Jose Pablo Díaz-Jimenez
Alicia N. Rodriguez
Editors

Interventions in Pulmonary Medicine

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To my wife Mercedes, to whom I owe so much, and who is by my side on the way of life.
To my father, my best friend.
To my grandchildren: Elia, Lluc, Quim, and Ferran from whom I am learning to live.
To Alicia Rodriguez, my dearest friend and superb pulmonologist, the true architect of this book.
To my mentors: Dr. J.F. Dumon from Marseille and Dr. D. Cortese from Mayo Clinic, who directed my first steps in Interventional Pulmonology.

Jose Pablo Díaz-Jimenez

To Manuel, Francisco, and Juan, who make my day everyday.
To Jose Pablo Díaz-Jimenez, always grateful to my great teacher and excellent friend.
To my mentors: Drs. M. Maxit, J.M. O'Donnell, J.F. Beamis, Jr., and A.W. Gray Jr., from whom I have learned that medical practice should be guided by kindness, knowledge, a strong work ethic, and a lot of common sense.

Alicia N. Rodriguez

Foreword

Interventional Pulmonology (IP) has been the most interesting and rewarding aspect of my medical career. In addition to benefiting patients, which is the main goal of Interventional Pulmonology, IP has brought me in contact with and allowed me to develop friendships with other IP physicians throughout the world. One such physician is Dr. Jose Pablo Díaz-Jimenez, one of the premier European interventional bronchoscopists. Dr. Díaz-Jimenez is widely respected internationally (recent past Chairman of the World Association for Bronchology and Interventional Pulmonology) and has greatly influenced the education of future IP physicians by his contributions to the medical literature and by organizing many educational courses and respiratory meetings in Barcelona and Sitges.

I have also been involved in the training of pulmonary fellows and I am very proud of Dr. Alicia Rodriguez who is a graduate of the Lahey Clinic Pulmonary Fellowship Program. Drs. Díaz-Jimenez and Rodriguez have collaborated in the past with the successful publication of their first IP book in Spanish in 2000.

This new collaboration between Drs. Díaz-Jimenez and Rodriguez brings together contributions by international IP experts to address current and future applications of IP. Sections on Basic Endoscopy cover anatomy, use of flexible and rigid bronchoscopy, and training. A section on Tracheobronchial Obstructions reviews the array of methods that are currently available to open obstructed airways. The section on Lung Cancer Diagnosis reviews important methods of detecting and diagnosing early, superficial airway tumors and diagnosing peripheral lung lesions. Lung Cancer staging with IP methods is becoming more and more commonplace, and this is addressed in the section on Lung Cancer Stratification. The last section on Interventional Pulmonology in Special Situations covers non-bronchoscopic IP procedures such as Percutaneous Tracheotomy and Medical Thoracoscopy and newer bronchoscopic therapies for emphysema and asthma.

The spirit of Interventional Pulmonology began with Dr. Jean François Dumon who perfected many interventional bronchoscopy techniques and shared his expertise with bronchcoscopists throughout the world through numerous publications, courses, and speaking engagements. Dr. Dumon has many disciples, including Dr. Diaz-Jimenez and myself and several authors in this book. This edition of *Interventional Pulmonology* by Díaz-Jimenez and

Rodriguez reflects the spirit of IP in that it offers a state-of-the art view of IP by bringing together international contributors who share their clinical IP expertise in procedures that if performed well can only benefit the care of patients.

Burlington, MA, USA
Honolulu, HI, USA

John F. Beamis

Preface

Nothing beats the pleasure of seeing a finished work.

This book is a reflection of what we do everyday in the endoscopy room, and it would not have been possible without the collaboration of the colleagues who have participated, sharing their knowledge and expertise to clearly set out the fundamental concepts of this wonderful Interventional Pulmonology world.

I have been working in the interventional area for more than 30 years, and one of the main concepts that I have learned is that success in daily work is not on one individual, but it is only achievable when everybody works with the conviction of being part of a team.

It would not be possible to perform a complex treatment such as releasing the airway from an obstructive malignant tumor without each and every team member's participation, applying their knowledge and abilities in a coordinated and complementary fashion. As team members, we all share responsibilities. I believe one of the main ones is to make the whole team function based on these three mainstays: coordination, communication, and complement, since they are the keys of a successful work.

Since the advent of bronchoscopy in 1887, the field of bronchology and interventional pulmonology has demonstrated its clinical value with amazingly rapid developments. The last three decades have brought to us spectacular advances in technology and their clinical applications, which have led to lifesaving therapies. We can predict that we will see newer clinical applications and improvement in established techniques in the near future. These dynamic changes will bring together the scientists and clinicians interested in our specialty and further expand the field.

It is our duty to keep updating the state of the art and maintain a continuous progress. The scientific and clinical training of the respiratory endoscopist must rest on solid principles and remain in constant forward motion, and therefore, constant teaching and learning become our obligations.

During all these years we have received pulmonary fellows from all continents who have spent long periods of time with us or have attended our courses or conferences, teaching them interventions and also learning from them. We have also learned from very respected physicians of the Interventional Pulmonology field who have honored us with their presence, sharing their experiences and making this learning process extremely easy, as if we were in a family reunion listening and exchanging everyday experiences. At the

end of the day, we were all enriched, and I believe all our patients benefited from our sessions and discussions.

Experience does not come only as a consequence of performing many procedures but also from having an open mind and listening to the advice and suggestions from other colleagues. The learning process takes a lifetime. At the beginning, we are all learners, and as time goes by, it becomes our turn to take the position of the teacher and to contribute to the growing number of fellows and residents interested in endoscopic procedures. What would have occurred if retired from daily practice Killian, Jackson, Andersen, Ikeda, Zavala, Hayata, Kato, Cortese, or Dumon had not transmitted their experiences to the rest of the scientific community? It would have been much more difficult for us to arrive to our present state of knowledge. However, the generosity of all of them made our way much easier.

Bertrand Russell said it is good from time to time to think on the present as if it were the past, and consider which of the elements of our time will enrich the permanent deposit of the universe and which ones will live and give life when our generation has disappeared. Having this contemplation, the human experience transforms and the personal experience vanishes.

With this in mind, I believe the teaching and learning process is crucial, and they both have to be taken with humility. To our teachers we always owe gratitude and respect, and when we become teachers, it is important to be generous, recognize limitations, and transmit what is worth, keeping always as a goal to benefit our patients in every possible way.

Following this line, Alicia and I would like to take this opportunity to thank the many teachers and colleagues around the world who helped us along the way, with their advice and continuous support:

- Dr. Udaya Prakash and Eric Edell form Mayo Clinic.
- The coworkers from the Bronchoscopy Department at Bellvitge University Hospital in Barcelona: A. Rosell, R. Lopez, and N. Cubero, and from the MD Anderson Cancer Center Team in Houston: R. Morice, G. Eapen, C. Jimenez., D. Ost, and BF. Dickey.
- The Pulmonary Department Team at Lahey Clinic in Massachusetts.
- The Pulmonary Department Team at Clinica Colon in Mar del Plata: L. Araya, N. Baillieau, R. Gonzalez Cuevas, S. Ruiz, C. Materazzi, and M. Rocha.

And finally, our especial thanks to all the colleagues who participated in this work, generously sharing their wisdom and making possible this small addition to the art of Respiratory Endoscopy. It is our hope that this book will contribute to improve our daily interventional pulmonology practice.

Barcelona, Spain Jose Pablo Díaz-Jimenez

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Part I

Basic Endoscopy

Tracheobronchial Anatomy

1

Juan Antonio Moya Amorós
and Anna Ureña Lluberas

Trachea

Introduction

The trachea or windpipe is a tube of approximately 12 cm length. In a lateral view, it assumes an oblique course, running from superoanterior to inferoposterior, from 23º to 34º related to the body's major axis. It ends up by dividing into two bronchial tubes at the level of the tracheobronchial bifurcation, which usually has an angle of 60º. Changes in the degree of angulation can orient to diagnose some conditions located distally to the bifurcation such as enlarged lymph nodes or left atrium dilatation in mitral stenosis. The tracheal tube extends from C6–C7 (limited by the cricoid cartilage superiorly) to D4–D5, approximately at 1 or 2 cm below a horizontal plane passing through the Louis sternal angle. Topographically its average length (12 cm as stated) is equally divided between the cervical and mediastinal region.

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External Morphology

The external tracheal layer configuration is characterized by the presence of roughness due to incomplete cartilage rings that are staggered and horizontally and segmentally distributed. Usually 20 rings are identified in the trachea.

In the cervical region, the tube has a flattened shape posteriorly, due to the absence of cartilage, so that the predominant diameter is the sagittal or anteroposterior (approximately 16 mm), but inside the chest, it predominates the transverse diameter (approximately 16 mm).

In the external tracheal wall, narrowing or depressions can be seen, produced by the imprint of organs in close proximity contacting to the tracheal wall. In the left side, two of them are visible: one due to the left thyroid gland lobe (neck) and the other one due to the aortic arch (mediastinum).

The posterior membrane closing the entire tracheal canal is flat, soft, and depressible; it is known as the *membranous pars* (Fig. 1.1).

The especial tracheal configuration and its elastic structure make it capable to elongate up to 1/3 of its length. This fact is of particular interest for tracheal reconstruction surgeries.

Dimensions of the trachea vary primarily according to age and less so with gender. Figures 1.2–1.5 present the normal size variations in all three axes, internal size, area, and volume.

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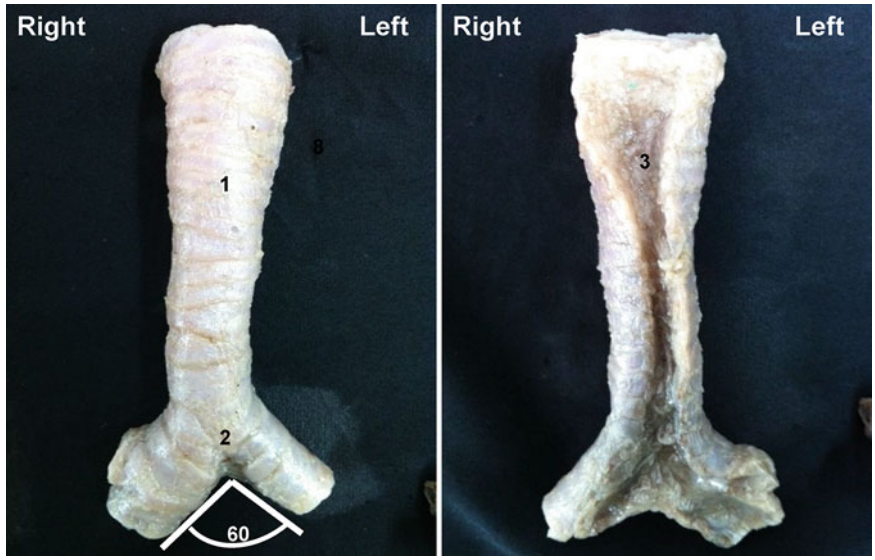
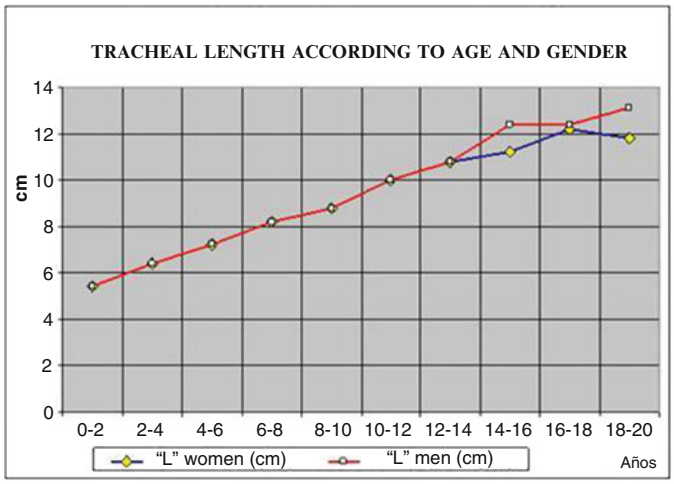


Fig. 1.1 Anterior view of the dissected trachea. Note the tracheal bifurcation angle of 60°: (*1*) anterior view—trachea and tracheal cartilage. (*2*) Tracheobronchial bifurcation. (*3*) Membranous pars or tracheal muscle. Unit of Human Anatomy and Embryology. Department of Pathology and Experimental Therapeutics. Universitat de Barcelona



	"L" women (cm)	"L" men (cm)
0-2	5.4	5.4
2-4	6.4	6.4
4-6	7.2	7.2
6-8	8.2	8.2
8-10	8.8	8.8
10-12	10	10
12-14	10.8	10.8
14-16	11,2	12,4
16-18	12,2	12,4
18-20	11,8	13,1

Medium length of the trachea increases similarly in both genders until the age of 14. After that it only increases in men.

Fig. 1.2 Medium length of the trachea increases similarly in both genders until the age of 14. After that it only increases in men

Among both genders, there are also differences in tracheal size especially in the sagittal and transverse axes, which are evident in tomographies and 3D reconstructions (Figs. 1.6 and 1.7).

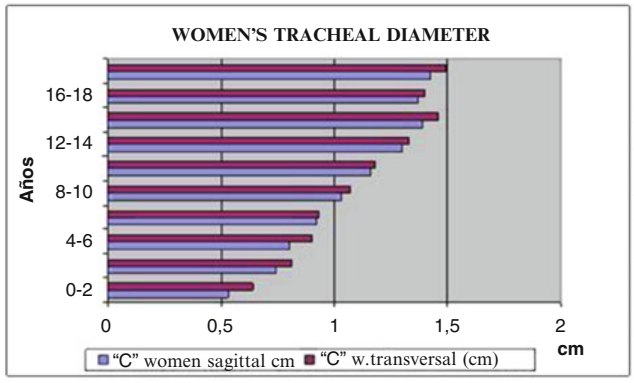
Internal Morphology

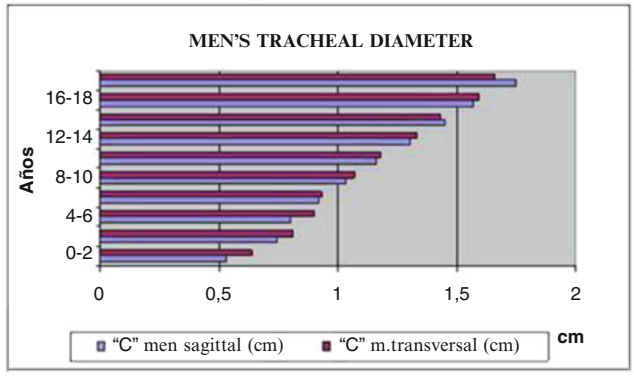
The tracheal tube has two covers or layers.

Main, Fibrochondro Elastic Layer

It is a completely circular, soft, and elastic connective tissue fundamental matrix. It affects the entire circumference of the windpipe, presenting tiny holes that represent the point of vascular entrance or exit to and from inside the trachea.

Enclosed to this layer there are bands of incomplete hyaline cartilage rings, horseshoe-shaped. The cartilage forms about four fifths

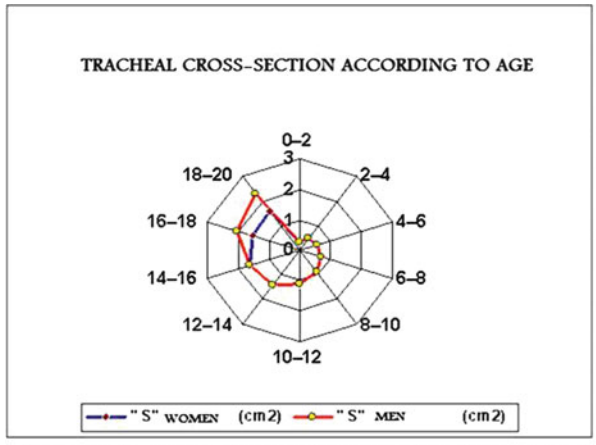




AGE in years	"C" sagittal women (cm)	"C" transv. women (cm)	"C" sagittal men (cm)	"C" transv. men (cm)
0-2	0.53	0.64	0.53	0.64
2-4	0.74	0.81	0.74	0.81
4-6	0.8	0.9	0.8	0.9
6-8	0.92	0.93	0.92	0.93
8-10	1.03	1.07	1.03	1.07
10-12	1.16	1.18	1.16	1.18
12-14	1.3	1.33	1.3	1.33
14-16	1,39	1,46	1,45	1,43
16-18	1,37	1,4	1,57	1,59
18-20	1,42	1,49	1,75	1,66

Medium tracheal diameter increase similarly in both genders until the age of 14. After that it only increases in men.

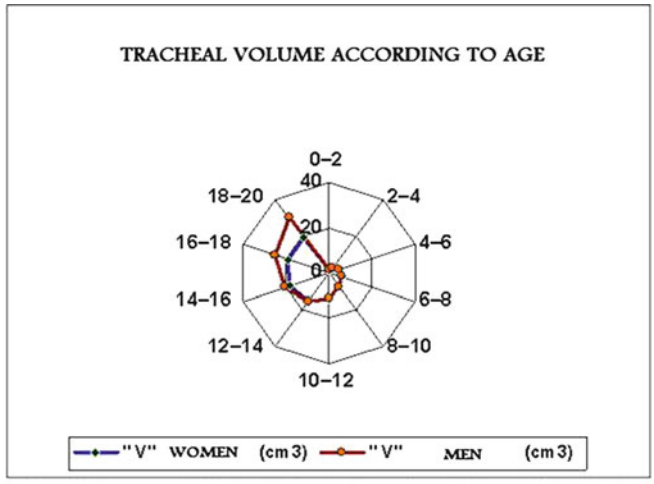
Fig. 1.3 Medium tracheal diameter increases similarly in both genders until the age of 14. After that, it only increases in men



AGE	" S" WOMEN (cm^2)	" S" MEN (cm^2)
0–2	0.28	0.28
2–4	0.48	0.48
4–6	0.58	0.58
6–8	0.69	0.69
8–10	0.89	0.89
10–12	1.1	1.1
12–14	1.39	1.39
14–16	1.62	1.62
16–18	1,54	2,01
18–20	1,59	2,3

- Medium tracheal area increases similarly in both genders until the age of 14.
- At age 20, tracheal area is 44.6% larger in men than in women.

Fig. 1.4 Medium tracheal area increases similarly in both genders until the age of 14. At age 20, tracheal area is 44.6% larger in men than in women



AGE	"V" WOMEN (cm^3)	"V" MEN (cm^3)
0–2	1.57	1.57
2–4	3.11	3.11
4–6	4.16	4.16
6–8	5.67	5.67
8–10	7.87	7.87
10–12	11.1	11.1
12–14	15.4	15.4
14–16	18,2	20,2
16–18	18,8	25,1
18–20	18,9	30,3

Fig. 1.5 Medium tracheal volume increases similarly in both genders until the age of 14. By age 20, men's tracheal volume is 60% larger than women's

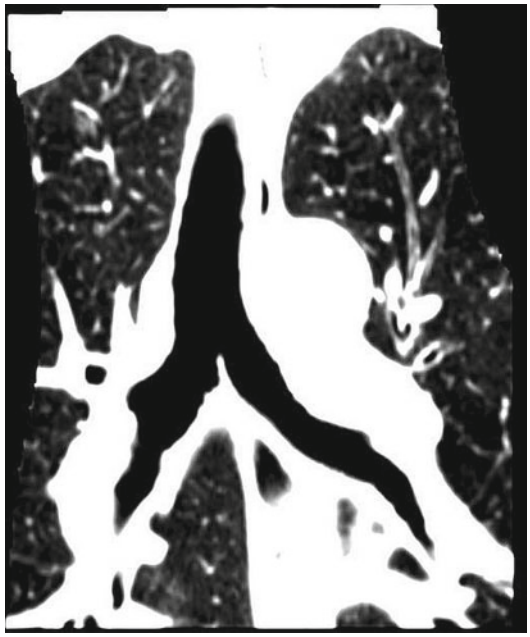


Fig. 1.6 At age 20, men's sagittal and transverse tracheal axes are 23% and 11.4% larger than women's, respectively. Coronal computerized tomography: view of mediastinal trachea, tracheobronchial bifurcation, and main bronchi

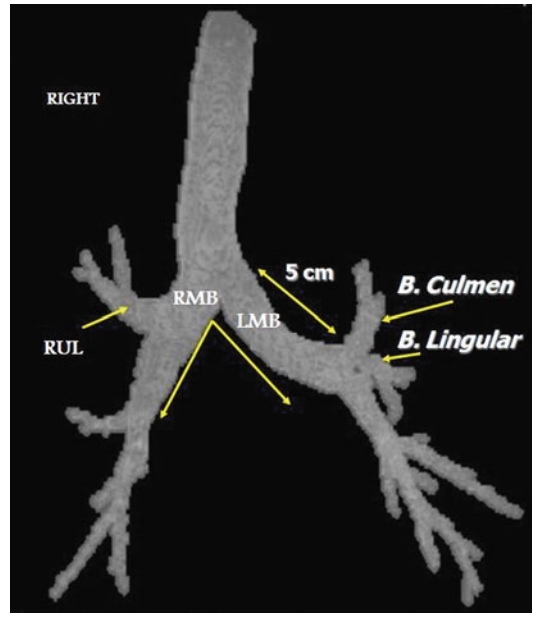


Fig. 1.7 Medium tracheal diameter is 1.5 mm larger in men than in women. Medium bronchial diameter is 1 mm larger in men. 2D tomographic reconstruction of the tracheobronchial tree. Note that the intra-carinal angle is 60°. Lengths are 5 cm for the LMB and 2.5 cm for the RMB

of the circumference of the trachea. Given that the posterior border of the trachea is formed by a fibromuscular membrane, tracheal cross-sectional shape is similar to a letter D, with the flat side located posteriorly. These are known as the tracheal muscles and have vegetative involuntary innervation. The tracheal muscles cross transversely and obliquely, forming a continuous of entangled fibers which constitute a large muscle: the common tracheal muscle. Contraction of this muscle produces adduction of the free cartilage edges, thus modulating the internal tracheal caliber. Wrapping the outer tracheal tube, we found the adventitia, a membrane that acts as a false pretracheal fascia. Between the adventitia and the tracheal wall, vascular and nervous branches are located, and they incorporate to the tracheal tube wall at the level of the interchondral spaces.

