varying trial inclusion criteria, outcome definitions and analysis time-points. This is highlighted by the extremely wide range of reported failure rates in the literature, which have been documented as being as low as 0% or as high as 40% in the larger trials [60]. A major multicentre study examining further the effectiveness of poudrage *versus* slurry will hopefully help to address some of these issues in the near future [69]. In some centres, the combined use of talc poudrage with indwelling pleural catheter placement during LAT has led to promising results. One small series has reported a 92% pleurodesis success rate at 6 months and a median inpatient duration of 2 days, both of which, if reproduced in larger studies, would represent significant advances in the management of MPE [70].

Early minor effects of talc may include pleuritic pain, transient hypoxaemia and gastrointestinal upset [71, 72]. Major complications from the use of talc poudrage are well documented but relatively uncommon, with reports focusing primarily on the development of acute respiratory distress syndrome in some patients [66, 73]. The incidence of this appears to have diminished following the more widespread use of "graded" talc, which is processed to ensure a larger mean particle size is present. This was following research suggesting that talc with a smaller mean diameter led to a greater degree of systemic absorption and subsequent inflammatory response [74, 75].

Treatment of pneumothorax

Although there are data to suggest that the treatment of pneumothorax (either primary or secondary) at LAT is feasible, this practice appears to remain relatively rare. This is likely

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because complex parenchymal intervention, such as bullectomy, is generally seen as the ideal method to ensure successful and permanent treatment, and that this is more appropriately undertaken at VATS under general anaesthesia [76].

Some evidence would suggest, however, that undertaking pleurodesis alone is an adequate method for pneumothorax prevention [77]. Following this logic, there have been a number of studies that have reported the use of LAT to inspect the lung and administer a pleurodesis agent in patients with pneumothorax [78–82]. The commonest agent used in this setting is talc, given *via* poudrage as described earlier, with a focus on patients presenting with primary spontaneous disease. The most robust of these was performed by Tschopp and colleagues who, having reported a retrospective series with a 95% success rate over a median follow-up of 5 years [83], went on to perform a randomised trial comparing poudrage at LAT to chest drain insertion (without attempt at chemical pleurodesis) [81]. Perhaps unsurprisingly, they were able to demonstrate a significant difference in long-term pneumothorax recurrence rates, strongly favouring the pleurodesis arm (5% *versus* 34%) [81], and this success rate was matched by a subsequent retrospective study of 112 patients [80].

It must be highlighted, however, that the normal (nondiseased) parietal pleural surface, as seen in the majority of pneumothoraces, tends to be exquisitely painful during any intervention, and thus the presence of a separate clinician to manage sedation and analgesia is perhaps even more vital in this setting [3].

LAT and poudrage have also been described in more complex or secondary pneumothoraces in patients who have been deemed too risky for general anaesthesia. Lee *et al.* [78] reported such an approach in 41 patients with COPD, who had a mean FEV_1 of 41% predicted. Although they experienced a 30-day mortality rate of 10% (in a group of patients with the worst airflow obstruction), the authors conclude that their overall 95% success rate at a median of 35 months for the rest may justify the use of this treatment.

LAT for pleural infection

Similar to the treatment of pneumothorax, the current general consensus among LAT practitioners is that thoracoscopic intervention with the infected pleural space should be the domain of the thoracic surgeon [84]. Despite this, there is a small group of studies (none of them prospective or randomised) which suggest that, in expert hands and in carefully selected cases, LAT may have a role in the management of pleural infection [85–87]. The theoretical attraction of LAT in this setting is being able to visually identify and break down fibrous pleural adhesions to improve outflow from the infected space (figure 11), as well as the more targeted placement of a chest tube. The largest of the studies comprised 127 patients treated over a 14-year period across three European hospitals [86]. The authors included only those patients with multiloculated effusions, without fibrothorax, who could theoretically benefit from adhesiolysis and targeted locule drainage. The reported early "success" rate was 91%, although it should be noted that almost half of those who underwent LAT also received fibrinolytic therapy. The predominant complication was persistent air leak, occurring in 7% of patients. Overall, 94% were managed without the need for surgical intervention [86]. The treatment of a further 41 patients over 6 years was more recently described by Ravaglia *et al.* [85], with a similarly high success rate (85%), but once again in conjunction with half of the patients receiving intrapleural urokinase.

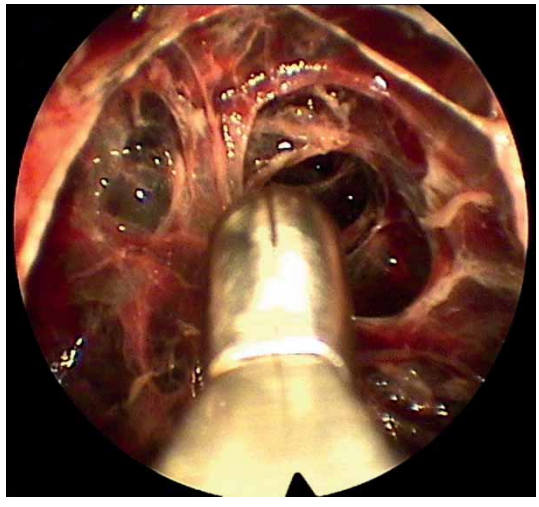

Figure 11. Example of a highly loculated infected pleural space.