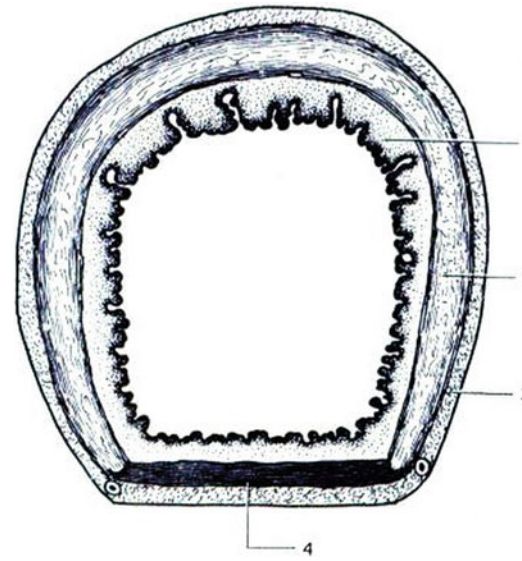


Fig. 1.8 Cross section, trachea: (*1*) respiratory cylindrical epithelium and mucous glands; (*2*) horseshoe-shaped cartilage, with a posterior opening; (*3*) main layer, connective tissue fundamental matrix, surrounded by the adventitia; and (*4*) pars membranosa

Mucous Layer

The trachea is lined by pseudostratified columnar epithelium that sits in an elastic *lamina propria* and covers the inside of the tracheal tube. Goblet mucous cells and small subepithelial glands that secrete into the luminal surface are interspersed among the ciliated columnar cells. The produced mucous adheres to inhaled foreign particles, which are then expelled by the action of cilia propelling the mucous lining upward towards the pharynx from which they can be coughed and sneezed out of the airway. At the end of the tracheal duct, when it is divided into the main bronchi, the mucosa presents a middle line elevation known as carina, similar to a medial ridge. The tracheal carina indicates the entrance to the right and left main bronchus (LMB) (Fig. 1.8a–c).

Blood Supply

Arterial: It is established by two arterial systems on each side of the trachea, communicating the aortic artery with the subclavian artery:

– From the aorta, the left paratracheal ascending artery (Demel arteries) and the tracheobronchial esophageal artery. Of the latter, the right bronchial artery, the esophageal artery, and the right paratracheal ascending artery are born.
– From both subclavian arteries: inferior thyroid arteries and from these in turn emerge the right and left paratracheal descending arteries (Haller arteries).

Each paratracheal descending artery anastomoses with the paratracheal ascending artery of the corresponding side, closing the vascular circuit at the back of the tracheal wall and along its side edges. From these two vascular axes, tracheal perforating arteries are born that supply tracheal layers entering through the interchondral spaces.

Anatomo-Clinical Relationships

The trachea is related to their surroundings through the peri-tracheal fascia, as if it were a hanger between the neck and the mediastinum. Vascular and nerve structures hung from or are in contact with it.

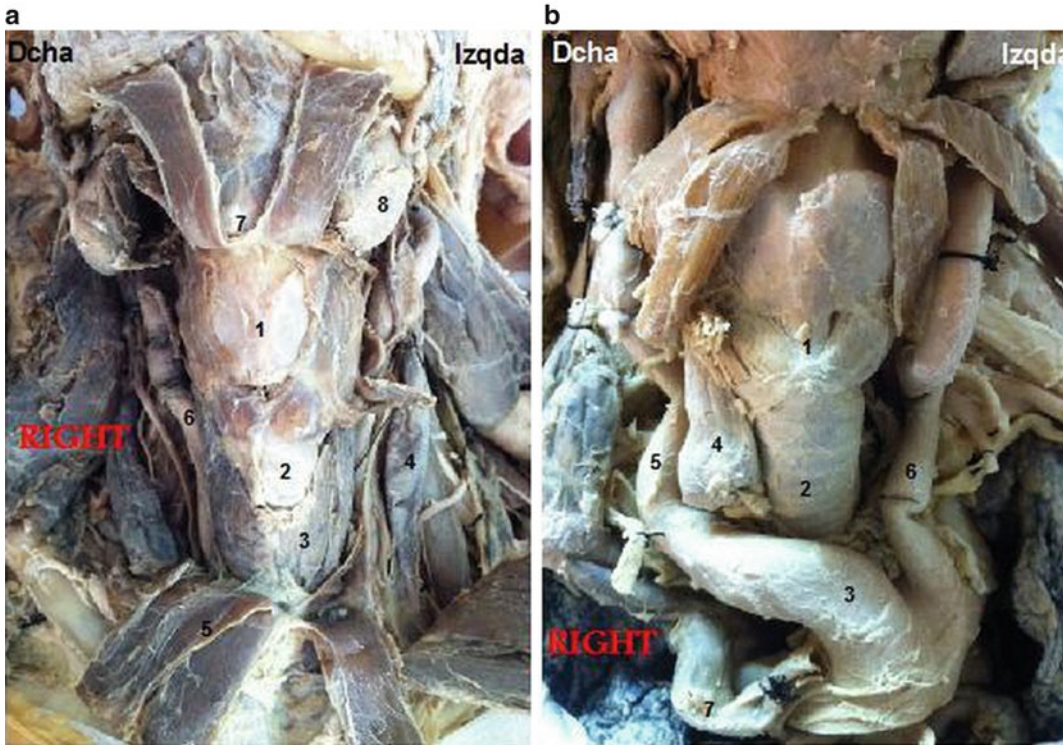


Fig. 1.9 (**a**) Dissection of the cervical trachea: (*1*) larynx, (*2*) trachea, (*3*) left thyroid lobe, (*4*) left internal jugular vein, (*5*) right infrahyoid muscles, (*6*) right common carotid artery, (*7*) hyoid bone, and (*8*) left submandibular gland. (**b**) Dissection of the cervical trachea: (*1*) larynx, (*2*) trachea, (*3*) brachiocephalic arterial trunk, (*4*) right internal jugular vein, (*5*) right common carotid artery, (*6*) left common carotid artery, and (*7*) left venous brachiocephalic trunk or innominate trunk. Unit of Human Anatomy and Embryology. Department of Pathology and Experimental Therapeutics. Universitat de Barcelona

Tracheal relationships from inside out are:

- Posterior: recurrent nerve, esophagus, and vertebral bodies covered by the deep cervical aponeurosis
- Anterior: thyroid gland, medium cervical aponeurosis, anterior jugular veins, and superficial cervical aponeurosis
- Lateral: thyroid gland, vessels and nerves, deep cervical aponeurosis, and superficial cervical aponeurosis (involving the sternocleidomastoid and trapezius muscles) (Fig. 1.9a, b)

The tracheobronchial bifurcation has similar topographical relationships in both genders, and it is located at 7 cm depth from the skin of the anterior midline chest (Figs. 1.10 and 1.11).

Bronchi

Main Bronchi

Main bronchi are located in a compartment known as the mediastinum. The mediastinum is delimited by the pleural cavity. This space does not have a regular shape (mediastinum—"servant" or "heart and major vessels service area"). There are two main bronchi, left and right. Each main bronchus is related to some elements of the mediastinum, and they are not equal in length or size.

LMB: It is 5 cm in length. It is longer than the right main bronchus (RMB), passing beneath the aortic arch and the left pulmonary artery.

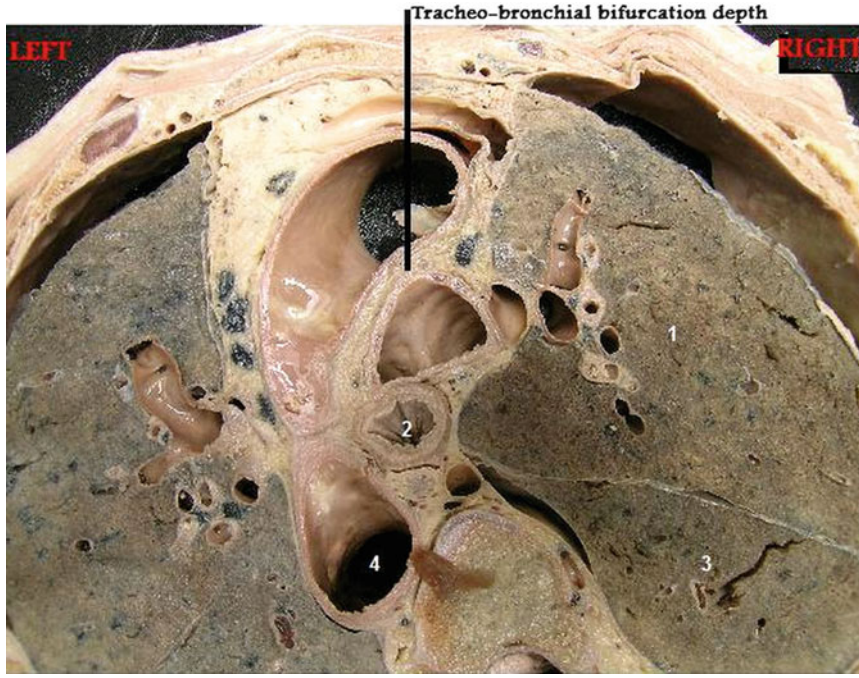


Fig. 1.10 Cranial view of thoracic cross section at the level of D4. Note the location of the tracheobronchial bifurcation at a depth of 7 cm from the surface. (*1*) Right upper lobe, (*2*) thoracic esophagus, (*3*) right lower lobe, (*4*) descending thoracic aorta. Unit of Human Anatomy and Embryology. Department of Pathology and Experimental Therapeutics. Universitat de Barcelona

RMB: It is 2.5 cm in length. It presents more vertical than the left bronchus and has a bigger diameter.

Inside the lung parenchyma, both bronchi will continue dividing into branches to the 24th order (Fig. 1.12).

Bronchial Division

Left Main Bronchus

- Left upper lobe bronchus—it divides into:
  - *Apicoposterior segmental bronchus (B1 + 2)*, from where B1 (apical) and B2 (dorsal or posterior) bronchi are born
  - *Anterior or ventral segmental bronchus (B3)*
  - *Lingular bronchus*, divided into *superior lingular segmental bronchus (B4)* and *inferior lingular segmental bronchus (B5)*
- Left lower lobe bronchus—it divides into:
  - Apical segmental bronchus form the left lower lobe or Nelson's bronchus (B6)
  - Posterior or dorsal bronchus(B10)
  - Lateral bronchus (B9)
  - Trunk (B7 + 8) or ventromedial bronchus, from which B7 (medial) and B8 (ventral) originate

Right Main Bronchus

- Right upper lobe bronchus—it divides into:
  - Apical segmental bronchus (B1)
  - Anterior or ventral segmental bronchus(B3)
  - Dorsal segmental bronchus (B2)
- Right middle lobe bronchus—it divides into:
  - Medial segmental bronchus (B5)
  - Lateral segmental bronchus (B4)
- Right lower lobe bronchus—it divides into:
  - Apical bronchus of the right lower lobe (Nelson's bronchus) (B6)
  - Posterior or dorsal bronchus (B10)
  - Lateral bronchus (B9)
  - Anterior bronchus(B8)
  - Paramediastinic bronchus (B7)

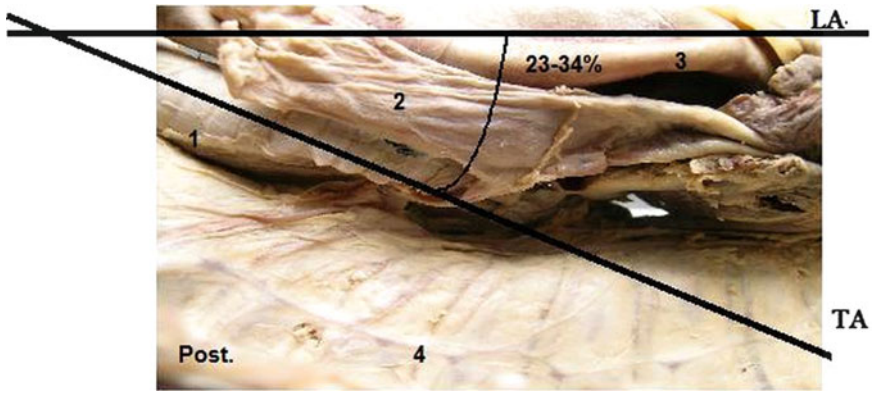


Fig. 1.11 Right lateral view of mediastinum: *TA* tracheal axis, *LA* long axis of the body. (*1*) Trachea, (*2*) superior vena cava, (*3*) ascending aorta, and (*4*) dorsal spine. Unit of Human Anatomy and Embryology. Department of Pathology and Experimental Therapeutics. Universitat de Barcelona

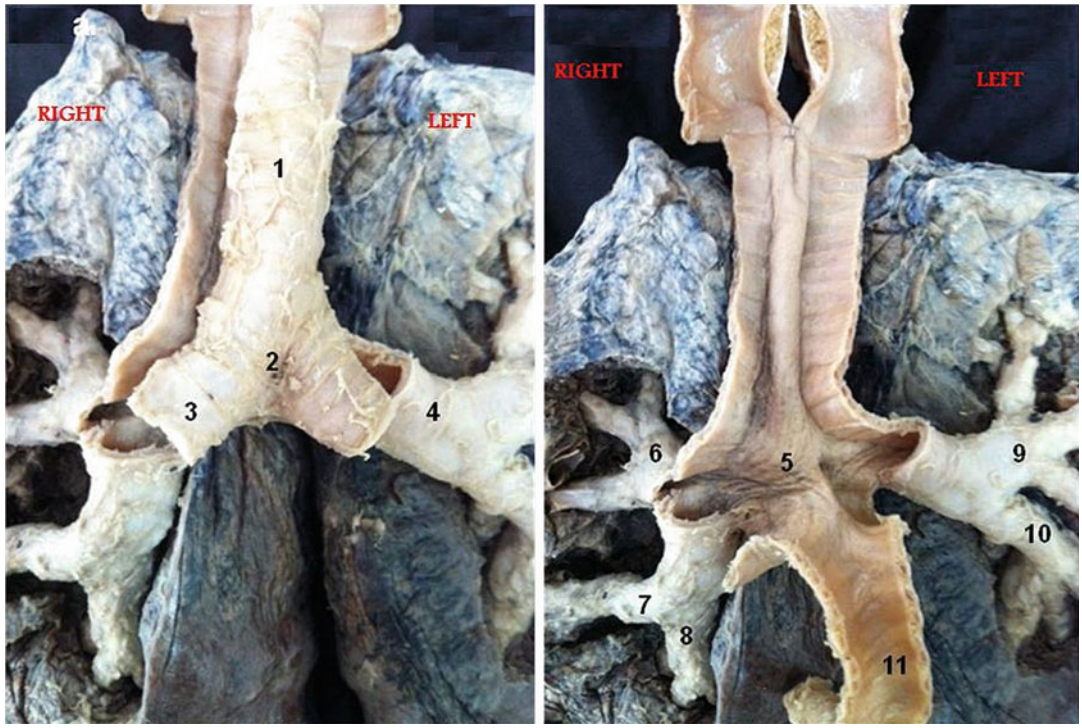


Fig. 1.12 Tracheobronchial bifurcation. Notice in the image on the right a tracheal cross section with anterior inclination of its ventral side. (*1*): Trachea, (*2*) tracheobronchial bifurcation, (*3*) right main bronchus, (*4*) left main bronchus, (*5*) bronchial carina, (*6*) right upper lobe bronchus, (*7*) right middle lobe bronchus, (*8*) right lower lobe bronchus, (*9*) left upper lobe bronchus, (*10*) left lower lobe bronchus, and (*11*) inner wall of the anterior trachea. Unit of Human Anatomy and Embryology. Department of Pathology and Experimental Therapeutics. Universitat de Barcelona

The RMB, after the superior lobe bronchus departure, is called intermedius bronchus. The intermedius bronchus after approximately 15 mm originates the right middle lobe bronchus. From that on, it is called right lower lobe bronchus.

Each bronchial division is accompanied by the corresponding segmental pulmonary artery, giving place to the different bronchopulmonary segments.

Blood Supply

Bronchial arterial supply depends upon the bronchial arteries, which are aortic branches. These bronchial arteries are small in size and are located at the posterior wall of the bronchus following the first bronchial divisions. Bronchial arteries can be divided into:

– Right bronchial artery
– Left superior bronchial artery
– Left inferior bronchial artery

We can also see the Demel artery and the tracheobroncho-esophageal artery, both aortic branches. The latter will divide into three more branches:

- *Ascending tracheal artery*.
- *Esophageal artery*.
- *Right bronchial artery:* It is a single artery located at the posterior bronchial wall that will be divided into two bronchial branches each time it finds a bronchial division.

There are anastomoses between arteries on each side, which close the territory between the left and right bronchial arteries. These interbronchial anastomoses are called *Juttin asa*.

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Flexible Bronchoscopy

2

Alicia N. Rodriguez

Introduction

Flexible Bronchoscopy (FB) is the most common form of bronchoscopy, term that refers to the direct visualization of the airway with diagnostic or therapeutic purposes.

It was Shigeto Ikeda, of Tokyo Japan, who introduced the first flexible fiberoptic bronchoscope in Copenhagen in 1966 [1] (Fig. 2.1). However, the interest on reviewing the airway goes back to 1823, when Horace Green introduced first a sponge and then a rubber catheter into the bronchi, applying silver nitrate to burn lesions located at the level of the larynx and trachea. Later, Joseph O'Dwyer introduced a tube to release adhesions of the lower airways caused by diphtheria, and he also constructed a thin-walled tube to assist in the removal of foreign bodies. In 1897, Gustav Killian in Freiburg, Germany, investigated the larynx and trachea using a laryngoscope designed by Kirstein. During the same year, using an esophagoscope, he removed a pork bone from the airway of a farmer. He then presented his experience in Heidelberg, naming it "direct bronchoscopy," becoming the Father of Bronchoscopy [2].

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At the same time in the US, Chevalier Jackson developed an esophagoscope, and built a smaller version to retrieve a coin from a child's airway. He practiced his skills on esophagus and larynxes of dogs and human cadavers. He also initiated the first laryngoscopy class at West Medical College, developing safety protocols and a systematic training to avoid adverse results of the technique when applied by untrained physicians. During 1904, he developed a bronchoscope with a light on its tip, designing an additional light source and a drainage tube. He also built and perfectioned several ancillary instruments and was able to perform rigid bronchoscopy reporting a procedure related death of less than 1% [3].

During more than 70 years, the rigid bronchoscope or open tube was the only available instrument to review the airway. At first, it was mainly used to remove foreign bodies or dilate strictures, but later new applications were described: aspiration of secretions, hemoptysis treatment, biopsies, etc.

As time passed, many other achievements such as the appearance of telescopes for magnification, and photography to document images became available, and along with the practical application of the optical properties of glass fibers, described by John Tyndall in 1870, provided a favorable field to the development of the flexible bronchoscope as we know it today [2, 3].

The arrival of the FB represented a huge shift in the endoscopic practice; soon it was evident that the procedure was easier to perform than rigid bronchoscopy and it allowed a better

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Fig. 2.1 Dr. Shigeto Ikeda, Surgeon at the National Cancer Center, Japan, 1977 (Photography: Burt Glinn-Magnum Photos)

visualization of the distal airways. As its clinical use broaded, more and more diagnostic and therapeutic indications were described. New technology became available, specially designed for application with the flexible bronchoscope: fluorescence bronchoscopy, transbronchial needle aspiration, laser application, electrocautery, argon plasma coagulation, cryotherapy, brachytherapy, photodynamic therapy, stent placement. Imaging was perfected as well: with the arrival of the videobronchoscope around 1980 it was possible for the bronchoscopy team to watch the procedure on a screen with excellent definition, and record it for documentation and educational purposes [4].

More recent technologic developments and new applications, both in diagnostic and intervention flexible bronchoscopy are the electromagnetical navigation, endobronchial ultrasound, endoscopic lung volume reduction, thermoplasty, high magnification bronchoscopy, narrow band an optical coherence tomography. All of them will be discussed in different chapters in this book.

The flexible bronchoscope has proved to be a versatile instrument with many clinical applications. Since its introduction 45 years ago, it has completely changed the perspective of diagnosis and treatment of multiple conditions affecting the airways. It is expected that in the future its application will further expand. At the present time, flexible bronchoscopy is the most requested invasive procedure to investigate the upper and lower airways, and its current indications and applications will be reviewed in this chapter.

Description

The flexible bronchoscope is a flexible hollow vinyl tube containing packages of optical fibers, a longitudinal channel to facilitate suction and another channel allowing the introduction of ancillary tools, a mechanism to flex the tip through a proximal control lever and objective lenses at the tip. Its outer diameter varies from 1.8 mm (ultrathin) to 6.9 mm (EBUS flexible bronchoscope). The working channel varies from 0.6 to 3.2 mm. The length of the tube varies from 400 to 600 mm and the angle of motion for the tip is 120° to 180 up and 60 to 130° down. Since Dr. Ikeda was left handed, the FB is designed for use with the left hand, the same that has control over the suction port and the bending mechanism (Fig. 2.2a–d).

The glass fibers are isolated by special glass cover lens, to improve vision. Smaller fibers provide better resolution but if they are very thin they lose illumination. There are two light transmitting bundles and one viewing bundle. Each bundle contains up to 30,000 fine glass fibers (8–15 μm in diameter) The light entering to the system is internally reflected and emitted at the opposite end. The videobronchoscope replaces the viewing bundle by the charge coupled device (CCD), which is an image sensor that operates on electrical potential wells, each represents a pixel of total image. Since each CCD has one million pixels, it provides a better image than the fiberoptic bronchoscope [5]. The videobronchoscope brings real time images of

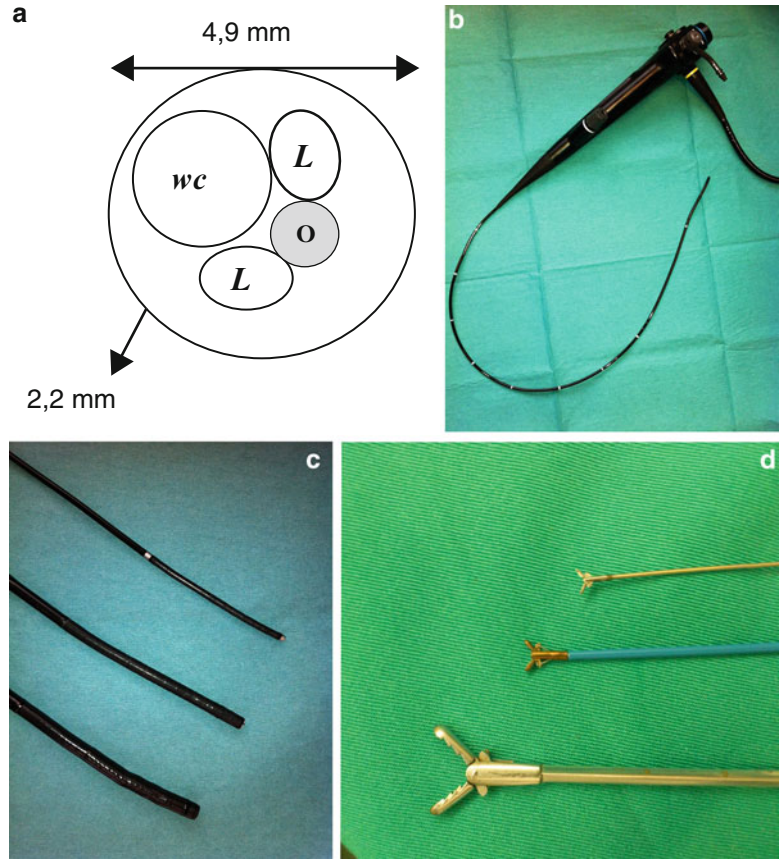

Fig. 2.2 (**a**) Cross-section of a flexible bronchoscope. *WC* work channel, *O* optic, *L* light. (**b**) Ultrathin videobronchoscope. (**c**) Diameter comparison: ultrathin videobronchoscope (1.6 mm diameter), diagnostic videobronchoscope (5.5 mm diameter) and therapeutic videobronchoscope (6.2 mm diameter). (**d**) Biopsy forceps: rigid forceps, VFB and ultrathin VFB forceps

the procedure allowing full documentation by recording the procedure (Fig. 2.3a–c).

Indications and Contraindications

Indications for flexible bronchoscopy are divided into diagnostic and therapeutic (Tables 2.1 and 2.2).

Diagnostic Flexible Bronchoscopy

According to the ACCP survey published in 1991[6] the main indications for bronchoscopy were cancer, mass, nodules, hemoptysis and diffuse lung disease.

There is no doubt that FB is very effective in diagnosing lung cancer, reporting a detection rate from 75% to 94% for visible tumors and 41–81% in non visible tumors [7]. Regarding diagnostic modality, a review of 30 studies revealed that the diagnosis of central, endobronchial tumors by bronchoscopy showed the highest sensitivity for endobronchial biopsies (74%) followed by bronchial brushing (59%), and washing (48%), giving a combined sensitivity of 88% [8] For peripheral lesions the yield is not as good: brushing demonstrated the highest sensitivity: 52%, followed by transbronchial biopsy 46%, and BAL/washing 43%, giving an overall sensitivity of 69% The most important factor impacting diagnosis is visibility of the tumor, location and, in peripheral lesions size is added, since the diagnostic yield

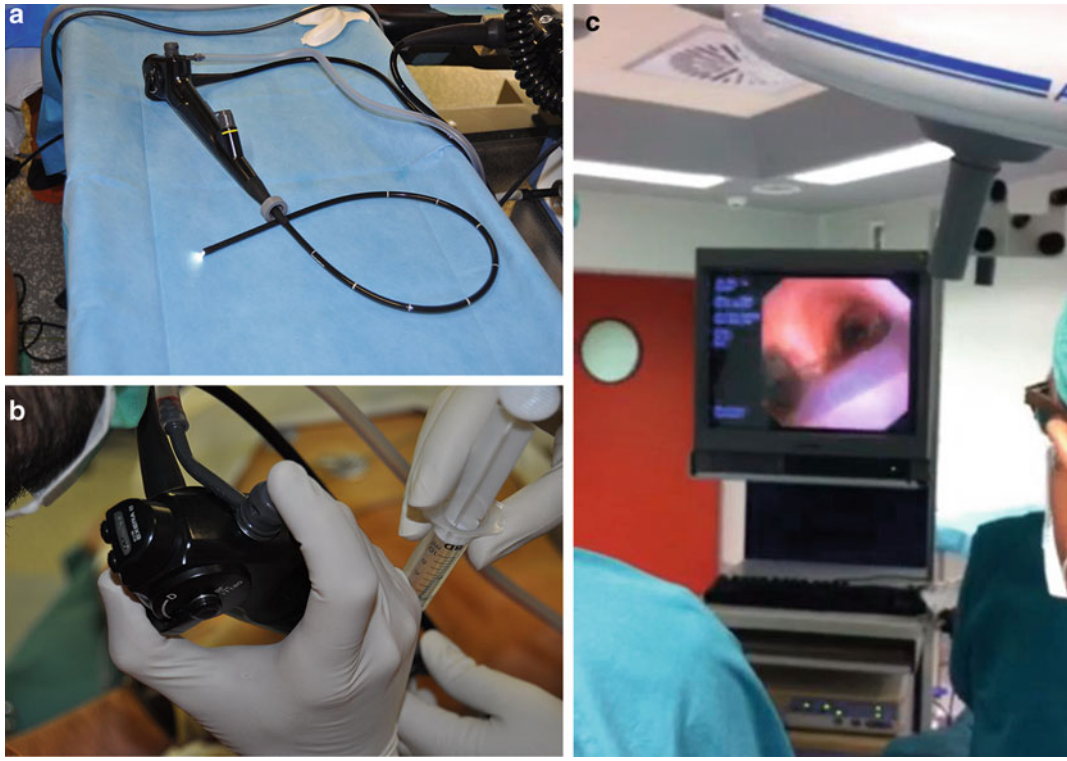

Fig. 2.3 (**a**, **b**) Videobronchoscope and (**c**) Videobronchoscopic image

increases in lesions greater than 3 cm [9]. The ultrathin flexible bronchoscope has allowed to reach small peripheral lesions that were not amenable to biopsy with the regular FB, significantly increasing the diagnostic yield in this situations (Fig. 2.4a–c). According to a Japanese study, the ultrathin bronchoscope (2.8 mm diameter) was able to reach the 5th to 11th bronchus and biopsy 1.4 × 1.1 cm (average size) lesions. Biopsies guided by computerized tomography and fluoroscopy had a diagnostic rate of 82% in lung cancer, 67% in metastatic lung cancer and 79% in inflammatory lesions [10].

The value of the FB in treating massive hemoptysis is a matter of controversy. Some authors consider the rigid bronchoscope to be far superior to the flexible bronchoscope in assessing and treating massive hemoptysis [6] To our knowledge, there are no studies comparing the utility of the rigid bronchoscope versus the flexible one on handling this situation, and the selection of the proper tool is up to the bronchoscopist, according to his/her experience and availability. It is reasonable, however, to have both instruments at hand. The flexible bronchoscope can be used through the rigid scope to take advantage of airway stabilization and better suctioning, while the FB is used to inspect the distal airway and locate the site of bleeding, and proceed to balloon tamponade, for instance (Fig. 2.5a, b).

According to 118 physicians interviewed during an interactive session of the ACCP meeting in 1988 [11], when dealing with massive hemoptysis 41% of the endoscopists favored FB through an endotracheal tube, 17% favored rigid bronchoscopy, and 7% suggested flexible fiberoptic bronchoscopy without an endotracheal tube.

Another common indication, chronic cough, was addressed in a retrospective study [12]. Flexible bronchoscopy was performed to patients with chronic cough and a nonlocalizing chest radiograph. They found that in visual inspection,

Table 2.1 Diagnostic indications for FB

• Suspected neoplasia: lung, tracheal, bronchial, metastatic
• Early detection of lung cancer
• Chest X-ray abnormalities
• Hemoptysis
• Diffuse lung disease/interstitial lung diseases
• Diaphragmatic paralysis
• Vocal cord paralysis, persistent hoarseness
• Persistent cough in selected patients
• Wheezing, stridor and dyspnea
• Suspected pneumonia, lung abscess, study of cavitated lesions
• Lung infiltrates in the immunocompromized patient
• Chest trauma (assessment of tracheal or bronchial rupture)
• Chemical and thermal burns of the airway, smoke inhalation
• Suspected airway fistula: trachealesophageal, bronchioesophageal, mediastinal, bronchopleural
• Suspected tracheobronchio malacia
• Suspected foreign body in the airway
• Suspected obstruction of the airway
• Evaluation of endotracheal tube positioning
• Evaluation of post transplant patients (status of sutures, stenosis, transplant rejection)
• Persistent lung collapse
• Persistent atelectasis
• Persistent pleural effusion
• Mediastinal adenopathies or masses

Table 2.2 Therapeutic indications for FB

• Bronchial washing (broncholithiasis, bronchiectasis, infected lung suppuration, cystic fibrosis)
• Lung lavage (alveolar proteinosis)
• Hemoptysis (bronchial tamponade, placement of Fogarti's catheter)
• Foreign body removal
• Laser, electrocoagulation, cryotherapy, argon plasma coagulation application
• Photodynamic therapy
• Brachytherapy
• Thermoplasty
• Baloon dilatation of stenosis, strictures
• Endobronchial lung volume reduction
• Percutanous dilatational tracheostomy
• Sealing of bronchopleural fistula/persistent pneumothorax
• Aspiration of bronchial, mediastinal, pericardial cysts
• Difficult airway intubation
• Intralesional injection
• Gene therapy

82% had no abnormalities while nine patients were found to have bronchitis. Microbiologic studies demonstrated potentially pathogenic organisms, but specific antibiotic treatment did not improve symptoms. Cytological studies showed no major findings. The authors concluded that flexible bronchoscopy did not contribute to the diagnosis of chronic cough etiology in patients without abnormalities in chest images.

In interstitial lung diseases, bronchoscopy is very often the first procedure indicated. A number of conditions can be accurately diagnosed performing bronchoalveolar lavage and transbronchial lung biopsies. Those are: sarcoidosis, amyloidosis, hypersensitivity pneumonitis, eosinophilic pneumonias, organizing pneumonia, pulmonary Langerhans cell disease (histiocytosis X), Goodpasture's syndrome, lymphocytic interstitial pneumonia, some pneumoconiosis, pulmonary lymphangioleiomyomatosis, and pulmonary alveolar proteinosis, as well as infections and neoplastic processes presenting with interstitial lung infiltrates [13, 14]. Transbronchial biopsies, however, play a minor role in the diagnosis of idiopathic pulmonary fibrosis (IPF) and surgical biopsy is considered the gold standard to diagnose this condition. Recently, the utility of flexible cryoprobes biopsies have been evaluated as a new tool in the study of the IPF patient. In a feasibility study [15], 49 patients with interstitial lung disease were biopsied with cryoprobes showing that the size of the samples was larger than conventional TBLB and had less crush artifacts, contributing to a definitive diagnosis in 39 of 41 patients, upon adding information from history, noninvasive testing and biopsy samples.

Early lung cancer diagnosis deserves special consideration. Lung cancer is today the leading cause of cancer related death in the world [16]. Unfortunately, most patients present with advanced disease, and survival is poor, 15% at 5 years [17]. Enormous efforts are made everyday in order to improve lung cancer survival, through

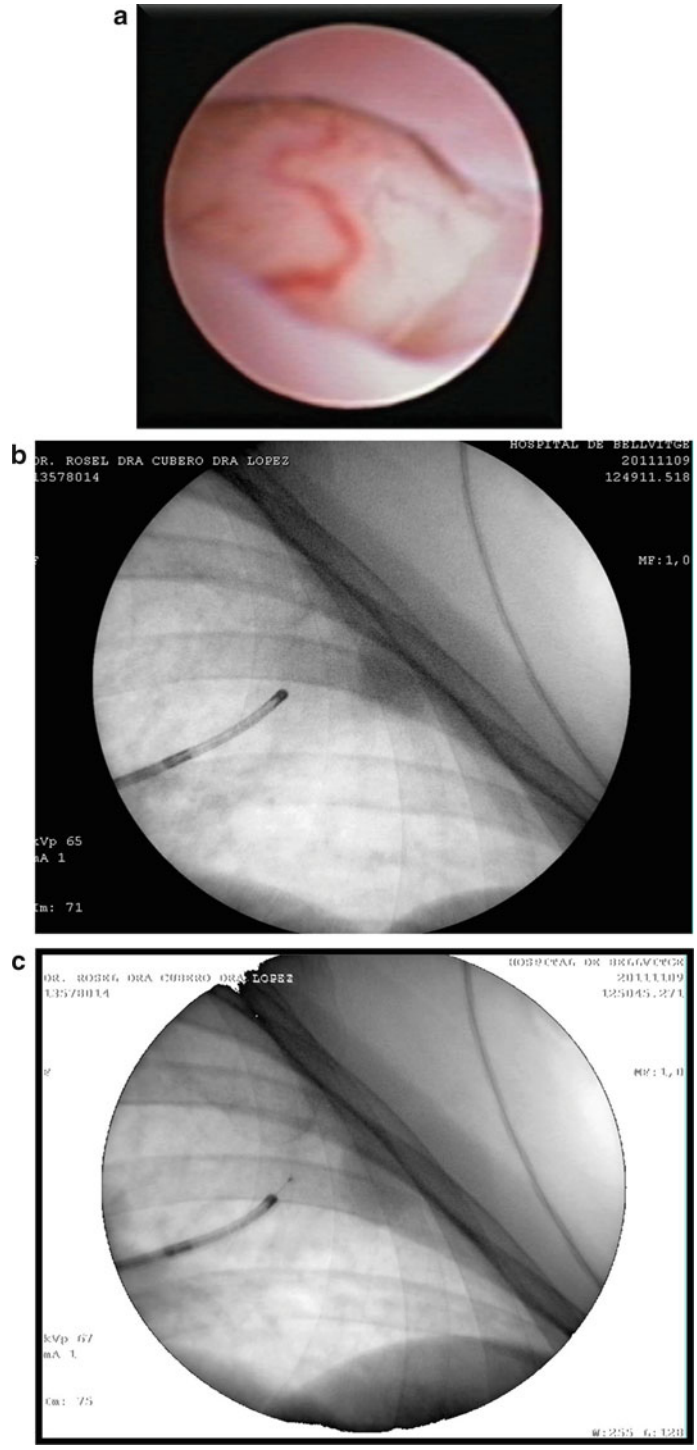

Fig. 2.4 (**a**) Endoscopic view of a peripheral adenocarcinoma, ultrathin VFB. Picture courtesy Dr. A. Rosell. (**b**) Fluoroscopy view of a peripheral biopsy. Ultrathin VFB Picture courtesy Dr A Rosell. (**c**) Fluoroscopy guided biopsy, ultrathin. The biopsy forceps can be seen advancing to the lesion. Picture courtesy Dr A Rosell

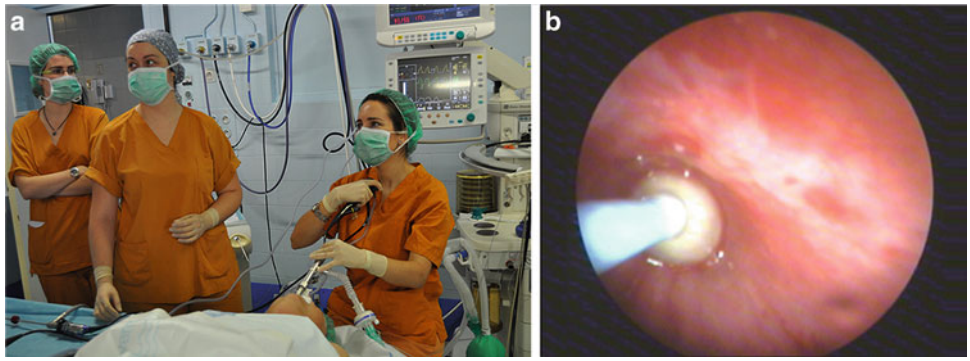

Fig. 2.5 (**a**) Flexible bronchoscope through the rigid bronchoscope. (**b**) Baloon tamponade performed with flexible bronchoscope

many lines of research; early detection is one of the most active ones, since it would be expected to change outcomes.

A complete discussion of the new available techniques is available in dedicated chapters of this book. Some of them are under research and there are no indications for clinical application outside this setting at the moment. In brief, those are:

1. Autofluorescence bronchoscopy: It takes advantage of the different appearance of normal, preneoplastic and neoplastic lesions when illuminated with light of different wavelengths.
2. High magnification bronchoscopy: It is a system that allows to magnify images of the bronchial mucosa, focusing in vascular changes (increased vascularity) present in inflammatory conditions (asthma, COPD, sarcoidosis) and neoplastic conditions. A maximum magnification of 110 times can be obtained.
3. Narrowband: It is a technique that also focus on microvascular structures. Through the use of a blue light (415 nm) combined with a green light (540 nm), enhanced visualization of microvascular structures in the mucosal and submucosal layers is obtained. Early changes in the microvasculature accompanying neoplastic lesions can be detected.
4. Multimodality fluorescein imaging: It involves the administration of fluorescein, and the use of combined techniques: white light and color light bronchoscopy along with three dimensional multidetector computerized tomography [18]. It also focuses on early vascular changes.
5. Endobronchial ultrasound: It refers to the application of acoustic waves of 20 MHz for demarcation of the different layers of the airway wall and peribronchial structures. In early lesions, ultrasound helps evaluating the extent of wall invasion, and selecting patients suited to undergo endobronchial therapies or surgery.
6. Optical coherence tomography: Similar to ultrasound, images are obtained by measuring the delay time for the light to be reflected back from structures within tissues. It provides better resolution than ultrasound, with a penetration of 2–3 mm depth.
7. Confocal endoscopy: It can bring images at a submicrometer level, by focusing the source light in a very small space. Its resolution is excellent, but the depth of penetration is very low (0.5 mm).
8. Electromagnetical navigation: Mainly indicated in diagnosing small distal parenchymal lesions of less than 2 cm in diameter. It involves electromagnetic guidance through a complex computer program that enables a reconstruction of the airways. A virtual bronchoscopy is obtained by computerized tomography images and then transferred to the software. The lesion can be located navigating through the airways through a global positioning system-like process.

Fig. 2.6 Flexible bronchoscopy though the endotracheal tube

Therapeutic Flexible Bronchoscopy

The flexible bronchoscope can be used to apply almost all current procedures in interventional bronchoscopy. However, since the FB has different capabilities when compared to the rigid bronchoscope (RB), the operator has to be knowledgeable in its strengths and limitations. The FB is easy to use, readily available and allows better inspection of the distal airway. Most of the procedures can be done under conscious sedation through an endotracheal tube (Fig. 2.6). On the other hand, procedure times are longer when compared to rigid bronchoscopy. The rigid bronchoscope allows removal of large volumes of tumor or foreign bodies much faster, and provides a better view of the central airway. It also allows for better airway control. It can be used as a resection tool, compress bleeding areas and the suctioning of blood or debris is faster than with the flexible bronchoscope. It can be used to dilate strictures as well, by applying different diameter tubes to the stenotic tracheo or bronchial area. In regard to prosthesis, placement of silicon stents is difficult to handle with the FB [19, 20]. The best advice for the interventionist is to be trained in the application of both instruments and select the appropriate one according to need. Since the rigid bronchoscope is the instrument of choice to confront the most severe situations, training in rigid bronchoscopy is indispensable for any pulmonary physician performing interventions in the airway.

A summery of indications and contraindications of interventional procedures performed with the flexible bronchoscope is depicted in Table 2.3. All procedures will be described in extent in different chapters of this book.

Contraindications

FB is a safe procedure to perform. Most of the contraindications are relative, and benefits of the procedure should be weighted against potential risks [20–22].

Absolute Contraindications:

- Lack of informed consent.
- Lack of an experienced bronchoscopist to perform or closely supervise the procedure.
- Lack of adequate facilities and personnel to care for emergencies that can occur, such as cardiopulmonary arrest, pneumothorax or bleeding.
- Inability to adequately oxygenate the patient during the procedure.