The authors of both studies conclude that LAT may be considered as an adjunct to the traditional "medical" treatment options for pleural infection, rather than a replacement for appropriate surgical referral, having found it to be safe and relatively easy to perform [85, 86]. Without prospective studies it is unlikely that this intervention will gain widespread acceptance but, in theory, there may be a group of patients in whom LAT is the best treatment option, especially those in whom minimising invasiveness is seen as key.

Removal of a foreign body from the pleural space

There are several case reports of pleural foreign bodies being removed at LAT, using both rigid and semirigid devices. Such events are uncommon problems and, except in the rarest of circumstances, would preferentially be removed using VATS. Foreign bodies fall into two main categories: those involving trauma and those that are iatrogenic in nature, and it is the latter group in which some LAT operators have limited experience: both needles and surgical blades having been successfully removed when accompanied by a large pleural effusion. In one example an 8 cm long needle was found in the pleural space following a successful medical thoracocentesis [88]. In all cases, forceps were used to grasp the foreign body and remove it through the introducer port, often en bloc [88, 89].

A decision to attempt foreign body removal should be made in consultation with thoracic surgical colleagues and ideally with them on standby in case of difficulty. A large pleural effusion (empyema or pleural fluid) so that the pleural space may be accessed should be considered a prerequisite and there should be good quality imaging to fully assess the position of the foreign body, which should not approach the mediastinum, major vasculature or the lung itself.

A more general discussion of foreign body removal is provided elsewhere in this *Monograph* [90].

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Conclusion

LAT is now a well-established tool for a significant proportion of pulmonologists, with basic procedures available to an increasing number of patients at an increasing number of hospitals. As experience of the use of LAT has grown and the accessibility of equipment has improved, so too has the confidence with which operators approach more challenging situations. This means that the cohort of pulmonologists who routinely undertake advanced diagnostics and interventions continues to grow, with some now considering cases that would historically have only been possible using VATS and general anaesthetic. In extremely isolated cases, a few respiratory interventionalists routinely perform even more complex procedures, including sympathectomy (*e.g.* for hyperhidrosis) and splanchnicolysis (*e.g.* for chronic pancreatitis pain), albeit with the support of full general anaesthetic [91–93]. It must be stressed, however, that such individuals are in the overwhelming minority and that there is likely to always be a need to refer for thoracic surgical expertise in cases of, for example, haemothorax, fibrothorax or persistent air leak.

Caution should also be exercised with regard to adopting advanced techniques if establishing a LAT service as, more often than not, simple methods will be sufficient. It is unlikely that the majority of techniques described in this chapter will become mainstream, especially as many remain experimental or research-only modalities for the time being. Nonetheless, as pressure increases on limited thoracic surgical resources in many areas, the role of the interventional and pleural pulmonologists expands, and technological advances continue apace, future years are likely to continue to see a greater blurring of the line between what has traditionally been considered a medical thoracoscopic or a "surgical" procedure.

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Chapter 22

Upcoming techniques

Daniela Gompelmann

Interventional bronchoscopy is a rapidly expanding field in pneumology offering minimally invasive therapeutic approaches in various pulmonary diseases. In the last decade, various bronchoscopic techniques have evolved for patients with COPD. Targeted lung denervation, the latest development in the field of endoscopic therapies in COPD, provides radiofrequency ablative therapy targeting the parasympathomimetic innervation of the airways leading to sustainable bronchodilation. Furthermore, endoscopic cryospray therapy that may destroy the mucus-producing glands in patients with chronic bronchitis presents an area of current investigation. Further fields of research include biodegradable stents in central airway obstruction that maintain the airway patency over time. One essential focus in bronchoscopy is the diagnostic and therapeutic approach for solitary pulmonary nodules. Bronchoscopic transparenchymal nodule access is the first guidance technique that allows access to the pulmonary nodules *via* the healthy lung parenchyma. Bronchoscopic therapies for early-stage peripheral lung cancer are also currently under investigation, including transbronchial brachytherapy, bronchoscopy-guided RFA, bronchoscopic thermal vapour ablation and bronchoscopy-guided microwave ablation.

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Therapeutic bronchoscopy had been performed using a rigid bronchoscope in the late 1800s by Gustav Killian, the father of bronchoscopy. At that time, instruments for foreign body extraction, dilators and endobronchial stents were already available. After the advent of flexible bronchoscopes in the 1960s, bronchoscopy spread rapidly, thus presenting one of the most important diagnostic and therapeutic tools in the field of pneumology. Nowadays, interventional bronchoscopic procedures facilitate minimally invasive therapeutic approaches in various pulmonary diseases.

Recent developments in the field of interventional pulmonology include therapeutic options in pulmonary diseases such as COPD, chronic bronchitis, central airway obstruction (CAO) or solitary pulmonary nodules (SPNs). This chapter summarises the upcoming techniques in interventional pulmonology: targeted lung denervation (TLD) for patients with obstructive lung diseases, cryospray therapy for the treatment of chronic bronchitis,

Pneumology and Critical Care Medicine, Thoraxklinik, University of Heidelberg and Member of the German Center for Lung Research (DZL), Heidelberg, Germany.

Correspondence: Daniela Gompelmann, Pneumology and Critical Care Medicine, Thoraxklinik at University of Heidelberg, Röntgenstrasse 1, 69126 Heidelberg, Germany. E-mail: daniela.gompelmann@med.uni-heidelberg.de

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biodegradable stents for CAO, bronchoscopic transparenchymal nodule access (BTPNA) and various endoscopic therapeutic modalities for peripheral lung cancer. Furthermore, the development of robotic endoscopy systems is also discussed.

TLD for treatment of obstructive lung diseases

COPD is pathophysiologically characterised by chronic bronchitis, expiratory airflow limitation and emphysematous destruction of the lung parenchyma associated with hyperinflation. The main symptoms are productive cough, shortness of breath and limited exercise capacity reducing quality of life. So far, there is no curative treatment approach, so that the fundamental therapeutic strategies, including cessation of cigarette smoking, exercise training, pulmonary rehabilitation and pharmacological therapy, are aimed at preventing progression of COPD [1]. In appropriately selected patients with very advanced COPD, lung transplantation may be considered as a therapeutic, symptom-modifying treatment approach. Moreover, lung volume reduction techniques comprising lung volume reduction surgery and various therapeutic endoscopic approaches may reduce hyperinflation in adequately selected patients with the emphysema phenotype and a residual volume >175% predicted [2].

Patients with predominant chronic bronchitis without significant emphysema and hyperinflation will, however, not benefit from lung volume reduction techniques, as airflow obstruction is the leading cause of symptoms. Airflow limitation results from irreversible airway remodelling and reversible bronchoconstriction due to increased cholinergic parasympathetic innervation. It seems that vagal dysregulation in patients with COPD contributes to enhanced bronchial smooth muscle contraction and greater mucus secretion [3]. Therefore, antimuscarinic drugs that block acetylcholine binding to muscarinic receptors and thus lead to bronchodilation are recommended as first-line therapy for patients with COPD [1].

The idea of the anticholinergic therapeutic approach came historically from parasympathetic nerve disruption *via* surgical vagotomy in patients with obstructive lung diseases. This surgical approach certainly showed proof of principle, but revealed generally poor results given the underlying invasiveness of this surgical method [4].

A new treatment approach, *i.e.* TLD (Holaira, Minneapolis, MN, USA), provides minimally invasive radiofrequency ablative therapy targeting the parasympathomimetic innervation of the airways, leading to sustainable bronchodilation.

In order to perform TLD, a dedicated catheter (dNerva dual-cooled radiofrequency catheter; Holaira) designed to target tissue heating at depth is advanced bronchoscopically into the main bronchus. After positioning the catheter, the balloon at its distal tip is inflated so that the silver electrode on the balloon that delivers the radiofrequency has contact with the airway wall (figure 1). Furthermore, a contrast-filled balloon is inserted into the oesophagus so that the proximity from the electrode of the dNerva catheter to the oesophagus can be estimated under fluoroscopy (figure 2). Depending on the distance to the oesophagus, an adequate energy dose is chosen and delivered to ablate the parasympathetic pulmonary nerves along the main bronchi. During delivery of radiofrequency current, a coolant circulates through an outflow conduit on the balloon to protect the inner surface of the airway wall. Once the energy has been delivered in one

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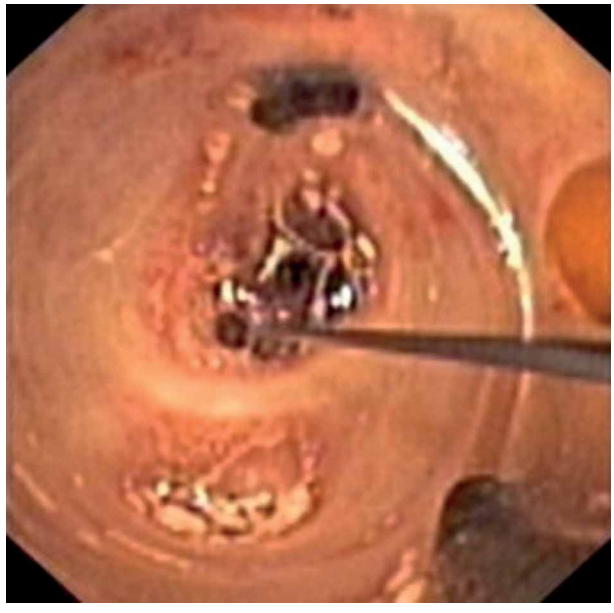

Figure 1. Bronchoscopic image. Positioning of the dNerva dual-cooled radiofrequency catheter (Holaira, Minneapolis, MN, USA) in the main bronchus. Reproduced with kind permission of D-J. Slebos (University Medical Center Groningen, Groningen, The Netherlands).

position, the balloon is deflated and rotated to the next position so that the electrode is activated in four rotational positions to achieve complete circumferential treatment. TLD can be performed bilaterally in both main bronchi in one single procedure.