Incremented Risk for Complications (Risk-Benefit Assessment):

- Uncorrected coagulopathy or bleeding diathesis.
- Severe refractory hypoxemia.

Table 2.3 Interventions

Procedure	Indications	Contraindications	Adverse Effects
BLIND TBNA/EBUS TBNA	Diagnosis and staging lung cancer and mediastinal nodules Also peripheral, submucosal or parenchymal nodules	FB or RB contraindications anesthesia contraindications Bleeding disorders	Bleeding Pneumothorax Pneumomediastinum Fever Bacteremia
Laser therapy/electrocautery/argon plasma coagulation	Resection of endobronchial lesions, benign or malignant	Abscense of endoluminal lesion Uncorrected coagulopathy Old atelectasis	Hypoxemia, major bleeding, airway rupture, endobronchial fire
Conventional cryotherapy[a]	Resection of endobronchial lesions, benign or malignant Foreign body removal Cryobiopsy	Critical obstruction ("slow" opening method) Lack of endobronchial lesion Coagulopathy Old atelectasis	Worsening obstrution due to edema
Brachytherapy	Curative treatment for early stage lung cancer in non surgical candidates Localized high radiotherapy in advanced tumors	Those related to FB Airway fistula	Major hemoptysis Tissue necrosis Airway fistula
Photodynamic therapy	Curative treatment for early stage lung cancer in non surgical candidates Palliation of endobronchial lesions in advanced cancer	Critical obstruction Invading tumor Porphyrin allergy	Photosensitivity Tissue necrosis Edema Airway fistula Hemoptysis
Baloon dilatation	Tracheobronchial stenosis (acute obstruction or favorable lesions in non surgical candidates)	Tracheomalacia Complex stenosis Laryngo tracheal stenosis	Chest pain, bronchoespasm, atelectasis, wall laceration, airway rupture
Airway stents (metallic self expandable or balloon expandable)	Palliation of inoperable tracheobronchial tumors	Benign conditions	Granuloma formation Mucus plugging Migration Tumoral overgrow
Foreign body removal[b]	Foreign body in the airway		Wall laceration, bleeding Laryngeal edema
Percutaneous dilatational tracheostomy	Need for tracheostomy	Skin infection Unstable cervical spine Increased intracraneal pressure	Bleeding, mucosal tear, submucosal tunelization, posterior tracheal wall laceration or rupture, barotrauma

(continued)

Table 2.3 (continued)

Procedure	Indications	Contraindications	Adverse Effects
Bronchoscopic lung volume reduction[c]	Selected patients with emphysema		Valve migration, COPD exacerbation, pneumonia
Bronchial thermoplasty	Selected patients with bronchial asthma		Bronchoespasm, asthma exacerbation, pneumonia
Electromagnetical navigation	Biopsy of small peripheral lung nodules Sampling of mediastinal nodules	Those related to FB	Pneumothorax

[a] Cryoresection can be considered a "fast method" along with laser, electrocautery and argon plasma coagulation

[b] Accessories for the FB: grasping forceps, baskets, multiprolonged snares, magnet extractor, balloon catheters. Cryoprobes to adhere the object to the probe by freezing the point of contact. Laser to break objects can be used as well. A RB should be available in case of need

[c] Using endobronchial valves or biological, see corresponding chapters

Table 2.4 Basic equipment for flexible bronchoscopy

– Bronchoscope
– Light source
– Cytology brushes
– Biopsy forceps
– Needle aspiration catheters
– Suction
– Containers for samples, syringes
– Supplemental oxygen
– Pulse oxymeter
– Sphygmomanometer
– Fluoroscopy
– Resuscitation equipment

Unstable hemodynamic status.

Relative Contraindications (Increased Risks for Complications):

Lack of patient cooperation.

Recent myocardial infarct or unstable angina.

Partial tracheal obstruction.

Moderate to severe hypoxemia or any degree of hypercapnia.

Uremia and pulmonary hypertension.

Lung abscess.

Superior vena cava syndrome.

Debility and malnutrition.

Disorders requiring laser therapy, biopsy of lesions obstructing the airway or multiple transbronchial lung biopsies.

Known or suspected pregnancy.

Asthmatic patients.

Increased intracranial pressure.

Inability to sedate (including time constraints of oral ingestion of solids or liquids).

Preparation for the Procedure

Flexible Bronchoscopy can be performed in a bronchoscopy suit or in the operating room. It can also be performed at the bedside in the ICU or at the emergency room, according to patient location and clinical status (Table 2.4).

Requirements to perform flexible bronchoscopy [20–22] (Fig. 2.7):

- Trained staff: a skilled operator and two assistants (at least one of them should be a qualified nurse).
- Bronchoscope and accessories: appropriate suction and biopsy valves.
- Light source, and any related video or photographic equipment.
- Cytology brushes, flexible forceps, transbronchial aspiration needles, retrieval baskets, etc. Compatibility of the external diameter of all scope accessories with the internal diameter of the bronchoscope should be verified in advance.
- Specimen collection devices.
- Syringes.
- Bite block.
- Laryngoscope and endotracheal tubes (different sizes). Laryngeal masks if available.
- Chest tube placement kit.
- IV line, sterile gauze.
- Connector tube to allow simultaneous ventilation.
- Water-soluble lubricant, lubricating jelly, or silicone spray.

Monitoring Devices:

- Pulse oxymeter
- ECG monitor
- Sphygmomanometer

Recommended Procedure Room Equipment:

- Oxygen and vacuum system
- Resuscitation equipment
- Fluoroscopy: Their presence is not required at the endoscopy suite, but it is recommended when transbronchial biopsies are planned. Personal protection devices are in order when fluoroscopy is used.
- Infections control devices, adequate ventilation to prevent transmission of infectious diseases.
- Decontamination area, protease enzymatic agent, disinfection agent.

Patient Preparation [20–23]

As a rule of thumb, bronchoscopists should never plan or proceed to a bronchoscoscopy without first reviewing the medical record and perform

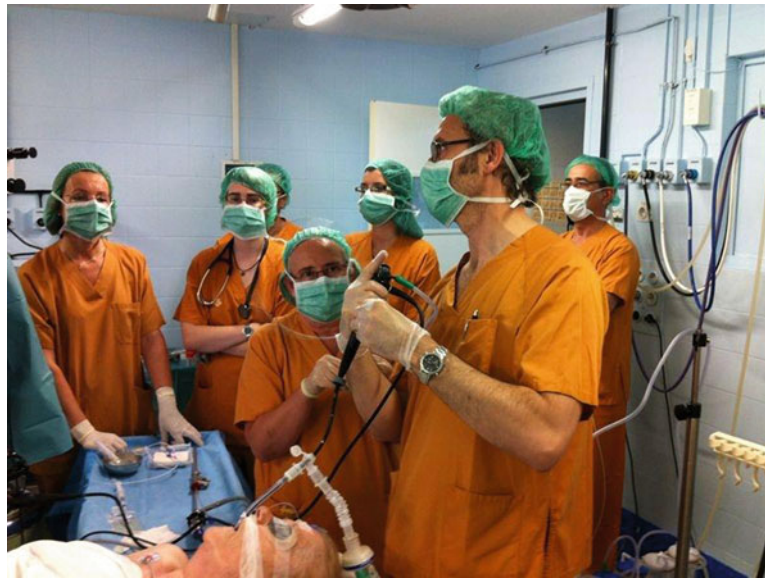

Fig. 2.7 The procedure room

physical exam. Chest images must be carefully evaluated and the approach should be planned in advance. While taking informed consent, sufficient explanation to the patient and family members about the procedure, its risk and benefits should be given. Understanding and taking part of the plan makes the patient more comfortable and cooperative.

- Fasting: six hours before the procedure and 2 h after exploration.
- Laboratory tests: The laboratory tests required before performing a bronchoscopy are very few. In the absence of risk factors, there is no need to have platelet counts. It is recommended that patients should be tested only if history or physical exam suggest a bleeding or coagulation disorder and transbronchial biopsies are planned.
- Anticoagulated patients should be reversed at least 3 days before the procedure, replacing oral anticoagulation by low molecular weight heparin.
- Antiplatelet treatment should be discontinued at least 5 days before the procedure. There is no need to discontinue aspirin (see below).
- Transbronchial biopsies should not be performed in patients with elevated BUN >45 or a creatinine level >3. Also, it is recommended that platelets level should be higher than 50,000. However, inspection of the airway and BAL can be safely performed even in the presence of renal failure and a low platelet count [6, 23].
- Electrocardiograms are indicated in patients at risk for heart disease or when pertinent history or physical findings are discovered. Institutions, however, have different policies regarding pre procedure studies and may require laboratory work and EKG to all patients regardless of risk factors.
- Spirometry is not necessary before proceeding with flexible bronchoscopy, since it is unlikely to influence the decision to perform it [19]. It is advisable to premedicate asthmatic patients with beta adrenergic bronchodilators.
- Premedication with atropine or glycopyrolate is not beneficial in decreasing bronchoscopy-related cough or secretions, and should not be prescribed rutinarily [20–22].
- Antibiotic prophylaxis is indicated in anesplenic patients or those with history of bacterial endocarditis or heart valve lesions. Flexible bronchoscopy is a recognized cause of bacteremia and although rare, bacterial endocarditis has been documented after bronchoscopy [24].

- IV placement before the procedure.
- Oxygen administration: Via nasal cannula.
- Local anesthesia: Lidocaine is the most indicated local anesthetic, provided there is no history of lidocaine adverse reactions. The recommendation is to administer 2 cc aliquots of 2% lidocaine to reach the lowest effective dose, not exceeding 5 mg/kg to avoid toxicity (seizures, arrhythmia). In this regard, some studies have shown that a higher dose is well tolerated by patients and do not produce toxic blood levels [25]. However, in a report of 48,000 bronchoscopies there were six documented cases of seizures attributed to lidocaine use [26].
- Sedation: All patients should be lightly sedated with a short acting agent, what it is called conscious sedation. Patient should be able to cooperate with the procedure and follow commands, and comfortable enough to tolerate it. Sedation improves tolerance to the procedure [27], but also increases the risk for respiratory depression and respiratory arrest, particularly when the combination of benzodiazepine and opiaceous are used [28]. Since this combination is the most commonly used, it is recommended a careful titration of medication, using small aliquots, assessing continuously status of sedation and comfort. Midazolam is the most used benzodiazepine since it has a rapid onset of action and produces sedation and amnesia. The combination of opiod and benzodiazepine produces a more profound sedation and also increases the risk for respiratory depression and apnea. Among opiods, fentanyl has a faster action and shorter duration of action than morphine, and is also more potent. Propofol can cause hypotension and myocardial depression, Some particular situations can benefit of less sedation or no sedation at all, such as foreign body retrieval or any other bronchoscopy requiring a dynamic examination. Some therapeutical procedures are performed under general intravenous anesthesia, placing the FB through the endotracheal tube or a laryngeal mask. Ventilation and oxygenation are provided by assisted ventilation or connected to jet ventilation [20–22].
- Radiological control: It is recommended that blind procedures should be taken under fluoroscopy guidance. In case it is not available, a chest X-ray is advisable 1 h after transbronchial biopsy to rule out pneumothorax [29].
- Activity: After the procedure, the patient will recover during a variable period of time, until sedation has washed out. He/she will not be allowed to drive or to engage in hazardous activities for at least 8 h after the procedure. It is recommended that all patients come with a companion whenever possible, and they should be instructed on the events that can follow a bronchoscopy: fever, blood tinged sputum, bronchoespasm. They should also know when to contact the bronchoscopist, in case they develop chest pain, shortness of breath and hemoptysis. Instructions should be given in written.

The Procedure

After obtaining an IV, and attaching monitors, oxygen is administered via nasal cannula. The patient can be placed in a semi recumbent position or in supine position. According to the ACCP survey, the nasal route was the preferred site of entrance for one third of the endoscopists [23], 6% used only the oral route. Preparation of the nasal route includes the application of topical anesthetic to the nostrils, nasal passages and pharynx. In case the mouth is chosen as an entrance, a bite block should be placed to avoid damage to the bronchoscope. The upper airway is carefully examined. When at the level of the vocal cords, lidocaine should be administered to allow a smooth passage of the bronchoscope. Vocal cords are examined: characteristics and movement. The bronchoscope is then passed through the cords and a complete examination of the tracheobronchial tree is performed. Regular aliquots of lidocaine are flushed through the work channel, usually at the level of trachea, main carina, and main bronchus.

The endoscopic exam should be thorough, starting at the healthy lung and leaving the diseased

side to the end. Following that order all the tracheobronchial tree will be already reviewed in case that an abrupt ending is necessary.

A complete knowledge of the airway anatomy is essential, otherwise it is easy to lose orientation, in which case the endoscope should be pulled back to a reference point, and then proceed.

Some characteristics should be carefully evaluated and documented:

- Abnormalities of the bronchial wall and mucosa (color, irregularities, hypervascularity, inflammation, edema, atrophy, infiltration, cartilaginous damage, extrinsic compression, presence of stenosis—stating an approximate percentage of compromise of the airway lumen).
- Abnormalities within the airway lumen (endobronchial tumor, nodular or polipoid lesions, granulomas, foreign bodies: size, color, extent, characteristics).
- Abnormal substances in the bronchial lumen (secretions: quantity, location, characteristics).
- Abnormalities in the normal tracheo-bronchial motion or dynamic disorders (loss of normal respiratory movements, malacia, excessive airway collapse).

It is recommended to use a systematic approach to evaluate the airway, and always indicate location, extent and size of the abnormality. The description should be simple but accurate. It is also very important to measure the distance between the lesions and the closest carina, which is a very relevant information that the surgeon will need to know. Whenever is possible to record the procedure or to take pictures, it should be done so in order to discuss the best approach for definitive treatment in a multidisciplinary fashion.

Complications

Diagnostic flexible bronchoscopy is a very safe procedure. The United Kingdom Survey [30] reported a mortality rate of 0.045% out of 60,100 procedures.

Other publications report different percentages: 0.01% out of 2,452 bronchoscopies [28], and 0.02% out of 48,000 procedures [26], still indicating a very low risk of death when performing bronchoscopy. Minor and major complications present at a very low rate as well [23]. As the indications for flexible bronchoscopy expand and new techniques are incorporated, complication rate can potentially increase. The most frequent ones are depicted in Table 2.5.

Table 2.5 FB complications

– Adverse events of medication used as sedatives or anesthetic agents
– Hypoxemia
– Hypercapnia
– Bronchospasm
– Hypotension
– Laryngospasm, bradycardia, vaso vagal effect
– Epistaxis
– Pneumothorax
– Hemoptysis
– Nausea and vomiting
– Fever and chills, bacteremia
– Arrhythmia
– Transient chest X-ray infiltrates
– Gas embolism
– Death

The most common one, appearing in almost all brochoscopies is desaturation. In some cases it can be transient, but its effects can persist for a period of hours after the procedure has ended, particularly when BAL has been performed on an already compromised lung [31]. PO2 fall can be important, and should be prevented with O2 administration via nasal cannula. Sedation, decreased respiratory reserve, diminished caliber of the airway due to the presence of the bronchoscope, excessive suction, bronchial washings and BAL of course, are all causes of hypoxemia that coexist during FB [30].

Cardiovascular abnormalities are also very common and their impact depends on duration of the procedure, previous patient status and medications used. The most frequently seen is tachycardia, but bradycardia can also present. Some other cardiac arrhythmias can arise, such as atrial tachycardia, atrial flutter and fibrillation, paroxysmal supra-ventricular tachycardia, atrial and ventricular premature complexes, right and left bundle branch blocks, AV nodal blocks of Wenckebach type and complete AV blocks.

They are mainly attributed to hypoxemia [32]. The risk for myocardial infarct is increased if patients have a history of hypertension, coronary artery disease, severe lung compromise, and old age [33].

Pneumothorax is a complication that usually occurs during bronchoscopy or soon after it, especially if transbronchial lung biopsies have been taken. Late pneumothorax is unusual. Not all pneumothoraces appearing after a FB have to be treated, but it is recommended that a chest tube kit is available at the bronchoscopy suite in case of need. Significant reduction in the rate of pneumothorax has been found when transbronchial biopsies are performed under fluoroscopy [34]. The UK survey however, only found a significant reduction in the frequency of pneumothorax requiring chest tube placement, when fluoroscopy was used [30].

It is very common to have minor, self-limited bleeding during bronchoscopy, particularly when biopsies are taken. Major hemoptysis is rare, usually seen during therapeutic procedures such as laser or electrocautery application. Pereira et al. [35] reported an incidence of 0.7% of hemoptysis (more than 50 ml of blood) following transbronchial biopsies (2 patients), bronchial biopsies (1 patient), brushing (2 patients) and bronchial washing (1 patient) with no associated deaths or need for transfusions. A prospective study developed to evaluate the risk of bleeding after transbronchial biopsies in patients taking aspirin [36] reported an overall incidence of major bleeding of less than 1% out of 1,217 procedures.

Hemoptysis can cause rapid death if not handled appropriately. It is well known that the airway dead space is around 150 cc and can be completely fill very fast causing asphyxia, therefore, immediate action should be taken. Securing the airway, lateralizing the patient with the bleeding side down, tamponading the bleeding bronchus with the bronchoscope, cold saline instillation, epinephrine instillation, double lumen intubation isolating the bleeding side are some of the available maneuvers to avoid profound desaturation, until a definite solution is offered. The risk of bleeding is increased in patents with uremia, platelets disorders, coagulopaty and liver failure. Patients taking aspirin have no increased risk of bleeding and therefore discontinuation of this medication is not indicated before the procedure [36].

Tables 2.6 and 2.7 present results of the UK survey and the ACCP survey on FB.

Basic Diagnostic Procedures

Bronchial aspiration: It represents the suction of secretions, with or without instillation of a variable amount of saline. Obtained material can be processed for cytology and cultures.

Bronchoalveolar lavage (BAL): It is performed instilling of 100–150 cc of normal saline through the bronchoscope. The bronchoscope should be placed occluding the selected segmental or subsegmental bronchus. Normal saline is flushed in 20–50 cc aliquots and then aspirated at low pressure, separating the first syringe that represents bronchial content, and using the rest of the aspirate (alveolar content) to analyze chemical, cytological and microbiological components. In a healthy non-smoking subject the normal cell counts is: 80–90% macrophages, 5–10% lymphocytes, 1–3% PMN neutrophils, <1% eosinophils and <1% mast cells.

Bronchial biopsies (BB): A biopsy forceps is introduced through the bronchoscope, obtaining tissue samples with approximately 1–3 mm size. That allows histological study of visible lesions.

Transbronchial lung biopsy (TBLB): It allows sampling of peripheral lung tissue (bronchioles and alveoli). It is obtained by inserting the biopsy forceps closed distally until resistance is felt. Then the forceps is pulled back about 2 cm, set to open position and readvanced until resistance is felt again. The forceps is then closed to take the sample. This maneuver is better achieved coordinating with the patient, in a way that the bite is taken at the end of expiration. If pain develops during this maneuver, the forceps should be open and reposition again, since that means that the visceral pleura has been touched. Samples obtained by TBLB can be used for histology and cultures. Possible complications are pneumothorax and bleeding. The risk of severe

Table 2.6 The ACCP Survey [23]

Number of procedures	Average 115 per physician per year
Type of procedure	Flexible bronchoscopy 92% Rigid bronchoscopy 8%
Recovery	Outpatient bronchoscopy 63% Overnight admission 12%
Location	Operating room 49% Patient's room 56% Broncoscopy suite 17% ICU 2.5%
Assistance	Nurses alone 39% Nurses and other 26% Pulmonary therapists alone 15% Pulmonary therapists and others 7.6% Physicians 15%
Fluoroscopy	Dedicated to bronchoscopy 21% Shared with others: 74%
Prebronchoscopy tests	Chest radiograph 89%, platelet count 70%, prothrombin time 70%, electrocardiograms 42%
Premedication	Atropine: 83% Meperidine 59%
Sedation	IV access: 77% Always sedation: 51%
Anesthesiologist	Routinely: 7.6%
Monitoring	Pulse Oxymetry: routinely 84% Electrocardiograms: 75%
Supplemental oxygen	Routinely 89%

Table 2.7 The UK survey [30]

Patient preparation	Fasting: between 4 and 8 h 77% Spirometry requested by 75% Arterial gas exam: 63% when clinical status suggested poor oxygenation Full blood count: routinely requested by 57% Clotting function requested by 88% when TBLB was planned
Drug therapy	Lidocaine was the most common local anesthesic. 53% used more than 5 mg/kg Antimuscarinic: indicated by 29% Prophylactic antibiotic in patients with known heart valve defect: 60%
Monitoring and support	Pulse oximeter: always in 99% ECG monitoring: always in 22% Supplemental oxygen: always in 66% IV line: always in 87% BP monitoring always in 10%
Endoscopist clothing and protection	Gloves, gown, eye protection and face mask used routinely for all procedures: 29%
Sampling techniques	Most used procedures: endobronchial biopsy, brush biopsy and bronchial washing TBNA used only by 10% Fluoroscopy for TBLB: always 35%, never 57%
Therapeutic procedures	Endobronchial stenting: 15% Brachytherapy, laser, balloon dilatation, fluorescence bronchoscopy, electrocoagulation: very low rate of use
Mortality	27 deaths in 60,100 procedures: (0.045%)

pneumothorax is significantly decreased when TBLB are performed under fluoroscopy.

Transbronchial needle aspiration (TBNA): It is performed with a cytology needle or a histology needle, and mainly indicated to investigate mediastinal nodules, peribronchial structures, or submucosal lesions. Computerized tomography should be evaluated very carefully to plan the point of entrance, and anatomic knowledge (location of major vascular structures) is crucial to obtain appropriate samples and avoid complications. Lymph nodes that are accessible to this technique are: 4R, 4L, 7, 11R and 11L.

Sensitivity for this technique varies according to experience of the operator, size of the lymph node, number of aspirates per node, and the availability of rapid on-site cytology [37].

A sensitivity of 78% has been reported for blind TBNA in the detection of malignancy [38] with a high specificity (99%) [33]. The diagnosis of nodal sarcoidosis can also benefit from blind TBNA [14].

The rate of complications is low: 0.8% in a meta-analysis by Holty et al. [39], being pneumodiastinum, pneumothorax, minor bleeding and puncture of adjacent structures the most commonly encountered. Blind TBNA is currently been replaced by EBUS TBNA, but since EBUS is not widely available, blind TBNA is still performed in many centers.

EBUS TBNA is the preferred method when available. It can sample paratracheal and peribronchial masses as well. The ultrasound provides real time images that allow a direct

visualization of the targeted abnormality, improving significantly the diagnostic yield. Some reports give this method a sensitivity that ranges from 85 to 100% [40], comparable to surgical mediastinoscopy [41]. Such as blind TBNA, EBUS TBNA can be useful in diagnosing sarcoidosis [20]. Lymph nodes that are accessible to this technique are: 2R, 2L, 3P, 4R, 4L, 7, 10R, 10L, 11R and 11L. Rate of complications is low: 0.15% in a meta-analysis published by Gu et al. [42]. A complete discussion of EBUS is presented in dedicated chapters of this book.

Bronchial brushing: It can be performed to visible lesions or under fluoroscopic guide to non visible lesions. It involves the introduction or a small protected brush. Once the lesion is located, the brush is advanced and rubbed against the lesion, producing injury to the mucosa and thus obtaining cytological material.

Therapeutic Procedures

Almost all therapeutical procedures can be accomplished with the flexible bronchoscope by well trained operators. When performing interventions with the FB, the bronchoscopist should be ready to use the rigid bronchoscope if needed, meaning that the dedicated interventional bronchoscopist must be equally trained to apply both instruments.

Since all interventions will be described in detail in different chapters, a brief summery will be outlined here (Table 2.3):

Debulking of benign and malignant tumors in central airway obstruction: a number of methods can be applied in order to achieve the re-opening of the airway. The rigid bronchoscope has been recommended by most of the experts in the interventional area to deal safely and rapidly with this situations [6, 19, 21, 43]. However, the FB is used more and more in therapeutic procedures and, knowing its strengths and limitations, it can be used to apply laser, electrocautery, argon plasma coagulation, cryotherapy, photodynamic therapy and brachytherapy in order to restore airway patency.

For laser application, mainly indicated for a fast airway opening of benign or malignant lesions, it is recommended to set to low power to coagulate (40 W), keeping the laser fiber tip at least 4 mm from both the target tissue and the tip of the bronchoscope. Fraction of inspired oxygen should be kept at 40% or less and frequent suction is in order, both measures oriented to avoid endobronchial fire [44]. Once the tumor is coagulated, biopsy forceps are used in order to extract small pieces. Vaporization also occurs, but in general laser treatments, when performed with the FB, are long and require a significant amount of patience, and they are not useful when the obstruction is severe or critical since this situations are better handle with the rigid bronchoscope[6]. In turn, small lesions such as granulomas are easily treated with FB laser application (Fig. 2.8a, b).

Laser is very effective in opening the airway, with a symptomatic improvement in around 70–80% [45, 46]. Complications related to laser application include: massive hemoptysis, pneumothorax and pneumomediastinum [45] with a procedural related death of 3% [46].

Electrocautery also acts through coagulation and vaporization. Energy setting should be started at 20 W to test the immediate results of the application. The electrical probe can be used to treat superficial lesions, while the snare can be applied to polipoid tumors protruding into the airway lumen.

Electrocautery is indicated in central airway obstructions from primary or metastatic malignant tumors of the airway [47]. Early stage lung cancer can also benefit from cautery applications, as also do benign lesions obstructing the airway. Similar to laser, electrocautery is contraindicated when the obstruction arises from extrinsic compression without intraluminal component [48].

Palliation of malignant obstructions is effective, having a high rate of reopening of the airway and symptomatic relief [49, 50] that has been reported as similar to laser debulking (69–94%) [51].

Complications are similar to those of laser application being bleeding the most feared one.

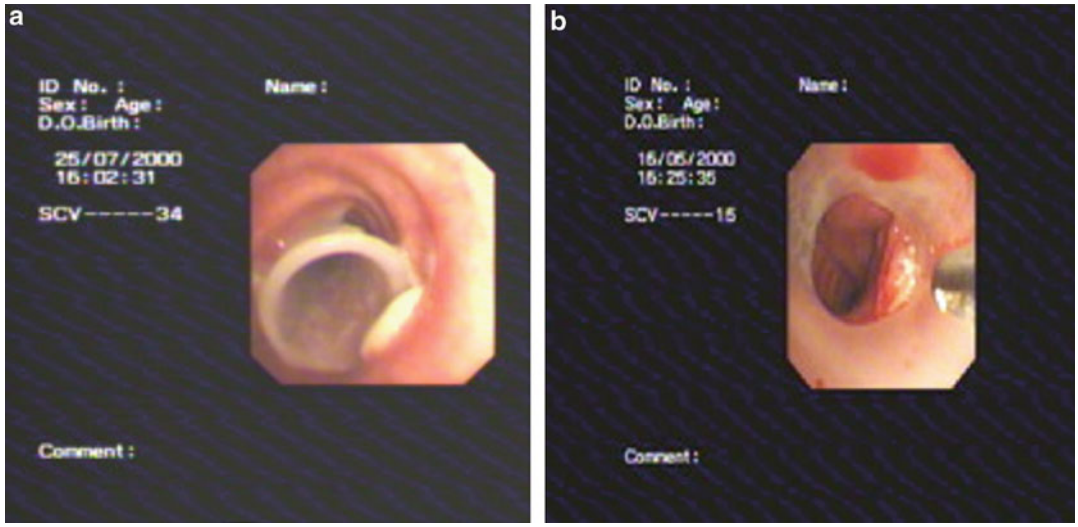

Fig. 2.8 (**a**, **b**) Small granulomas located proximally to a Dumon prosthesis and distally of a Montgomery stent. Both lesions can be easily treated by FB laser application. Special precautions should be taken to avoid endobronchial fire

Suggested settings to avoid fire during the procedure are: FiO2 less than 40%, power 20–30 W.

Argon Plasma Coagulation (APC) is a non-contact mode of electrocautery that causes coagulation and vaporization. It is indicated to treat exophytic endobronchial tumors, and also has good results on treating bleeding tumors, when they are visible to flexible bronchoscopy. APC can be applied to other benign lesions compromising the airway, such as granulomas resulting from airway stents.

Results of ACP when applied to central airway obstruction are good, with a partial or complete reopening of the airway in 66% of patients, reporting a successful rate of 99% for APC when treating hemoptysis [52].

Complications related to APC are: airway perforation and gas embolism [53].

Cryotherapy refers to the use of cold to cause tissue destruction. The cryoprobe is inserted through the working channel of the flexible bronchoscope and cycles of freezing and thawing are applied to the target, causing delayed necrosis. A repeated bronchoscopy should be performed 3 to 7 days after the application in order to remove necrotic tissue. Cryotherapy does not open the airway fast and it is not indicated in critical airway obstruction since its application generates edema and can in fact worsen the degree of the obstruction. A new modality of cryotherapy application, cryoextraction or cryorecanalization, can be considered a fast re opening method since it involves the extraction of tumor pieces attached to the cryoprobe, obtaining inmediate results (Fig. 2.9).

Conventional cryotherapy is indicated in malignant airway obstruction as a palliative method. Success rate has been reported in 61% in re opening of the airway and improvement in symptoms such as hemoptysis, cough and dyspnea (up to 76%, 69% and 81%, respectively) [54, 55].

Complications related to cryotherapy are hemoptysis, bronchospasm, cardiac arrhythmia and death [56].

Photodynamic therapy: It involves the administration of a photosensitizer substance (the most common one being porfimer sodium) followed by its activation with a laser light of a given wavelength. This generates a photodynamic reaction that produces oxygen radicals, very damaging for tumor cells, ultimately resulting in cellular death. Photodynamic therapy can be applied to both early and advanced malignant lesions with good results.

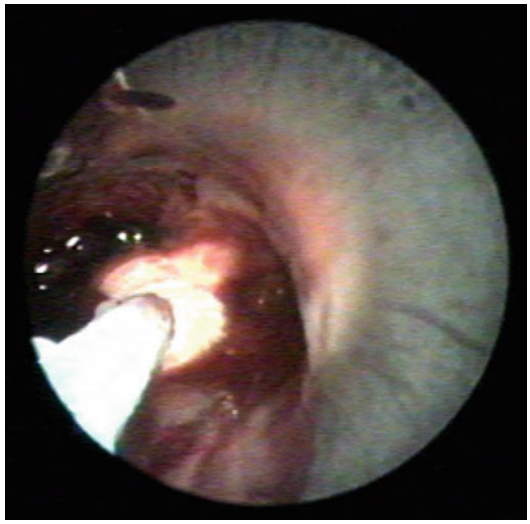

Fig. 2.9 Cryoresection: The flexible bronchoscope has been introduced through the RB

Complications related to this procedure are: photosensitivity that can last up to 6 weeks and hemoptysis.

Stent placement: The flexible bronchoscope can be used to deploy self expandable metallic stents in the airway. Their application is limited to malignant conditions since long term permanence inside the airway has been linked to severe complications such as erosion and perforation of the airway wall, excessive granulation tissue, bacterial colonization, stent disruption and fracture [57]. The FDA made clear that recommendation in 2005 [58], making the following advice to follow when planning a metallic stent placement:

- Appropriate patient selection is crucial.
- Use metallic tracheal stents in patients with benign airway disorders only after thoroughly exploring all other treatment options (such as tracheal surgical procedures or placement of silicone stents).
- Using metallic tracheal stents as a bridging therapy is not recommended, because removal of the metallic stent can result in serious complications.
- If a metallic tracheal stent is the only option for a patient, insertion should be done by a physician trained or experienced in metallic tracheal stent procedures.
- Should removal be necessary, the procedure should be performed by a physician trained or experienced in removing metallic tracheal stents.
- Always review the manufacturer indications for use, warnings and precautions.
- Be aware of the guidelines from professional organizations regarding recommended provider skills and competency for these procedures (i.e. training requirements and clinical experience).

Recommendations from experts are to avoid metallic stents and consider other therapeutic strategies. Debridement or dilatation and placement of a silicon stent can be performed in the majority of patients, and represent safest alternatives [59].

Postsurgical stenosis that follow lung transplant or tracheal resection can be an indication for metallic stents. Bronchial dehiscence after lung transplantation can present as a life threatening respiratory insufficiency, and deployment of a metallic stent can be not only life saving but also can favor dehiscence healing taking advantage of the granulation tissue formation secondary to the stent placement [60]. However, this indication is left to the team of experts managing lung transplanted patients, not applicable to the general interventional bronchoscopy practice.

After placement of a metallic stent, patients should be follow up closely to diagnose and treat complications if they arise.

Training and Certification

The ARS/ATS statement in Interventional Bronchoscopy [20] and ACCP guidelines for Interventional Pulmonary Procedures [22] have both issued recommendations on training and number of procedures required to obtain and maintain proficiency in performing both rigid and flexible bronchoscopy (Table 2.8). Training in interventions involves theoretical knowledge, practice on a model, and hands-on experience. Definition of competency by numbers has the

Table 2.8 Training recommendations ACCP [22]

Procedure	Number of procedures per year	
	Obtain proficiency	Maintain
Flexible bronchoscopy	100	25
Rigid Bronchoscopy	20	10
TBNA	25	10
Autofluorescence bronchoscopy	20	10
EBUS	50	20
Laser therapy	20	10
Electrocautery-argon plasma coagulation	15	10
Cryotherapy	10	5
Brachytherapy	5	5
Photodynamic therapy	10	5
Airway stents	20	10
Thoracic percutaneous needle aspiration	10	10
Percutaneous dilatational tracheostomy	20	10

limitation of not considering that the learning curve is very different from one physician to the other.

The application of a standardized curriculum for training developed by Bronchoscopy International (available at http://www.bronchoscopy.org) can help facilitating the process through an outcome based assessment. Program directors should be in charge of ultimately deciding if a physician is capable of performing procedures without supervision.

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Rigid Bronchoscopy

3

Jose Pablo Díaz-Jimenez and Alicia N. Rodriguez

Introduction and History

Bronchoscopy is an invasive procedure most commonly indicated to diagnose and treat pulmonary problems. There are two kinds of bronchoscopes: the flexible bronchoscope (FB) and the rigid bronchoscope (RB). The first one is the most utilized in clinical practice. However, the rigid bronchoscope is a very important instrument for the diagnosis and treatment of many pulmonary disorders, and it has been applied to the airway for many decades.

The interest on reviewing the airway goes back to 1823, when Horace Green introduced first a sponge and then a rubber catheter into the bronchi, applying silver nitrate to burn lesions located at the level of the larynx and trachea. Later, Joseph O'Dwyer introduced a tube to release adhesions of the lower airways caused by diphtheria, and he also constructed a thin-walled tube to assist in the removal of foreign bodies.

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The rigid bronchoscope was introduced by Gustav Killian (Germany) in 1897, for the extraction of a foreign object (a small piece of a pig bone) from a 63-year-old man, becoming the father of bronchoscopy. For the procedure, Killian used an esophagoscope and rigid forceps. [1]. Chevalier Jackson, from Philadelphia, PA (USA), made popular this new bronchoscopic technique and developed the most commonly used rigid bronchoscope. His idea of placing a small light in the distal part of the endoscope revolutionized the endoscopist's ability to examine the airways. In 1916 he established bronchoesophagology departments in five hospitals in Philadelphia, training many well-known bronchoesophagology professionals [2, 3].

During more than 70 years, the rigid bronchoscope or open tube was the only available instrument to review the airway. At first, it was mainly used to remove foreign bodies or dilate strictures, but later new applications were described: aspiration of secretions, hemoptysis treatment, biopsies, etc.

Shigeto Ikeda's flexible bronchoscope (FB) development in the 1960s [4] has been the most significant advance in the area of bronchoscopy and has changed the practice to our days, allowing the pulmonology physicians to develop ability in performing flexible bronchoscopy and also giving place to the introduction of new technologies specifically designed to apply with FB.

Short after its invention, the FB almost replaced the RB in the clinical practice. However, the rigid bronchoscope is still a very important

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instrument in the study and treatment of airway disorders.

RB and flexible bronchoscope complement each other in many indications, and there is no reason to see their application in opposite terms, since each instrument has strengths and limitations. In this chapter, we will review our experience on RB, along with a complete discussion on indications and contraindications.

Overview of RB

The RB is a stainless steel open tube with variable lengths and widths. It has a distal end, beveled and smooth, and a proximal end that can be adapted to a metallic universal head with several side ports. The distal end is used to lift the epiglottis during intubation and is also very useful to dilate strictures and to "core" tumors. Lateral openings or fenestrations are present to allow contralateral lung ventilation while working.

The RB is the preferred instrument for endoscopic resections. The rigid tube is the only device that allows a complete control on the airway, assuring proper oxygenation and ventilation while performing, for instance, a laser resection. Aspiration of blood, secretions, and smokes can be easily achieved at the same time than an excellent view of the central airway is depicted.

One of its main strengths is the ability to confront serious hemorrhagic accidents or airway obstruction from various etiologies: benign or malignant conditions, foreign bodies, mucus plugs, etc. Although unusual, massive hemorrhages can occur even in routine fibrobronchoscopies. The RB allows the application of pressure on the hemorrhagic area until hemostasis occurs, giving sufficient time to apply other therapeutic modalities, which can bring a definitive solution to the problem. It is also particularly useful in the pediatric population. Children airway diameter is very small, and it is preferable to use a hollow tube in order to allow spontaneous breathing or assisted ventilation. The FB blocks the airway, and the patient has to breathe around it, increasing significantly the airway resistance and work of breathing, making the procedures difficult. The RB, in turn, allows the patient to breathe through it, favoring spontaneous breathing and mechanical ventilation while performing the procedure.

Fig. 3.1 Dr. JF Dumon

The rigid bronchoscope has undergone modifications over time, particularly after laser resection and stent placement became regular indications for different airway conditions. The most used brand names today are Efer(R), Storz(R), and Wolf (R).

Innovations

The first rigid bronchoscope for laser application was designed by Jean François Dumon (Fig. 3.1), from Marseille, France, for the brand Wolf. In contrast to other rigid bronchoscopes, the Wolf system has two lateral ports (one for the laser fiber and the other one for the suction catheter) and a rotating ventilation connector that allows assisted ventilation without interrupting the treatment. All ports can be occluded to allow closed-circuit ventilation. Based on this experience, the Dumon–Harrel (Efer) universal rigid bronchoscope was later developed; it associated modifications already present in the Wolf system with other advantages, such as the possibility of using a series of 11 interchangeable tubes with increasing diameters available in two different lengths; the short tubes (Fig. 3.2) for endotracheal treatments, with no side orifices (diminishing the air lost in the trachea); and the long tubes for endobronchial treatments, with lateral orifices that allow an adequate ventilation even when the bronchoscope is placed in a

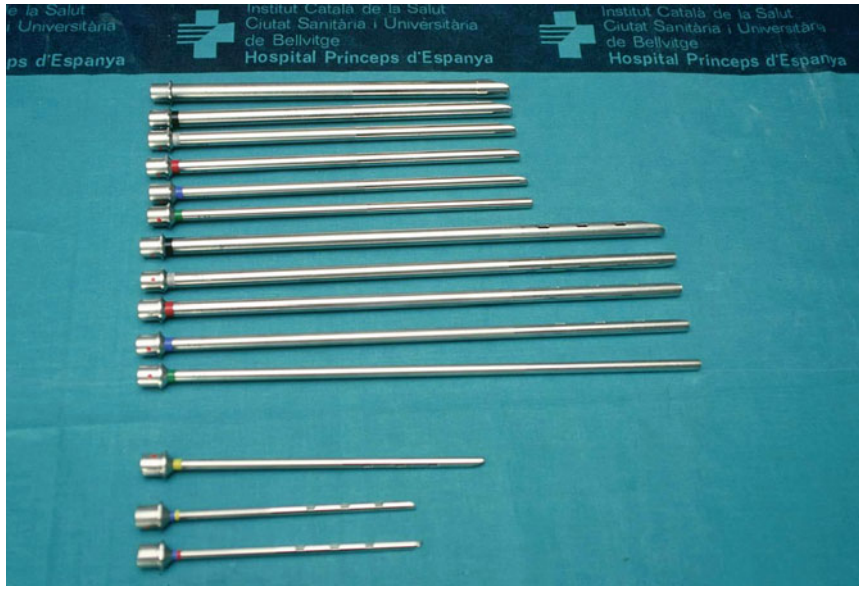

Fig. 3.2 Dumon rigid bronchoscope

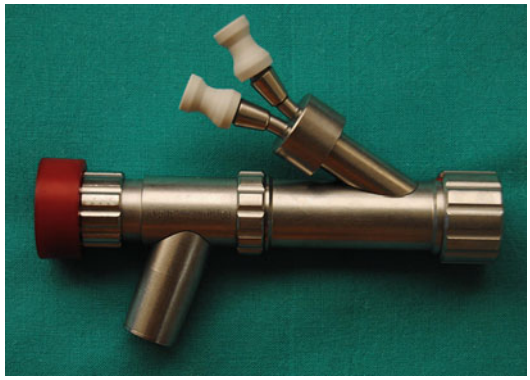

Fig. 3.3 Universal head of the rigid bronchoscope

peripheral bronchus. Internal and external diameters are color coded on each tube (from 3.5 to 10 mm internal diameter and from 4 to 12 mm external diameter). Available tubes for pediatric use have an internal diameter from 3 to 5 mm and 20 cm in length.

The head of the rigid bronchoscope can be adapted to the desired tube, according to the different needs (Figs. 3.3 and 3.4).

The Dumon–Harrel rigid bronchoscope comes with a separate deployment system for the silicon (Dumon) prosthesis.

Another Dumon–Harrel system innovation is the fact that it is possible to lift the superior part of the lateral door, allowing the aspiration of large tumor fragments without modifying the position of the suction catheter. The securing caps are made of Silastic, with one or several orifices of different sizes. These caps are much more solid than the usual rubber ones, allowing a more hermetic closure, optimizing ventilation.

The rigid optics offer direct 0 degrees vision (Fig. 3.5); they come in three diameters: 3.5 mm, 5.5 mm, and 7 mm, and they are not fixed. There is also a smaller pediatric optic for pediatric use. These instruments easily slide through the Silastic caps and can be moved back and forth according to need. It is a very useful feature to avoid sudden movements that can injure the airway. The rigid optic can be pulled back to avoid midst or loss of visualization due to blood or detritus. The rigid optic, suction catheter, and laser fiber are independent inside the rigid tube, making handling easier.

The most comfortable position when applying laser is placing the tip of the laser fiber advanced within the airway, the suction catheter located slightly back to the laser tip, and the rigid optic further back from the working field (Fig. 3.6). The independence of these elements allows modifying at any time their position according to the intervention needs.