TLD is currently under clinical investigation and is not yet commercially available. The first-in-human study published in 2015 demonstrated the safety and feasibility of TLD in patients with moderate to severe COPD [5]. In this prospective multicentre trial, TLD was performed at 20 W in 12 patients or 15 W in 10 patients in two endoscopic procedures that were well tolerated in all subjects. One year following intervention, patients treated with 20 W experienced a mild, but not statistically significant improvement in lung function parameters and exercise tests, but a significant improvement in heath-related quality of life measured by the St George's Respiratory Questionnaire. These improvements tended to be larger than those observed in patients treated with 15 W. Furthermore, early data suggested that the combination of anticholinergic drugs and TLD might result in an increase in FEV_1 over that seen with an antimuscarinic drug alone. Within the first month following intervention, seven severe adverse events occurred, including COPD exacerbation, anaphylactic drug reaction, coronary artery bypass, chest pain and gastroparesis. Bronchial perforation was observed in two patients, and bronchial stenosis and bronchial ulceration were observed in one patient each.

Further trials are necessary to support the preliminary encouraging results and to show the safety of this new technology. Two prospective randomised controlled trials, the "Targeted Lung Denervation for Patients With Moderate to Severe COPD" trials known as AIRFLOW-1 and AIRFLOW-2, are currently ongoing in Europe (ClinicalTrials.gov: identifier NCT02058459). As TLD focuses on reversible bronchodilation, it may also present a treatment approach for patients with uncontrolled asthma, but this has to be evaluated in a pilot trial (ClinicalTrials.gov: identifier NCT02872298).

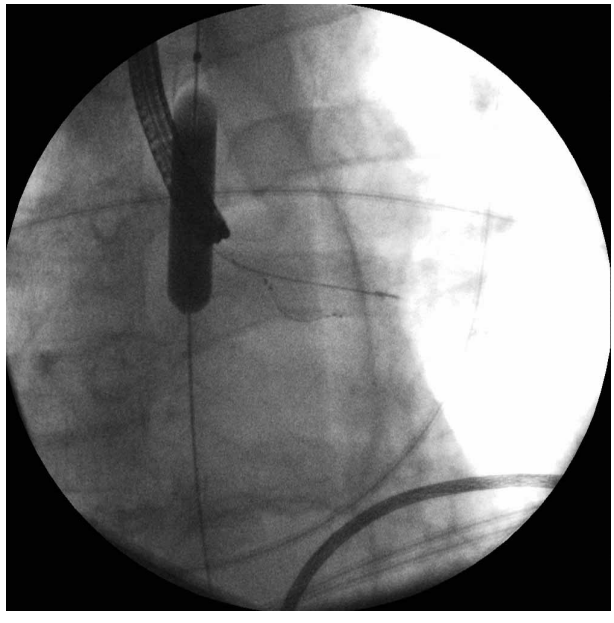

Figure 2. Fluoroscopic image. A contrast-filled balloon is inserted into the oesophagus so that the proximity of the electrode of the dNerva catheter (Holaira, Minneapolis, MN, USA) to the oesophagus can be estimated.

Liquid nitrogen metered cryospray for treatment of chronic bronchitis

Chronic bronchitis is defined as the presence of cough and sputum production for at least 3 months in 2 consecutive years. Mucus hypersecretion is pathophysiologically caused by chronic inflammation of the bronchial lining, submucosal mucus-producing gland hypertrophy and goblet cell hyperplasia [6]. The excess mucus in the bronchi may result in airway obstruction leading to impaired ventilation, and thus to dyspnoea and limited exercise capacity. Furthermore, mucociliary clearance is compromised, which enhances bacterial colonisation and exacerbations. There is no curative treatment at present; the current therapeutic options focus on promoting mucus clearance and symptom relief.

The RejuvenAir system (CSA Medical, Lexington, MA, USA) provides a new bronchoscopic treatment approach that addresses chronic bronchitis by destroying the mucus-producing glands and goblet cells by delivery of liquid nitrogen as a metered cryospray (MCS) (figure 3).

Initially, cryospray therapy was developed for the treatment of oesophageal malignancies, particularly for the eradication of low-grade and high-grade dysplasia in Barrett's oesophagus [7, 8]. Cryospray therapy provides a noncontact cryogenic effect on tissues. By spraying liquid nitrogen through a catheter, the target mucosa is frozen and cellular apoptosis due to intracellular ice crystallisation of the cryosensitive tissue is achieved. The boiling point of nitrogen liquid (–196°C) is very low, leading to a rapid flash-freezing on the tissue. Due to the uniform and planar distribution of the liquid nitrogen, a relatively large area is addressed despite irregular surfaces. When using cryospray therapy in the gastrointestinal tract, the nitrogen gas that is produced by the phase transformation of the liquid nitrogen droplets is evacuated by an additional suction tube.