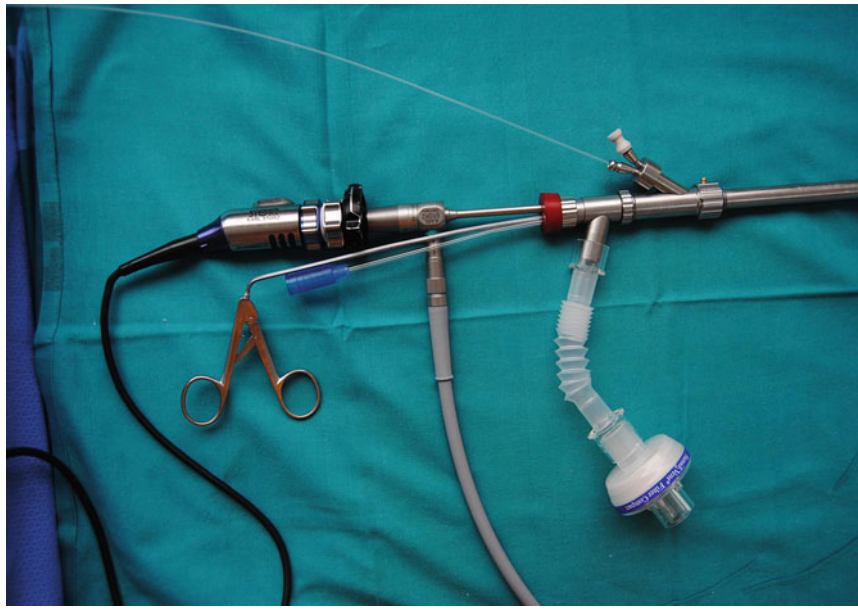

Fig. 3.4 Rigid bronchoscope with ancillary tools and connection for ventilation

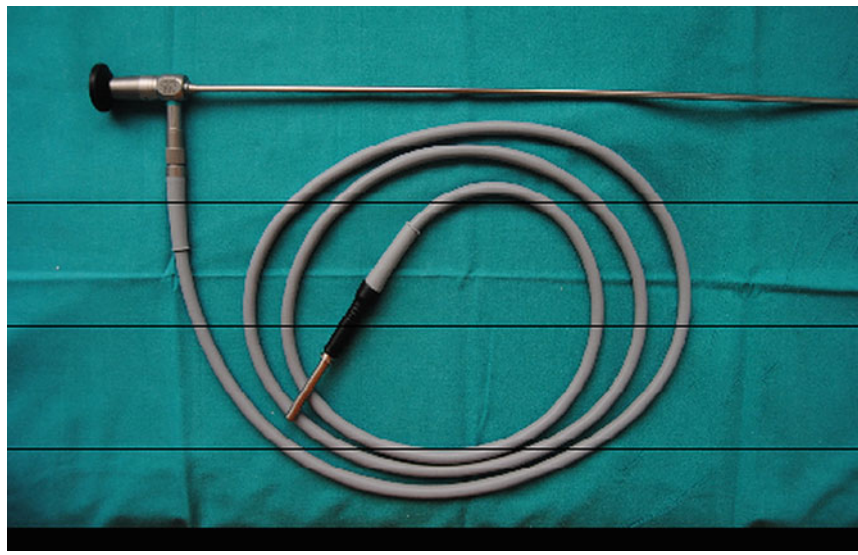

Fig. 3.5 Rigid telescope (optic)

The RB has been designed to present a universal character, in other words, to adapt to multiple endoscopic situations. In addition to laser application settings described above, this instrument can take other configurations: all or some of the entrance ports can be used (from one to three), open or closed ventilation circuit (for "jet ventilation," manually assisted ventilation or spontaneous ventilation), use of short or long tubes, adult or pediatric tubes, allowing diagnostic and/or therapeutic procedures on practically any group of patients.

The Storz rigid bronchoscope was designed by Shapshay from Boston, USA. It is specially manufactured for jet ventilation, and for this reason, it has a fixed port designed to serve this

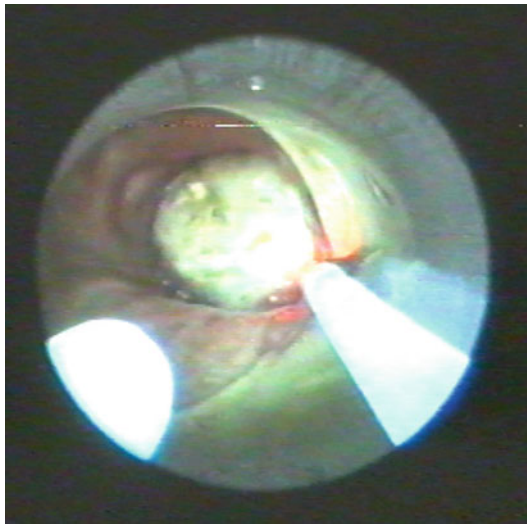

Fig. 3.6 Correct position of the suction catheter and laser fiber into the RB. It is important to always see the tip of the bronchoscope during the procedure

purpose. It is available in 10 mm internal diameter size (12 mm external diameter), presenting also a connection for ventilation and two additional ports [5].

A recently introduced rigid bronchoscope, called rigid integrated bronchoscope developed by Wolf, presents separate channels for optics and instruments and integrates the operator head with the camera. It has also an irrigation port to wash the distal lens. It has the advantage of increasing the working space and thus improves manipulation within the bronchoscope. However, the vision is limited since the camera does not go further distal to the end of the rigid bronchoscope.

It is clear that the RB, although keeping its original basic shape, has suffered several modifications to adapt to specialized procedures, like laser application, prosthesis placement, and dilatation of tracheobronchial strictures. The RB allows flexible bronchoscopes to get through it, taking advantage of both instruments at the same time.

Ancillary Equipment

Suction catheters: They play a very important role during procedures. In addition to suction of blood, smokes, and debris, they are useful in palpating lesions to give an idea on consistency. They are also used to instill medications such as saline, epinephrine, and lidocaine. It is recommended that they do not exceed 3 mm in diameter and are made of rigid transparent material. In that way the laser beam will not burn them, and they will not collapse during suction.

Other ancillary instruments that should be available are foreign body rigid forceps (used to retrieve different elements from the airway and to adjust position of silicone stents), scissors, scalpel, balloons, mechanical dilators, endoscopic resectors, prostheses, and laser equipment, most of them designed by Dumon (Fig. 3.7).

The capability of project images is very important as well. That serves various purposes: it allows all the team to follow the procedure in detail and anticipate steps. It also permits recording the procedure, for both educational and documentation purposes.

Applications and Contraindications

RB's most important applications are therapeutic and include laser application, electrocautery, argon plasma coagulation, or cryotherapy; and dilatation of tracheobronchial stenosis using balloon dilatation or directly with the rigid tube, airway stent placement, and foreign body removal, particularly in children. Massive hemoptysis is also another therapeutic indication. Diagnostic applications are hemoptysis and the need for deep biopsies, better obtained with the rigid biopsy forceps (Table 3.1 [6]).

There are not many absolute contraindications for the use of the rigid bronchoscope: unstable cardiovascular state, significant cardiac arrhythmias, severe hypoxemia that will not improve with the procedure, and cervical spine instability. The most important contraindication is lack of appropriately trained personnel [7].

Some clinic situations, however, must be considered as relative contraindications for RB. A unstable neck that makes unsafe the excessive mobilization during the bronchoscopy, microstomy,

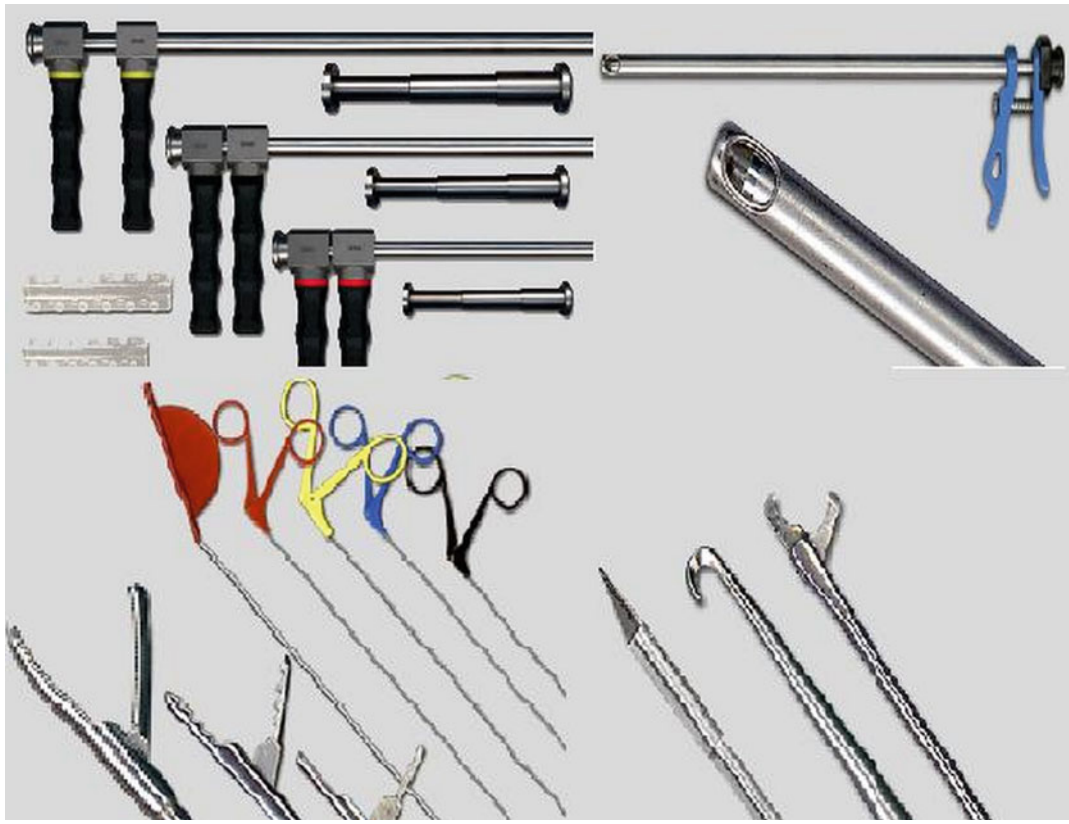

Fig. 3.7 Ancillary equipment designed by Dr. Dumon

Table 3.1 Indications for rigid bronchoscopy

Foreign body removal
Hemoptysis
Tracheobronchial stenosis
Tracheobronchomalacia
Central airway obstruction
Extrinsic compression
Therapeutic procedures
Stents
Laser
Electrocautery
Cryotherapy
Argon plasma coagulation
Dilatational balloons

Modified from Lamb and Beamis [6]

maxillofacial trauma, or other oral lesions that prevent an appropriate mouth opening to introduce the rigid tube and technical difficulties related with cervical ankylosis and severe cifoescoliosis, among the most important ones.

Rigid Bronchoscopy Applications

Laser Bronchoscopy

Laser bronchoscopy application has diminished in the last years. Reasons include high cost of the equipment, lack of adequate training, need for RB in most of the cases, long procedure time, the absence of improvement in mortality when applied to malignant conditions (even though quality of life and survival definitely gets better), and the insufficient number of patients in some centers. In addition to this, other therapeutic modalities such as electrocautery and argon plasma coagulation have become more popular given their availability, low cost, and similar good results.

However, the application of laser therapy through the RB has not been replaced in some indications, and it is still the technique offering the

best results. RB laser resection is an important tool in treating central airway obstructions (benign or malignant) and provides an immediate reopening of the trachea or bronchus when stenotic lesions are found. For most of the treatments, Nd:YAG (neodymium, yttrium–aluminum–garnet) or Nd:YAP (neodymium, yttrium–aluminum–phosphate) is used. Diodos laser is also equally useful and has become more popular given its lower cost.

In a published series about laser applications in malignant lesions, 1,585 patients were treated with 2,253 therapy sessions of Nd:YAG laser during a period of 11 years. More than 93% showed immediate good results. Complications included 18 hemorrhages, 6 pneumothoraces, and 10 deaths [8].

Similar results have been published on low-grade malignant tumors that are unresectable or present in nonsurgical candidates for advanced age or severe cardiorespiratory insufficiency. In a prospective study, 19 patients that presented with carcinoid tumor and cylindroma with inoperability criteria, the use of laser was associated with an immediate symptomatic improvement following the treatment in 100% of the cases. Fifteen patients were free from disease during a follow-up time of average 20 months (from 6 to 50 months), and two patients died of unrelated causes at 21 and 6 months of treatment. Although low-grade malignant tumor recurrence is hard to predict, the use of laser is an excellent way to keep inoperable patients free from symptoms [9].

In a retrospective review on laser bronchoscopy application, laser resection was offered to 17 patients with inoperable lung carcinoma requiring mechanical ventilation secondary to acute respiratory failure. All of them received Nd:YAG laser treatment through a RB, with respiratory assistance (jet ventilation) at the operating room. A subgroup of seven patients could be weaned from mechanical ventilation and were able to receive other therapies showing an improved survival. The rest of the patients had tumoral extrinsic compression of the airway or submucosal growing of the tumor and had almost no benefit from laser application. They died on mechanical ventilation or after been extubated when the order "comfort measures only" was established. Survival improvement seen in the first group of patients ($p = 0.0038$) was associated with the presence of obstructive endobronchial tumor as the cause of respiratory insufficiency [10]. These results show that even those patients with acute respiratory failure due to obstructive lesions can be treated with laser bronchoscopy with good results.

Tracheobronchial Prosthesis

On the last years, tracheobronchial stenosis has received much interest from bronchoscopists due to the several available techniques to treat this problem. Endoscopic treatment of tracheobronchial stenosis can be achieved through balloon dilatation, stent placement, laser resection, and even with dilatation with the rigid bronchoscope.

Balloon dilatation can be done through a RB or through a flexible bronchoscope with a wide working channel. The balloons are designed for esophagus dilatation but are also used in the airway; angioplasty balloons can be used as well.

RB dilatation is performed by applying a smooth rotation to the rigid tube, simultaneously advancing, and passing through the stenotic area several times until a safe airway diameter is achieved. Laser resection can be applied before this dilatation if needed. All fibrous stenoses treated by mechanical dilatation have the tendency to recur, and repeated procedures are needed to keep the airway open. In addition, sometimes forceful maneuvers cause mucosal damage with more scar formation, and in the long term, they can worsen the stenosis. Thus, mechanical dilatation is only recommended to solve an acute situation and as a bridge to a more definitive treatment. Benign airway stenosis is discussed in detail in a dedicated chapter of this book.

Tracheobronchial prostheses can be indicated in benign or malignant airway stenosis [11].

Several types of prosthesis are available to use with both the RB and the flexible bronchoscope. Many of the autoexpandable metallic prostheses

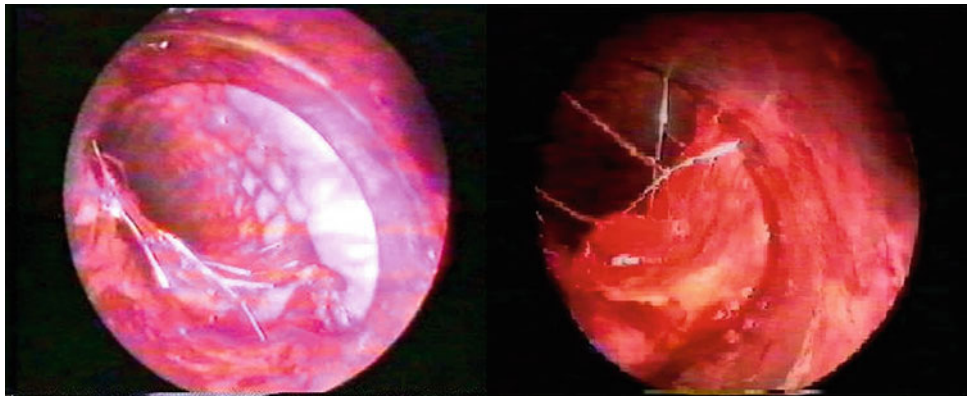

Fig. 3.8 Metallic prosthesis removal with the rigid bronchoscope

have been designed specially to allow placement with the flexible bronchoscope under fluoroscopic control. Airway prosthesis is discussed in detail someplace else in this book. However, we have to say that the RB is the only instrument suited for silicon prosthesis placement. We recommend the use of silicon prosthesis to treat most of the airway lesions, particularly benign conditions since metallic stents are associated with significant complications, that have been recognized for many experts and made clear by the FDA during 2005, when it recommended against metallic stent application to airway benign conditions. (Available at http://www.fda.gov/cdrh/safety/072905-tracheal.html.)

Results on the application of the RB are presented in a study were this instrument was used under general anesthesia to insert silicone prostheses (Dumon) in 31 adult patients with more than 50% malignant airway obstruction. After laser resection, a stent was placed and all patients presented immediate improvement in respiratory symptoms. All patients but three tolerated well the prostheses. Stents were placed in the trachea in 14 cases, right main bronchus 13, left main bronchus 8, and intermedius bronchus 3. Complications following the procedure included: migration in 5 patients, mucous obstruction in 2, and hemoptysis in 1 patient [12].

We consider training in RB use crucial to any interventional pulmonologist. Regardless the type of stent selected for a given treatment, expertise working with the RB will be needed at some point during the course of therapy. For instance, when a complication arises (i.e., migration, stent disruption) and the prosthesis needs to be removed or replaced, the best instrument to retrieve it is the RB. In addition, most of the prostheses placed via FB are very difficult to remove with the flexible bronchoscope, requiring the application of the RB to extract or adjust them. When metallic uncovered stents stay for a given period of time within the airway, they became embedded to the mucosa. In order to remove them, the beveled end of the RB should be placed between the metallic stent wall and the tracheal mucosa, and with soft rotating movements, the RB is advanced distally "dissecting" the stent from the airway wall until it is totally detached. Then it can be removed with a forceps (Fig. 3.8).

Likewise, the growth of tumor tissue through uncovered metallic stents requires RB and laser to relieve the obstruction, remove the prosthesis, and replace it in case of need. Training in RB is one of the most important skills that an interventionist has to learn and be proficient at, and is a requisite when placing silicon (Dumon) prosthesis [12, 13]. Such training also involves the staff assisting and collaborating during the procedure: assisting nurse or scrub nurse, anesthesiologist, circulating assistant, etc.

Transbronchial Needle Aspiration

Transbronchial needle aspiration (TBNA) of subcarinal and paratracheal nodules was described in 1950. Wang, in 1978, reported a diagnostic sensibility of 90% for this technique when applied with the RB [14]. After the introduction of the FB

during the 1960s, most of the bronchoscopists have been using this instrument to perform TBNA in subcarinal and perihilar lymph nodes. Diagnostic sensibility for TBNA when performed with the FB has been reported as 80–89%, especially when the 19-gauge needle is used [15, 16].

The appearance of EBUS (endobronchial ultrasound) has completely changed the approach to lymph node sampling, and this technique has virtually replaced all blind procedures given the high diagnostic yield, particularly in mediastinal sampling [17]. However, in spite of EBUS generalized use, it can still be a place for blind TBNA applied with both the RB and the FB, particularly where EBUS is not available given its high cost.

A study published in 1996 described results on needle aspiration through the RB. Twenty-four procedures were performed in 24 patients using RB and a 2-cm long rigid needle, under general anesthesia and guided with computerized tomography. Samples taken were tracheal wall ($n=11$), main carina ($n=3$), right secondary carina ($n=3$), left main bronchus ($n=2$), and right main bronchus ($n=3$). The average amount of samples was 6 (from 1 to 19). An in situ cytopathologist immediately reviewed the samples to determine the number needed. Diagnostic sensibility and specificity were 88 and 100%, respectively. TBNA resulted diagnostic in 18 patients. Findings helped in therapeutic decisions in 21 patients. There were no false positives during a follow-up period of 6 months. Three false negatives were present, and follow-up showed that these three patients ultimately had malignant lesions. There were no complications [18]. Those findings suggest that even though the technique has been improved by using EBUS or blind TBNA with the FB, the RB can have a role in the diagnostic of intrathoracic lymphadenopathies if no other method is available.

Rigid Bronchoscope in Other Treatments for Bronchial Obstruction

Laser treatments in tracheobronchial obstructions are effective, but expensive. As a result, other therapeutic options have been developed and applied with good results. Electrocautery is broadly available, and results in airway resections are comparable to laser. Also, cryotherapy and argon plasma coagulation can be applied with RB.

Results on electrocautery application with the RB are depicted in a study that performed this procedure under general anesthesia in 29 patients with tracheobronchial obstruction, 24 of which had malignant conditions. In nine patients, stents were placed immediately after electrocoagulation. All patients but one presented immediate improvement of the symptoms, and an objective improvement in the pulmonary function was also observed in eight patients who had been tested with spirometry before surgery. There were neither intraoperative deaths nor complications [19]. Electrocautery can be also applied through the FB, but similar to laser applications, procedures are more time-consuming since the RB allows better vision, optimal suction, and the possibility to remove large tumoral pieces. Cryotherapy has been presented as an alternative therapy for obstructions. However, it is called a "slow" opening method since it lacks immediate effects. Initially, all treatments with cryotherapy were performed with RB, but more recently, the cryotherapy probes have been designed for application with the FB, and new modalities of cryotherapy are available, such as cryoextraction or cryosection and also cryospray, that make this technique more versatile. These new modalities can be applied as fast opening methods.

Balloon dilatation can be applied both with the RB or FB.