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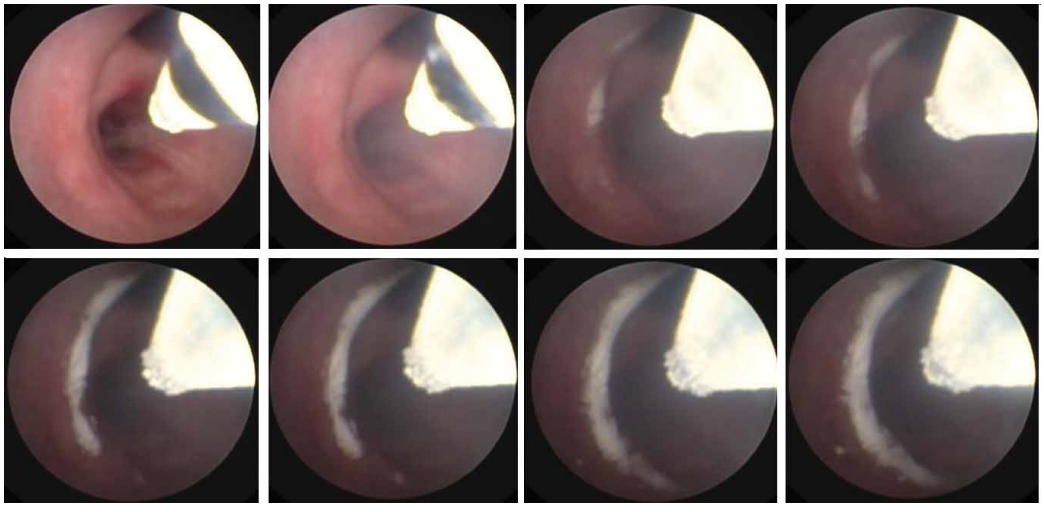

Figure 3. Bronchoscopic images. Cryospray therapy in the right main bronchus. Reproduced with kind permission of D-J. Slebos (University Medical Center Groningen, Groningen, The Netherlands).

In bronchoscopic procedures, however, no additional suction tube can be placed due to lack of space, so that the expansion of nitrogen gas may result in barotrauma or pneumothorax. Therefore, sufficient venting of nitrogen gas using a rigid bronchoscope or an endotracheal tube with the cuff deflated and disconnected from the ventilator is crucial. In 2010, Krimsky *et al.* [9] reported the first three cases where cryospray therapy was used successfully for the treatment of glottic or subglottic stenosis. After encouraging results in the initial trials and after modifying the device for the liquid nitrogen delivery, the cryospray device (G2 TruFreeze system; CSA Medical) received US Food and Drug Administration approval. Since then, different trials have been performed demonstrating the feasibility, safety and efficacy of cryospray therapy in patients with malignant or benign airway obstructions [10, 11, 12]. In the first trial using the new-generation device, the authors reported successful cryospray therapy in three patients with CAO due to lung cancer and in one patient with benign post-intubation tracheal stenosis [10]. In another trial published in 2016, 12 patients with malignant CAO and 10 patients with benign CAO underwent cryospray therapy [12]. An improvement in grade of stenosis after treatment was observed in 86.4% of the patients. No intraprocedural death occurred; the rate of procedure-related morbidity was 1.5%.

The RejuvenAir system is the latest development in the field of cryospray therapy. This system consists of a catheter and console with pressure and temperature controls that enable the delivery of liquid nitrogen in a circumferential pattern to meet a predetermined level of cooling for each MCS delivered. The amount of liquid nitrogen is adjusted so that each airway is treated by a standardised amount of nitrogen based on airway size, leading to a 10 mm circular cryoablation with a depth between 0.1 and 0.5 mm. It is hypothesised that the rapid freezing of the epithelial layer of the airway walls will destroy the mucus-producing goblet cells while preserving the extracellular matrix, thereby enabling the regrowth of healthy cells. The RejuvenAir system is currently under clinical investigation and is not commercially available.

The first description of the feasibility and safety of liquid nitrogen MCS therapy was by Slebos *et al.* [13]. 16 patients who were scheduled to undergo lobectomy or pneumonectomy

received MCS therapy prior to surgical intervention. MCS treatment was performed by flexible bronchoscopy under general anaesthesia using an endotracheal tube. During delivery of liquid nitrogen, the endotracheal tube was disconnected from the ventilator and the cuff deflated to allow the nitrogen gas to exit. In all subjects, MCS delivery was feasible and safe. Serious adverse events included atrial fibrillation, mucus plugging, intra- and postoperative bleeding after VATS, and one death >30 days following pneumonectomy due to pneumonia in the nontreated lung. All of these serious adverse events were determined to be unrelated to the MCS treatment. Histological examination from immediate resection specimens revealed minimal to mild acute inflammation with extension into the submucosa with cryothermic changes involving the submucosal glands.

In this first trial, the intended indication (*i.e.* chronic bronchitis) was not specifically studied, although these patients presented some features of the condition. A larger clinical trial in subjects with a known diagnosis of chronic bronchitis who have daily symptoms of cough and sputum despite being on optimal medication is ongoing (ClinicalTrials.gov: identifier NCT02483637).

Biodegradable stents for CAO

CAO due to malignant or benign processes can lead to cough, dyspnoea, stridor and post-stenotic pneumonia, and may also present an acute life-threatening situation due to ventilatory failure. Malignant CAOs are caused by lung cancer, neoplasms of the oesophagus, larynx or thyroid, metastases of extrathoracic carcinomas, or malignant lymphomas. Benign stenoses often result from scarred tissue, *e.g.* following intubation, tracheostomy or transplantation, but are also observed in the course of various diseases involving the central airways, *e.g.* vasculitis, papillomatosis, tuberculosis or sarcoidosis. Implantation of airway stents can re-establish the patency of narrowed airways to attenuate symptoms. Thereby, airway stenting stabilises the lumen of the trachea or main bronchi in the case of extrinsic airway compression, but also provides maintenance of airway patency after debulking of intraluminal malignant or benign obstruction. Airway stenting is particularly considered in malignant CAO, whereby in benign stenoses, surgical intervention is still the treatment of choice and stent placement should be only discussed for those who are technically inoperable or with a very high risk. Silicone or metallic stents are available that differ in terms of implantation technique, complication rate and removability. Airway stenting is often considered as palliative treatment to relieve symptoms so that stent removability is irrelevant in these cases. However, stent placement may also present a bridging therapy in curative approaches, *e.g.* in malignant diseases prior to commencing antineoplastic therapy, and can also present a curative treatment approach itself, *e.g.* anastomotic airway stenosis after lung transplantation [14].

In particular, the removal of metallic airway stents can be associated with complications after long-term stenting. Retained stent pieces or mucosal tears with bleeding may occur after stent removal [15]. Therefore, biodegradable stents that would maintain the airway patency over time, then gradually degrade and vanish from the airway, present an area of current research [16]. In 2011, the first use of biodegradable stents in six patients with bronchial anastomotic stenosis after lung transplantation was described [17]. Stent implantation led to stenosis relief in all six patients. However, multiple stenting was necessary in four out of the six patients because of restenosis. Overall, this small pilot study showed that biodegradable stents are safe and effective, and may present an alternative to

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metallic or silicone stents in transient stenotic processes. Further smaller trials reported successful biodegradable stent implantation in children [18, 19]. One concern, however, is that stent particles may be produced during the stent degradation process that could lead to severe airway obstruction, particularly in small sized paediatric airways [20].

Overall, the data are still very limited, and the safety and efficacy of biodegradable stents need to be evaluated in larger trials. In general, implantation of airway stents is always a procedure of last resort and is only recommended if no other therapeutic approaches are available in an individual patient. Biodegradable stents may present a therapeutic option for transient CAO with the advantage that no stent removal that can be associated with complications is necessary.

BTPNA for sampling SPNs

SPNs present an increasingly frequent problem due to lung cancer screening that has been recommended for appropriate individuals for a few years. Screening with low-dose CT leads to a 20% reduction in deaths from lung cancer, but is often associated with the concern of overdiagnosis of SPNs. The nodule detection rate in a selected cohort screened with low-dose CT is ∼20%, whereby >90% of the nodules are benign [21]. Therefore, it is of great importance to offer various minimally invasive approaches that enable tissue diagnosis with a low-risk profile and thus avoid unnecessary surgery in cases of benign nodules. Transthoracic procedures, particularly CT-guided lung biopsies, enable SPNs to be assessed, but are associated with a high complication rate; pneumothorax with a rate of 19% following transthoracic fine-needle aspiration and 25% following transthoracic core biopsies is the most common adverse event [22]. In the last decade, several endoscopic approaches have evolved to aid identifying and sampling these peripheral lesions, *e.g.* EBUS, electromagnetic navigation bronchoscopy (ENB) and virtual bronchoscopy. These navigation techniques provide guidance to enable the bronchoscopist to choose the correct endobronchial pathway to reach the target nodule. However, if there is no visible bronchus leading to the lesion, the probability of reaching the SPN still remains low despite these new guidance technologies.

BTPNA differs completely from the other guidance techniques as this method does not provide an endobronchial pathway, but allows access to nodules *via* the healthy lung parenchyma and thus is independent of the need to have an airway leading into the lesion [23, 24]. Prior to the bronchoscopic procedure, CT scans of the patient are uploaded on the Archimedes virtual bronchoscopy navigation system (Broncus Medical, Mountain View, CA, USA) that reconstructs the CT data into a three-dimensional (3D) model. After marking the target lesion to which navigation is desired, the Archimedes systems calculates the point of entry (POE) in the central airways with a straight-line, vessel-free access through the healthy lung parenchyma to the lesion and displays the tunnel path from the POE on the airway wall to the target nodule. During the bronchoscopic procedure, the Archimedes system integrates real-time fluoroscopy data and 3D CT data. First, the POE is identified under virtual guidance and a coring needle is used to penetrate the airway wall. The hole at the POE is then enlarged by a balloon dilator, and a sheath with radiopaque bands and a blunt dissection stylet is advanced through the lung parenchyma in order to create a tunnel to the target lesion under fluoroscopic guidance. A projection of the 3D target nodule and tunnel "guide rails" is displayed on the merged fluoroscopy image. Once the nodule is reached, the stylet can be removed and biopsy forceps are advanced through the sheath in order to sample the lesion.