Mechanical Debridement

Even though laser, electrocautery, cryotherapy, and argon plasma coagulation are useful coagulating during debridement of airway lesions, most of the obstructive tumors are generally extracted in a mechanical mode. In fact, all opening procedures involve the use of forceps. When performed with a FB, this procedure is invariably long and tedious, especially if large tumors are involved. The removal of big tumor pieces through the narrow channel of FB is very complicated, since the

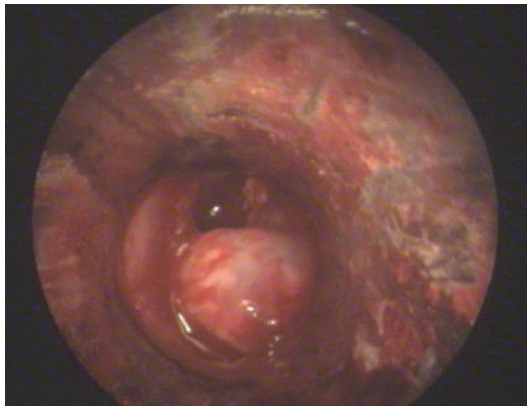

Fig. 3.9 Resection of a tumor with the beveled end of the rigid bronchoscope

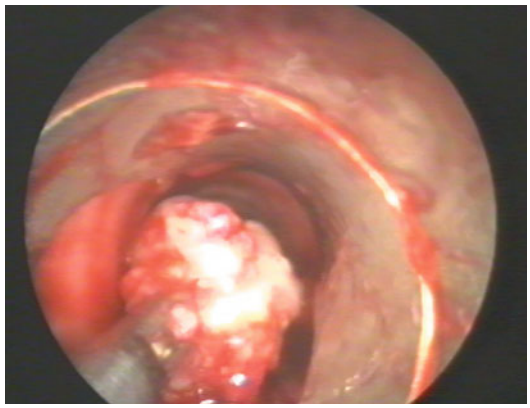

Fig. 3.10 Aspiration of a tumor piece with the rigid aspiration catheter

biggest pieces that can be extracted fit in a small biopsy forceps. It is obvious that a bigger channel such as the one of the RB will accomplish the same task in a much short period of time.

Most of the experienced bronchoscopists use laser only to coagulate the tumor and, when that is accomplished, dissect large tumoral pieces with the beveled rigid tube, (Figs. 3.9 and 3.10) obtaining a much efficient procedure [20]. Grillo et al. [21] affirm that the use of auxiliary methods like laser is not necessary to reopen the airway and only adds costs and risks to the procedure. However, their study on 56 patients whose tumors were removed only by mechanical means showed a 7% mortality associated to the treatment, considerately higher than when other methods are applied, including laser.

The RB itself acts as an airway dilatator and can achieve reopening of an obstruction in a shorter time than is required by the FB. There is an important and statistically significant difference in the total number of sessions needed to permeabilize the airway with RB and FB; the RB requires only one session and the FB an average of two [22]. In fact, bronchoscopists who use only FB to extract tumors usually require several sessions. The theoretical advantage of the FB in opening peripheral airway obstructions is rarely needed, since these cases are infrequent and the need of reopening a distal airway as a palliative measure is questionable, unless postobstructive infection is present. Even though, the FB can be more easily introduced through the RB (Fig. 3.11) and thus take advantage of the strengths of both instruments [23].

Pediatric Rigid Bronchoscopy

In 1997 the Pediatric Bronchoscopy Group of the European Respiratory Society (ERS) presented the current pediatric bronchoscopy state in Europe. From the 125 contacted centers, it was informed that during the 12 months previous to the survey, 7,446 bronchoscopies had been done on pediatric patients. 4,587 (61.6%) of these bronchoscopies were completed with FB and 2.859 with RB. While 29 centers were utilizing both techniques, 17 centers were using only FB and 5 centers just RB. Twenty-three centers were applying RB in the operating room, 7 centers in the intensive care unit, and 15 centers in a specially equipped room.

The most frequent indications included the following: persistent/recurrent pneumonia, wheezing refractory to medical treatment, persistent atelectasis, stridor, chronic cough, interstitial pneumonia, pulmonary tuberculosis, suspected foreign body, hemoptysis, and suspicion of pulmonary malformation, among others. The RB was completed under general anesthesia in 31 centers and under local anesthesia and intravenous sedation in 2. A bronchoalveolar lavage (BAL) was performed in 2,231 children, 812 of them were immunosuppressed.

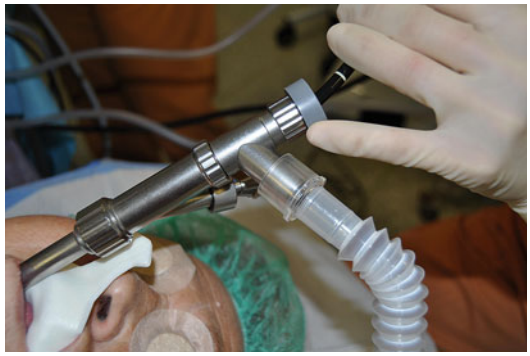

Fig. 3.11 Use of the flexible bronchoscope through the RB

Diagnostic success was variable. For centers using only FB, only RB, and the combination of both (FB+RB), diagnostic application was almost invariably superior when the use of FB and RB were combined, except for persistent/recurrent pneumonia [24].

Advantages of the RB in the pediatric population are mainly due to the fact that, in a small diameter airway, it is safer to use an instrument that does not produce increased resistance in the airway. The rigid scope provides complete airway control and, at the same time, the possibility of applying diagnostic or therapeutic interventions.

Tracheobronchial Dilatation

The RB has been used to perform tracheobronchial stenosis dilatation in children. The dilatation technique with an angioplasty catheter can be performed as follows: the catheter (6 F, 8 mm diameter) is placed under direct vision with the RB, and balloon inflation is controlled with a manometer. Children so treated showed a significant improvement in the size of the intraoperatory lumen, and an important postoperative clinic improvement, confirmed with endoscopies and radiographies. Recurrence of stenosis many times requires a repeated procedure until a more definitive therapy can be offered, or the natural increment of the airway diameter as the child grows up relieves the stenosis without the need of further procedures [25].

Other therapeutic options include the progressive dilatation using the rigid bronchoscope.

Foreign Body Removal

The RB is the instrument of choice to extract foreign objects in pediatric patients. It is a safe, effective, and a lifesaving technique. The number of ancillary instruments such as forceps and baskets to use with the RB is important; almost every type of foreign body can be extracted. However, the flexible 1-mm channel bronchoscope can also be utilized for the same purpose [26]. Urologic instruments (like ureteral baskets and forceps) can go easily through this narrow 1-mm channel and capture big foreign bodies.

Nevertheless, it is recognized that the BR is still the best instrument to extract foreign bodies from the pediatric airway, and it is also preferred in adults. In a retrospective study of 60 adults presenting foreign body aspiration, the foreign body was successfully removed by FB in 61% of cases, while the RB had a success rate of 96% [27]. In adults, however, the FB is frequently applied first to inspect and to try removal, and if it is not possible, then RB is considered [28].

Opinions about RB use on children, though, are divided. A prospective study evaluating the role of both instruments (rigid and flexible) showed that the predictive value of clinical and the radiologic findings in 83 children with foreign bodies in the airway was useful in deciding selection of RB or FB. The study concluded that the rigid bronchoscope must be used if any of the following clinic signs were present: asphyxia, a radiopaque foreign body present in the radiography, and the association of decreased air sounds along with obstructive overinflation in the chest radiograph. The FB can be used in the rest of the cases, and if during the procedure a foreign body is identified, RB must be utilized for its extraction. Application of the RB was always successful, except in one child who required a second session for the extraction of the foreign body. Postsurgical complications included laryngospasm ($n=1$) and laryngeal edema ($n=6$), and 2 of them required brief intubation. The extracted

foreign bodies comprised peanuts, vegetables, inert metals, bones and teeth, plastic pieces, and other inorganic objects [29]. The authors conclude that following this protocol was cost-effective, limiting the number of unsuccessful procedures and the use of RB. Many of the recommendations and conclusions of this study have been questioned, however. The study implies that the RB cannot examine the distal airway as good as the flexible bronchoscope. However, with the rigid bronchoscopes and smaller optics, the presence of foreign bodies can be detected as much as with a flexible bronchoscope. Procedures performed with the RB versus the FB are not more time-consuming at all; on the contrary, general anesthesia for RB can be completed with intravenous sedation, and the required time is similar to that of flexible bronchoscopy. In addition to this, most of the foreign body removal performed with FB is also under general anesthesia, introducing the FB through an endotracheal tube, making manipulation cumbersome. Besides, children who were treated with RB did not have longer hospitalizations than children treated with FB [30]. In conclusion, we prefer the RB for foreign body retrieval in the pediatric population since it is safer and easier to do, and the number of ancillary elements is such that virtually all foreign bodies can be removed in one session.

Rigid Bronchoscopy in Intensive Care Units

RB indications in the intensive care units (ICU) are limited. The most common are massive hemoptysis, large foreign bodies, obstructive lesions of the central airway, laser treatments, and prosthesis placement. All of these cases constitute relative indications, and the RB is, in practice, used only when the FB cannot fix the problem.

In the event of lung cancer patients ventilated for tumoral airway obstruction, the application of rigid laser bronchoscopy and airway stent according to need can result in a change of level of care allowing immediate discontinuation of mechanical ventilation as was published by Colt et al. [31].

Two important inconveniences in applying the RB in an ICU are the need of the bronchoscopist to be situated behind the patient and the difficulty of positioning the patient to easily insert the device. If the RB is indicated, it may be better to transfer the patient to the operating room to proceed.

Other Indications

The RB can be a lifesaving instrument in situations other than massive hemoptysis and foreign body removal.

In difficult tracheal intubations, the FB is used to guide the endotracheal tube to the trachea. Occasionally, when this technique fails, the RB may act as endotracheal tube.

Impacted mucus plugs, difficult to aspirate with the FB, can be easily extracted with the RB. This is especially useful in pediatric patients with cystic fibrosis, asthma, and post-operatory atelectasis.

Complications

Most of the complications arise from a poor RB insertion technique: laryngeal or vocal cord trauma, hypercapnia, hypoxemia, or hemodynamic instability. The bronchoscopist must not forget that he/she shares the airway control with the anesthetists and that oxygenation and ventilation have priority.

Complications associated to the use of RB include teeth, lips, gums, and throat lesions. Moderate laryngeal edema is very common but rarely produces relevant problems. Post-procedure throat and neck pain are frequent and usually last from 24 to 36 h. Vocal cord lesion is inversely related to the ability of the operator: on trained hands, it hardly occurs. Luxation of arytenoids may be also seen when a bad technique is used during intubation or when the procedure is executed with a poor local anesthesia or with an awake patient. A very infrequent and severe complication is rupture of the posterior tracheal wall. This requires surgical repair. Minimum or massive

Table 3.2 Complications

Hypoxemia
Cardiovascular instability
Tracheobronchial perforation
Esophageal perforation
Laryngeal edema
Vocal cord damage
Dental trauma
Pneumothorax
Severe bleeding
Mediastinal emphysema
Laryngospasm
Bronchospasm

bleeding may occur during tumor resections. Most of the complications diminish as the bronchoscopist ability increases. Lack of training of the endoscopist or his/her assistants must be considered an absolute contraindication for the use of the RB [32] (Table 3.2 [6]).

Drummond et al. published their 8 years of experience using the RB in a university hospital [33]. During this time 775 procedures were performed. The authors found that 13.4% of the patients experienced an associated complication. Most of them were minor complications. Patients presenting abnormal pulmonary function or basal hypoxemia, known cardiac disease, and those with coagulation abnormalities (prolonged prothrombin time or thrombocytopenia) were more susceptible to complications than those without comorbid conditions. Preoperative risk increased when the following parameters were present:

- PaO2 < 55 mmHg
- FEV1 < 50% of the predicted value
- Unstable angina or cardiac failure
- Severe arrhythmia
- Heart attack during the 6 months prior to the procedure
- Thrombocytopenia < to 50 × 10 [9]
- Abnormal prothrombin time

Patient presenting with any of these risk factors had a 37% rate of complication during rigid bronchoscopy. The group of patients with more complications presented malignant conditions involving the main carina. Also, those undergoing RB for airway obstruction had more chance to complicate. Only three deaths resulted from RB application. The cause of death was bleeding in two of the patients and respiratory insufficiency in the remaining one.

Complications were also frequent in the group of patients receiving RB to remove foreign bodies. The least complicated group was the one presenting benign conditions (benign tumor removal or benign stenosis treatment). In general, these patients showed less comorbidities.

One patient presented pneumothorax associated to the use of laser for airway resection. Other complications were those associated with anesthesia (hypoxemia, arrhythmia) and a dental piece rupture.

The experience published by this group reinforces the notion that patients must be carefully selected according to risk before performing RB. It also reminds us that the RB is a powerful therapeutic tool that can cause damage if not properly handled.

The Procedure

When rigid bronchoscopy was introduced, it used to be performed in waked patients. Nowadays, it would be an exception to proceed under those conditions. All patients we treat with RB are under general anesthesia, and they are carefully evaluated just as we do for any other surgical procedure. History taken should be detailed, noting all comorbid conditions and medications in use. Physical exam should focus on temporomandibular disorders, cervical spine mobility, and spine abnormalities. Minimum laboratory values must be obtained: coagulation profile, blood count, chemistry profile, acid base status, and electrocardiogram. Usually patients already have images of the pulmonary lesions: chest radiograph and thoracic computerized tomography, which must be carefully reviewed before the procedure.

The patient and his/her family must receive a clear explanation about what will be done and sign informed consent.

The procedure can be performed in the bronchoscopy suit or the operating room, and a minimum of four persons is needed: bronchoscopist, anesthesiologist, assistant nurse, and a circulating assistant.

Table 3.3 Requirements to perform RB

• Rigid bronchoscope and tracheoscopy
• Light source
• Video monitor if available
• Rigid optic 0 degree angulation
• Ancillary equipment (alligator forceps, scissors, foreign body retrieval elements)
• Rigid suction catheter
• Ventilation system (jet ventilation, ventilation bag)
• Eye protection
• Mouth protection
• Flexible bronchoscope with additional light source and suction port
• Interventional tools: stents and deployment systems, laser, electrocautery, dilatational balloons, etc. according to the procedure taking place

Preparation involves positioning the patient in a supine position, with a little pillow under the head, and application of topical anesthesia, lidocaine, or tetracaine. Dental prosthesis should be removed and proceed to the inspection of teeth and gums. Additional local anesthesia is also flushed on the chords and high trachea with a syringe, under direct view via laryngoscopy. Then, an oxygen mask is placed for preoxygenation, and anesthetic induction and muscle relaxant medications are administered according to the usual practice.

A protection for the superior teeth is placed; it can be made of plastic or simply be a thick folded gauze that works as the rigid tube support, and protects teeth and gums (Table 3.3).

RB procedures have become common practice, and the anesthetic techniques have evolved. All procedures are performed under general intravenous anesthesia. Muscular relaxation and paralysis can be avoided by administering appropriate sedation. This technique shortens the recovery period. We do not apply muscle relaxants since we have found that with appropriate sedation, there is no need for administration of these agents. Many centers apply jet ventilation, but we prefer to perform all rigid procedures with manually assisted spontaneous ventilation. There is a special chapter in this book discussing in detail anesthesia in interventional procedures.

Once the equipment is prepared and the video camera system is connected, the conditions are given to initiate the procedure. The classic intubation technique requires considerable experience. It is performed with the RB, and the rigid optic is connected to the video system if available. The steps are the following (Fig. 3.12a–i):

1. The RB is held with a hand, adjusting the optic a little retracted in a way that the distal end of the RB is interiorly visible. The other hand is used to open the patient's mouth, advance the RB, and adjust the tongue. Then, with the index finger and thumb, the tip of the RB is held to direct it and to keep it in the middle line at the same time. When initiating the maneuvers, the instrument edge must be looking forward, and an appropriated protection for the teeth must be observed.
2. Keeping the instrument in the middle line, it is advanced slowly. Soft back-and-forth movements are simultaneously performed in order to position it properly without causing any mouth injury and to get a better vision. The advance direction must be perpendicular to the operating table.
3. The RB should be thus advanced until the uvula is visible in the 6 o'clock position.
4. From there on, the advance angle is changed approximately 45° to the procedure table, and with soft rotation movements, the RB is introduced until the epiglottis is visible in the 12 o'clock position.
5. The RB tip is used then to softly lift the epiglottis, using the same rotation movements, and it is carefully crossed through until the vocal cords are visible.
6. Moving forward to immediately above the vocal cords, the BR is given a 90° clockwise turn, so the beveled edge is softly leaned on a vocal cord while turning and simultaneous advancing through the chords.
7. Once this is done, the trachea will be intubated, and the RB is again rotated 90° counterclockwise. The rigid tube is then introduced further. Following, the universal head is disconnected and reconnected to a bronchial tube, which is then inserted through the tracheal tube (Figs. 3.13 and 3.14).
8. Ventilation is connected, and the therapeutic procedure can start. It is very important that the operator works in a comfortable position (Fig. 3.15).

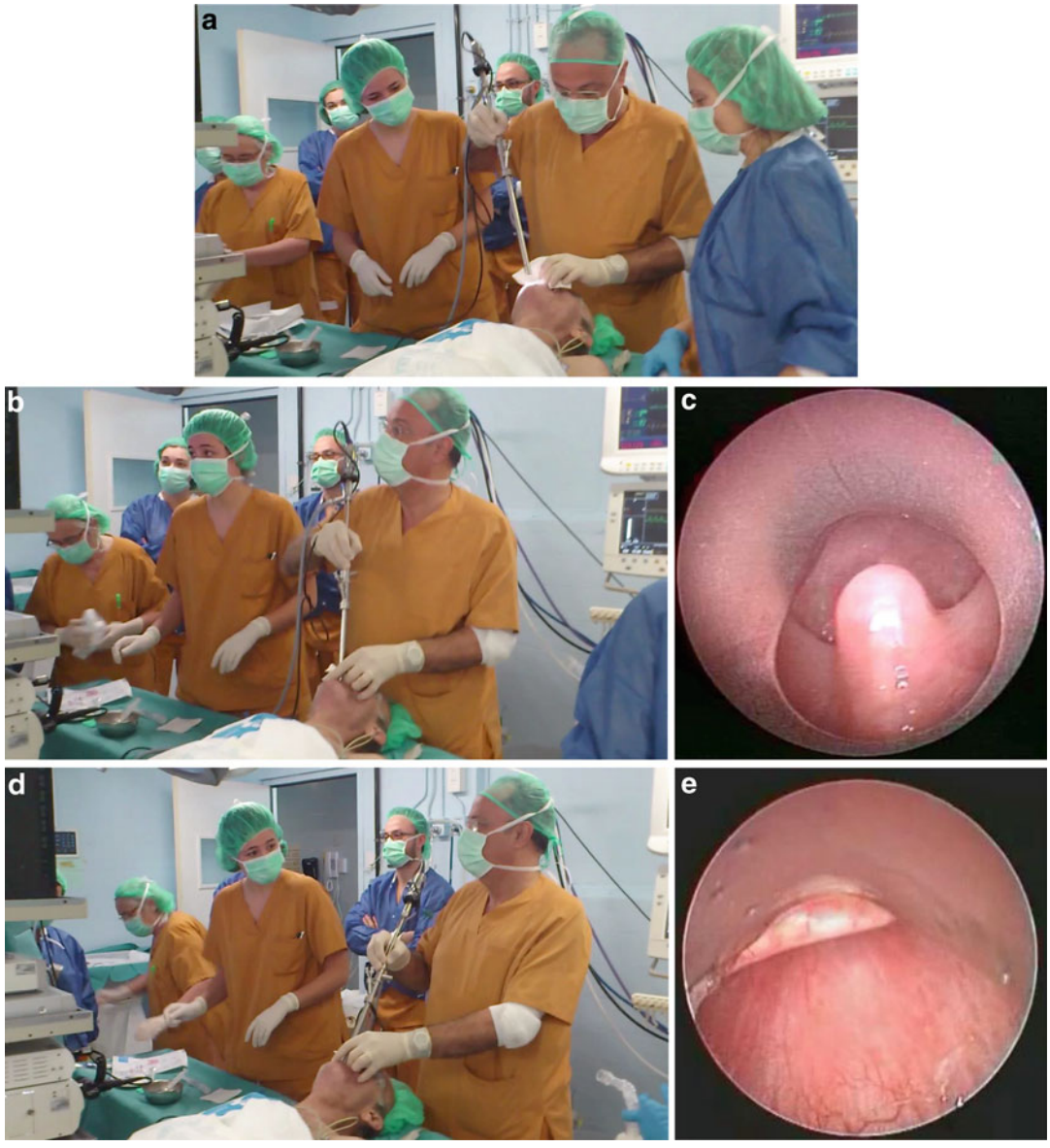

Fig. 3.12 Sequence of RB intubation: (**a**) initial positioning, protection for teeth and tongue. (**b**) Slowly advancing with the RB perpendicular to the operation table until the uvula is in view. (**c**) Uvula. (**d**) Advancing from uvula, changing the angle to 45° until the epiglottis is in view. (**e**) Epiglottis. (**f**) The epiglottis is lifted changing to a more acute angle, until the arytenoid cartilages can be seen. (**g**) Once the arytenoids are in view, the RB should be positioned more horizontally until the chords are visible. (**h**) When vocal cords are in view, the RB is rotated 90° clockwise to place the beveled end leaning on the right vocal cord to protect it, while simultaneously advancing. Once in the trachea, the RB is rotated counterclockwise and advanced further. (**i**) Finally, ventilation is connected to oxygenate the patient for a while