The pilot human trial enrolled 12 patients with lesions up to 40 mm diameter (mean diameter 25 mm) from suspected lung cancer or metastatic disease and who were suitable for surgical resection [23]. BTPNA was performed in the operating room and after the bronchoscopic procedure, all patients underwent a subsequent surgical resection of the nodule. BTPNA was completed successfully in 10 out of the 12 enrolled patients. Only in two patients with lesions in the apical section of the left upper lobe, the tunnel from the POE to the lesion could not be created as it was not possible to orientate the bronchoscope properly at the POE location. Adequate biopsies sufficient for a histological diagnosis were obtained in all of the 10 patients in whom the tunnel was successfully created. No significant intraprocedural adverse events were observed. The only adverse event was a transient rise in troponin levels in one patient post-BTPNA and surgical resection. In a following trial, the BTPNA procedure was performed in six patients with peripheral lesions up to 30 mm in diameter (mean diameter 18 mm) in the endoscopic unit [25]. In five out of the six patients, the tunnel path was successfully created and adequate histological sampling was attained. Pneumothorax occurred in two patients, whereby a chest tube insertion was necessary in one of those patients. There were no other complications within 72 h following BTPNA.

BTPNA is still investigational. One prospective trial (EAST2) in the USA, China and Germany is ongoing to evaluate the diagnostic yield of BTPNA (ClinicalTrials.gov: identifier NCT02867371).

Bronchoscopic therapies for peripheral early lung cancer

The treatment of choice for malignant peripheral pulmonary nodules is surgical resection. However, many patients are poor candidates for surgery due to poor lung function or comorbidities, thus stimulating the search for other therapeutic options [26]. For these medically inoperable patients, SBRT is the preferred treatment [27]. Bronchoscopy may serve an adjunctive role, as endoscopically placed fiducial markers within or directly adjacent to the tumour may provide guidance for this focused radiotherapy [28]. This SBRT with fiducial-based tumour tracking allows accurate dose delivery and thus reduction of radiation exposure to healthy adjacent tissue. As well as SBRT, CT-guided percutaneous RFA may be considered for SPNs <3 cm. Other percutaneous therapeutic approaches comprise CT-guided microwave ablation and CT-guided cryoablation, which have been shown to be safe and effective for treatment of medically inoperable stage I peripheral lung cancer [29, 30]. However, percutaneous approaches are associated with a higher risk of pneumothorax, presenting a serious complication in patients with poor pulmonary reserve.

In recent years, various bronchoscopic treatment modalities for early-stage peripheral lung cancer have been developed, including transbronchial brachytherapy, bronchoscopy-guided RFA, bronchoscopy-guided microwave ablation and bronchoscopic thermal vapour ablation. These therapeutic methods may be combined with the bronchoscopic approaches that enable localisation of the peripheral lung lesions, *e.g.* EBUS, ENB or virtual bronchoscopic navigation.

Transbronchial brachytherapy

Endobronchial brachytherapy can be successfully applied as palliative treatment for patients with symptomatic malignant CAO [31]. However, there is little data on the use of brachytherapy in patients with malignant peripheral nodules. Harms *et al.* [32] reported

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electromagnetically navigated brachytherapy in one patient with medically inoperable nonsmall cell lung cancer in the right upper lobe. After identifying the pulmonary lesion using the electromagnetic navigation system (superDimension, Herzliya, Israel), a catheter was endoscopically advanced into the lesion. After confirmation of the correct position of the catheter within the lesion by using a radial ultrasound probe, a brachytherapy catheter was placed and fixed to the nose of the patient. After planning the brachytherapy on the basis of a 3D CT reconstruction with the catheter *in situ*, high-dose rate brachytherapy was performed three times within 5 days. Partial remission was observed at 12 months following intervention. However, prospective, larger trials are required to evaluate the safety and efficacy of transbronchial brachytherapy.

Bronchoscopy-guided RFA

In addition to SBRT, CT-guided percutaneous RFA presents a therapeutic option for medically inoperable patients with SPNs <3 cm. The percutaneous techniques are, however, associated with a higher risk of pneumothorax, prompting the search for safer endoscopic methods. The first description of a CT imaging/bronchoscopy-guided RFA was in 2010 [33]. In this trial, 10 patients with pathologically diagnosed nonsmall cell lung cancer, clinical stage T1N0M0, underwent bronchoscopy-guided RFA followed by surgical resection. Three types of internally cooled RFA catheters differing in the length of the activation tip were used. After insertion of the bronchoscope into the segment known to be the location of the lesion, one of the RFA catheters was advanced into the tumour under CT guidance and RFA was performed. During the RFA procedure, the catheter was cooled by infusion of cold water into the internal lumen of the catheter and the temperature was measured continuously. The RFA was well tolerated without major complications in all patients. Histopathologically, necrosis of the ablated area was found whereby the extent of the necrotic area correlated with the length of the activation tip of the RFA catheter used. A maximum ablated area of 12×10 mm was achieved using the RFA catheter with the longest activation tip; however, histological examination revealed tumour cells around the necrotic tissue in these cases, thus indicating incomplete ablation. However, subsequent case reports and smaller prospective trials reported successful bronchoscopy-guided RFA in patients with peripheral lung cancer [34, 35]. Local tumour control was achieved in the majority of patients and long-term follow-up revealed encouraging results. The reported median progression-free survival in 20 patients treated by bronchoscopy-guided RFA was 35 months and the 5-year overall survival rate was 61.5%, which is superior to the 5-year survival rates reported in early-stage lung cancer treated with SBRT [35].

One prospective trial comparing transbronchial RFA, transbronchial microwave ablation and SBRT in patients with peripheral lung cancer is ongoing with the response rate to the treatment as the primary end-point (ClinicalTrials.gov: identifier NCT02972177).

Bronchoscopy-guided microwave ablation

CT-guided percutaneous microwave ablation was found to be a safe and effective treatment for medically inoperable peripheral early lung cancer [29]. To reduce the risk associated with puncturing the chest wall, the idea of bronchoscopy-guided microwave ablation was raised. Ferguson *et al.* [36] developed a flexible, gas-cooled microwave antenna capable of delivering microwave energy bronchoscopically and examined this system in *in vivo* swine lung [36]. Four microwave ablations at different power and time settings were performed.

The subsequent histological examination of the ablative zones revealed central necrosis surrounded by a zone of oedema, a transition zone and then viable tissue. It was found that the size of the ablation zones correlated with the energy power. During the 12 procedures, three pneumothoraces occurred requiring chest tube insertion. Two of the three pneumothoraces were due to inadvertent distal placement of the antenna and one to a damaged antenna. This first trial demonstrated the feasibility of bronchoscopy-guided microwave ablation. Safety and efficacy need to be evaluated in further trials.

Bronchoscopic vapour ablation for malignant pulmonary nodules

Bronchoscopic thermal vapour ablation is one of the various endoscopic lung volume reduction techniques that has shown efficacy for the treatment of patients with COPD and upper lobe predominant emphysema [37]. The water vapour that is delivered to the emphysematous lung segments induces an inflammatory reaction that leads to fibrosis and remodelling, and thus to lung volume reduction. In a human *ex vivo* lung model it has recently been demonstrated that the vapour that creates a segmental ablation may also be used in the therapy of lung malignancies [38]. In this initial experiment, vapour was delivered to 107 subsegments of 10 *ex vivo* lung models, including normal lungs, emphysematous lungs and lungs with malignancies. Subsequent histological examination revealed a uniform and well-defined field of ablation that followed anatomical boundaries. However, to date, it is uncertain if this technique can be used reliably to treat malignancies.

Robotic endoscopy systems

Robotic systems for laparoscopic and thoracoscopic surgery have already found widespread acceptance. The development of robotic endoscopy systems is stimulated by the rapidly evolving advanced endoscopic therapies that often require dexterity and high precision. In gastrointestinal endoscopy, various robotic systems are already available that currently focus on robotic locomotion and robotic instrument control [39].

In pneumology, robotic systems are also being developed that may aid sampling peripheral lung nodules that are traditionally inaccessible with currently available devices. So far, EBUS, ENB and virtual bronchoscopy present guidance techniques that suggest pathways to the chosen target or assist in localising the lesions. These guidance techniques provide an endobronchial pathway to the suspicious lesion and thus only provide access to peripheral nodules that are in close proximity to the bronchi. In contrast to these technologies, BTPNA allows access to nodules that are distant from the bronchi by creating a path through the healthy lung parenchyma. However, the accessibility is also limited to lesions that are reachable by a vessel-free, straight-line path.

To overcome these limitations and expand the accessibility to peripheral nodules, Swaney *et al.* [40] described a new system that combines robots and steerable needles. This system uses a bronchoscope to navigate in the airway, a concentric tube robot that is advanced through the working channel of the bronchoscope to move through the bronchial wall and towards the targeted lesion, and a bevel-tip steerable needle with magnetic tracking to manoeuvre through lung parenchyma to the suspicious nodule. This new system has already been evaluated in phantom bronchial trees and in *ex vivo* porcine lungs. It could be demonstrated that the system provides accurate targeting to the lesion and that the

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steerable needles could be guided around obstacles along the path to the desired target. Further experimental trials are necessary to validate the system in inflated biological tissue.

The future evolution of robotic endoscopes will, however, not only focus on navigation to peripheral lesions, but also concentrate on additional functions that provide augmented minimally invasive surgical procedures.

Conclusions

Interventional bronchoscopy is expanding rapidly and thus offers treatment modalities in various pulmonary diseases. Numerous trials are currently ongoing to evaluate the feasibility, safety and efficacy of different bronchosopic diagnostic and therapeutic technologies. As these bronchoscopic procedures are minimally invasive and are usually associated with a low-risk profile, these interventions can be offered to patients with poor general status and pulmonary reserve.

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The role of bronchoscopy in the evaluation and treatment of respiratory disease has evolved dramatically over the last decade. Originally a tool for examining and sampling the central endobronchial tree, it has broadened considerably to include techniques that now enable the treatment of an increasing number of conditions. In this *ERS Monograph*, the Guest Editors make this broad area easy to navigate by separating the book into three sections: technical aspects, diagnostic procedures and therapeutic interventions. Within these sections, leading authors in the field provide chapters that include: flexible and rigid bronchoscopy, bronchoscopy in intensive care, laryngoscopy, biopsy techniques, EBUS and EUS, cryobiopsy, early cancer therapies and airway stents.

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