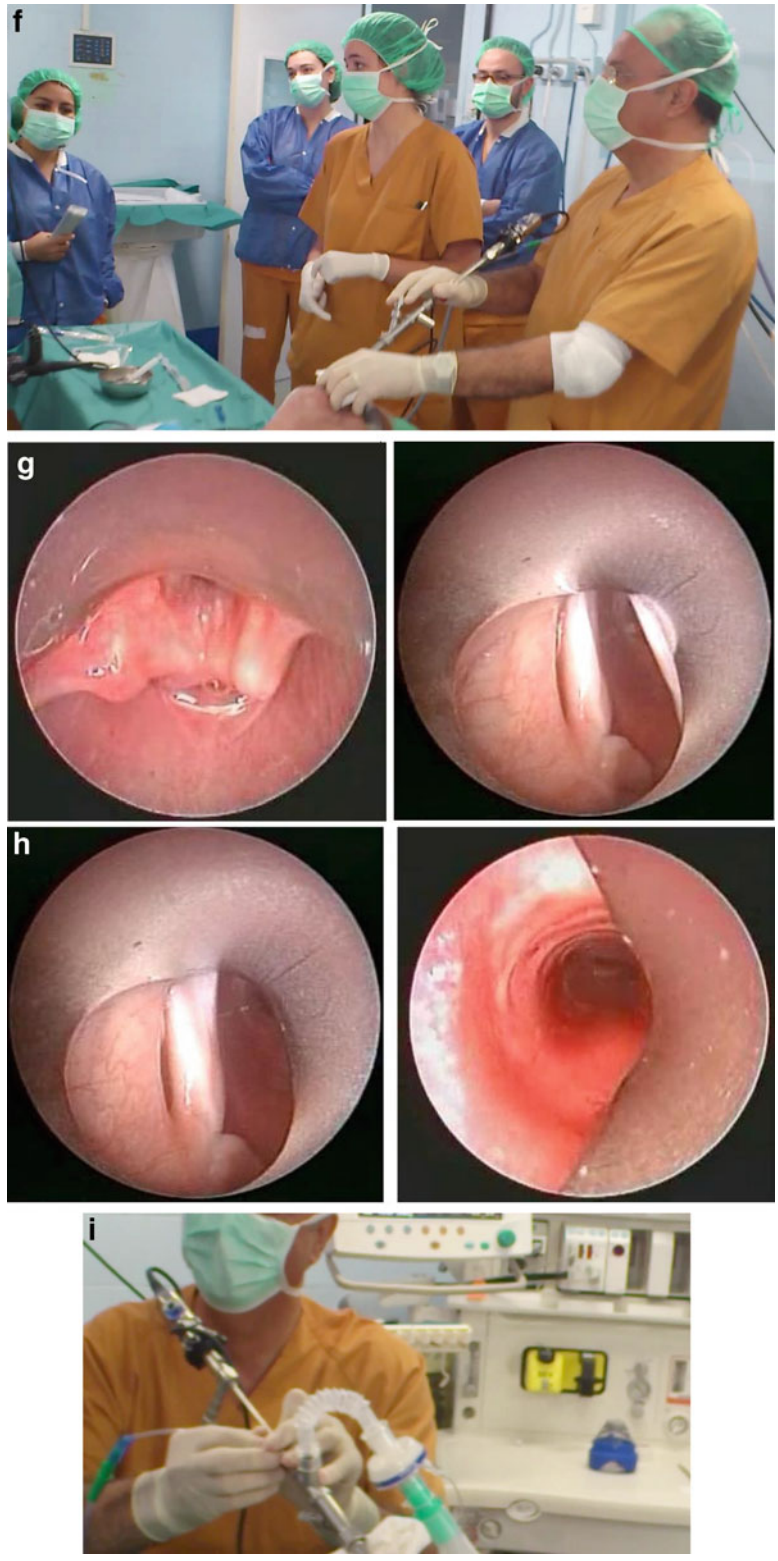

Fig. 3.12 (continued)

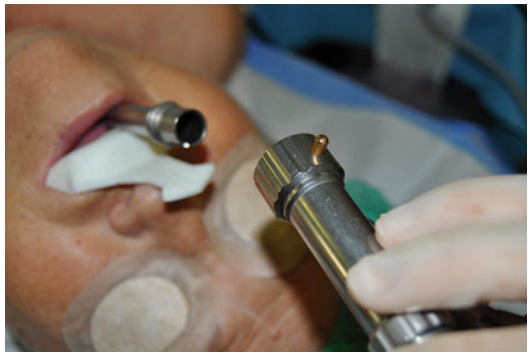

Fig. 3.13 Once the rigid tracheoscopy is in the airway, the head of the RB is removed

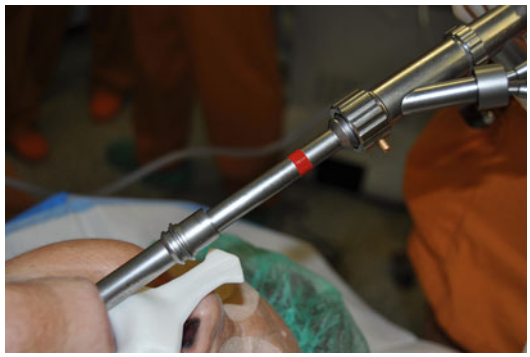

Fig. 3.14 Head of the RB connected to a bronchial rigid tube. They are then introduced through the tracheal tube, and the procedure can start

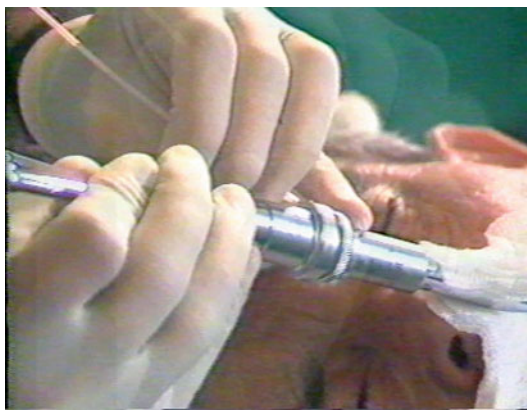

Fig. 3.15 Comfortable position of the hands for manipulation of ancillary tools

It takes time and experience to be able to perform rigid intubation as described above. There are other techniques to place a rigid bronchoscope that are very useful during the training period. The first of them implies to intubate the patient with a conventional endotracheal tube and as a second step to execute the intubation with the rigid tube, along the side of the ETT. This method has the advantage of giving the operator all the time needed to maneuver, since it does not require the patient to be in apnea like during the conventional technique, but ventilated until the tubes are changed. The other alternative is to complete the intubation with the help of a laryngoscope.

This intubation is achieved observing the chords with a conventional laryngoscope. After lifting the epiglottis with it, the RB is inserted by the side of the mouth, directing it toward the larynx. Then, it is introduced between the vocal chords and softly rotated to keep it on the middle line without injuring the subglottic area. At this moment, the laryngoscope is removed and the rigid optic is placed through the RB and advanced within the trachea under direct vision.

Intubation with RB through a tracheotomy is also possible. For this method, the rigid tube is introduced obliquely through the tracheotomy, previously numbed with local anesthetics. This maneuver must be carefully performed to avoid lesion of the posterior tracheal wall.

Some Conclusions

Before the FB introduction, the use of RB was almost limited to surgeons. During a British study, it was observed that, even though only 2% of the 39,564 bronchoscopies completed between 1974 and 1986 used RB, more than 90% were performed by surgeons. This work also noted that the 81% of the bronchoscopists used FB, 9% of them were using both techniques and an 8% used the FB through the RB [34].

In a review made by the American College of Chest Physicians, only 8% of the responding endoscopists were using RB [20]. The reasons are multiple, but some of the most important ones are that the FB is more available and easier to use than the RB and that the rigid technique requires special training not given routinely during training programs.

This data ratifies a known fact: obtaining training on the RB technique is difficult, for several reasons. The first one is that its teaching is not part of the pulmonary specialist training as we discuss, while FB training is included. Besides, its use is generally associated with therapeutic procedures such as laser and stents placement, and that requires specific technology not always available. Another inconvenient is that the technique is indeed difficult and requires full dedication to learn it. The number of procedures to become proficient varies from person to person. In addition, when proficiency is obtained, a number of regular procedures are required in order to maintain the ability and to get the interest of the involved team: nurses and anesthesiologists. In general, it is advisable that the person who is interested in learning interventionism follows a formal training with an expert, in a place where an adequate number of procedures are performed per year. Many experts agree that expertise on RB takes years and that courses and seminaries (although indispensable to a complete learning) are not enough to initiate the individual practice without supervision. The ACCP guidelines published in 2003 recommended that a trainee should perform at least 20 procedures in a supervised setting to establish basic competency in patients with normal airways, and then he/she should perform 10 procedures per year in order to maintain competency. They also recommended that program directors should decide whether or not the candidate is able to perform RB procedures without supervision [35].

The ideal bronchoscopist should be able to perform both FB and RB, on pediatric and adult population. Given that lung cancer incidence continues rising and today the multimodality approach to treatment includes a pulmonary physician able to perform palliative procedures according to need, the RB will continue to be indicated. This instrument has unique features that make it irreplaceable, and it is also complementary to many other tools, particularly when treating central airway diseases. Though still RB is performed by a minority of physicians, there is an increased interest to train and maintain proficiency in rigid bronchoscopy, and we are sure that it will be more so in the future.

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Anesthesia for Interventional Bronchoscopic Procedures

4

Mona Sarkiss

Introduction and Definitions

Introducing the bronchoscope into the airway has proved to be a challenge since the invention of the first bronchoscope. Airway reflexes, such as the gag reflex, cough, laryngospasm, hemodynamic alteration, and the associated anxiety stimulated by the passage of the bronchoscope into the airway forced the bronchoscopist to be skilled and quick to perform the procedure. As a result interest emerged in using anesthesia to ameliorate the airway reflexes and patient's anxiety associated with bronchoscopy. A wide range of anesthesia techniques were developed to accommodate a variety of interventional bronchoscopic procedures such as simple diagnostic bronchoscopy, advanced diagnostic bronchoscopy, therapeutic bronchoscopic interventions, and pleural procedures. Anesthesia for interventional bronchoscopy varies from local anesthesia as the sole anesthetic modality to moderate sedation/analgesia ("conscious sedation") with or without local anesthesia to general anesthesia. Moderate sedation/analgesia ("conscious sedation") is defined by the American Society of Anesthesiologist (ASA) as "a drug-induced depression of consciousness during which patients respond purposefully to verbal commands, either alone or accompanied by light tactile stimulation. No interventions are required to maintain a patent airway, and spontaneous ventilation is adequate. Cardiovascular function is usually maintained." Moderate sedation may progress to deep sedation/analgesia or even general anesthesia during the same procedure. Once under deep sedation, "the patients cannot be easily aroused but respond purposefully following repeated or painful stimulation. The ability to independently maintain ventilatory function may be impaired. Patients may require assistance in maintaining a patent airway, and spontaneous ventilation may be inadequate. Cardiovascular function is usually maintained." At the other end of the spectrum, during general anesthesia, "patients are not arousable, even by painful stimulation. The ability to independently maintain ventilatory function is often impaired. Patients often require assistance in maintaining a patent airway, and positive pressure ventilation may be required because of depressed spontaneous ventilation or drug-induced depression of neuromuscular function. Cardiovascular function may be impaired."

Although the current guidelines do not define which anesthesia technique to use for each procedure, it is generally accepted that simple diagnostic and interventional airway procedures

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of short duration are well tolerated by the patient when performed under local anesthesia and/or moderate sedation, whereas more complex interventional bronchoscopic procedures that require a still field, have a longer duration, and entail more risk to the patient due to comorbidities or a compromised airway are best performed under general anesthesia. General anesthesia has the added advantage of the availability of special modes of ventilation and monitoring that can be provided and managed by anesthesia providers. This chapter will first provide a brief historical perspective. Then, the indications and contraindications for different levels of anesthesia are described. Next, the equipment required and the application of the techniques are discussed. Finally, a summary and recommendations are presented.

History and Historical Perspective

When the rigid bronchoscope was invented in 1865 by Dr. Killian, anesthesia had not been discovered, and the procedure was performed in conscious patients. In order to desensitize the airway reflexes, patients were advised to repeatedly touch their pharynx and vocal cords for several weeks before the procedure. In addition, the physicians performing the procedures were trained by practicing on an excised head that had been severed from a corpse and hung from a hook or by practicing on healthy volunteers. According to early reports, this practice allowed the bronchoscopists to become "extremely skilled and swift as operations had to be performed within seconds before the view disappeared." Multiple attempts to anesthetize the airway with ammonia, iodine, belladonna, or potassium bromide had failed. In 1884 Jellinek introduced cocaine, the first local anesthetic, for airway exam and reported its benefits by stating that "by eliminating the reflexes of the pharynx and the larynx it was possible to perform some of the operations in which even the most skillful artists in surgery had failed. The procedure completely changed. Virtuosity gave way to careful methodology, skill to exactness and the former almost endless preparation that so often tried the patience of the physician as well as of the patient could be almost completely abandoned." Similarly, Killian emphasized the advantages of using cocaine during bronchoscopy by saying that "whether one stops inspection with the rigid tube at the bifurcation or passes on for some distance into a major bronchus does not matter for the patient. If he is sufficiently cocainized he does not even realize it."

In 1968, the flexible bronchoscope was invented by Ikeda and gradually replaced the rigid bronchoscope. Compared to the rigid bronchoscope, the flexible bronchoscope is well tolerated by the patient, even without anesthesia due to its small diameter and plasticity. Flexible bronchoscopy was initially used for simple diagnostic bronchoscopic procedures of short duration making local anesthetics an ideal technique for anesthesia. However, subsets of anxious patients remained unable to tolerate the procedure. As a result, conscious sedation with anxiolytics and opioids, to ameliorate anxiety and cough, respectively, in addition to local anesthetics became common practice for airway procedures. As the field of interventional bronchoscopy expanded, a growing number of lengthy and technically demanding procedures especially in patients with severe comorbidities and compromised central airway emerged. As a result the use of the rigid bronchoscope was revived to aid in the management of large airway tumors and procedure-related complications and to allow for ventilation during lengthy procedures. Accordingly, a renewed interest in monitored anesthesia care (MAC) or general anesthesia has emerged. Currently, some centers in the USA and Europe made it their standard practice to have an anesthesiologist provide either sedation or general anesthesia to selected patients undergoing interventional bronchoscopic procedures. This arrangement allows the interventionalist to direct his or her full attention to the procedure, the patient undergo the procedure with minimal or no discomfort, and the anesthesiologist to vigilantly manage the patient's airway, medical condition, and the anesthesia.

Indications and Contraindications

In its 2003 guidelines for interventional pulmonary procedures, the American College of Chest Physicians (ACCP) left the choice of anesthesia to the interventionalist, depending on the guidelines and resources available at their practice. This was due to the lack of evidence and consensus on what are the indications for different types of anesthesia. However, general anesthesia was recommended "for rigid bronchoscopy and for pediatric bronchoscopic procedures." More specific guidelines on anesthesia for interventional pulmonology, published by the European Respiratory Society and the American Thoracic Society (ERS/ATS) in 2002, alerted the interventional bronchoscopists "to be prepared to convert to general anesthesia, if the situation requires" (page 358) and recommended that "the design of the bronchoscopy suite should account for the presence of anesthesia equipment." It is important to note that the availability of anesthesia support in different practices, especially in nonacademic settings, remains limited. Some facilities have anesthesia support only when procedures are performed in the operating room, and others have anesthesia support in the bronchoscopy suite and/or the operating room, but some practices have no access to anesthesia support. Under all circumstances pre-procedural evaluation of the patient along with the nature of the procedure and consideration of the available resources should direct the interventionalist to determine the most appropriate form and location of anesthesia needed for a particular procedure.

Pre-procedural Evaluation and Preparation

Medical history should be elicited with particular interest in respiratory and cardiovascular diseases, exercise tolerance, and performance status. In addition, history of stridor, snoring and sleep apnea, drug allergy, current medication, tobacco, alcohol, or drug used should be documented. Complications related to previous sedation and anesthesia such as prolonged sedation unplanned hospital admission or intubation should be sought. The American Society of Anesthesiologist (ASA) score is commonly assigned to the patient to assess the patient physical status and severity of illness; however, the ASA status is not intended to predict anesthesia or procedure-related risk (Table 4.1). Women of childbearing age should be questioned about possibility of pregnancy and counseled regarding effect of anesthesia and the procedure on pregnancy.

Physical Examination

Airway should be assessed to determine difficulty of intubation in case of airway compromise or if rigid bronchoscopy is planned. Direct inspection of pharyngeal structure when the mouth is wide open and the tongue is protruding as far as possible is used to assess difficulty of intubation by direct laryngoscopy according to the Mallampati classification (Fig. 4.1). Other parameters that predict difficult intubation are decreased extension of the atlanto-occipital joint (normally 35° from neutral midline position) by more than two-thirds, decreased mouth opening below the normal range of 50–60 mm, thyromental distance measured in an extended neck from the mentum to the notch of the thyroid cartilage ≤6 cm in adults, short muscular neck, and receding mandible.

Dental inspection is necessary to identify the presence of loose teeth, dental prosthesis, chipped, missing teeth, bridges, crowns, or denture. The presence of prominent or protruding maxillary incisors may alert the bronchoscopist to the possibility of difficult intubation and/or damage to the teeth during direct laryngoscopy or rigid bronchoscopy.

Respiratory system assessment should be performed with emphasis on baseline saturation, requirement of supplemental oxygen, and use of accessory respiratory muscle.

Cardiovascular system exam should be focused on baseline vital signs and signs of cardiovascular compromise due to intrathoracic disease, e.g., superior vena cava syndrome and pericardial effusion.

Table 4.1 ASA physical status

ASA physical status 1	A normal healthy patient
ASA physical status 2	A patient with mild systemic disease
ASA physical status 3	A patient with severe systemic disease
ASA physical status 4	A patient with severe systemic disease that is a constant threat to life
ASA physical status 5	A moribund patient who is not expected to survive without the operation
ASA physical status 6	A declared brain-dead patient whose organs are being removed for donor purposes

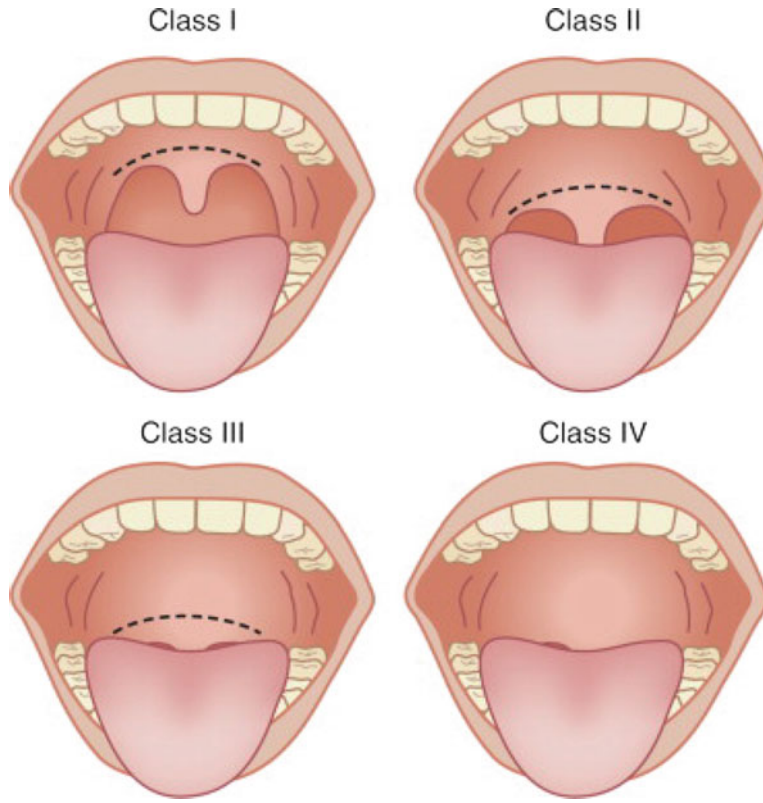

Fig. 4.1 The Mallampati classification

Laboratory testing should be performed based on the baseline comorbidities and nature of the procedure (e.g., complete blood count, electrolytes, coagulation profile).

Radiographic studies, e.g., chest X-ray, computed tomography (CT), and electrocardiogram, are recommended.

Pulmonary function tests and assessment of arterial blood gases may be required depending on the nature of the procedure.

Informed consent should be obtained from the patient after detailed explanation of the risks, benefits, and possible alternatives of the procedure and sedation or anesthesia.

Nothing per os (NPO) is indicated for 2 h for clear liquids and 6–8 h for solids before the procedure according to the current ASA guidelines. Patients with history of uncontrolled or untreated acid reflux, post-esophagectomy, or gastroparesis should be instructed to take the anti-reflux medication on the day of the procedure and can benefit

from airway protection by endotracheal intubation.

Procedure-Related Indications

Despite few reports of rigid bronchoscopy performed under local anesthesia or general anesthesia with spontaneous ventilation, the most common practice is to perform rigid bronchoscopy under general anesthesia with muscle relaxation. The rationale for utilizing general anesthesia for rigid bronchoscopy is the lengthy nature of the procedures and the resulting occurrence of hypoxemia and hypercapnia. Spontaneous, assisted, mechanical, or jet ventilation can be used during rigid bronchoscopy to overcome such occurrences.

Controversy exists over performing EBUS under moderate sedation or general anesthesia. The EBUS bronchoscope has a larger external diameter of 6.9 mm and is more tolerated when inserted through the mouth compared to the nose. Therefore, some practitioners prefer to perform all EBUS procedures or only the lengthy staging EBUS procedures under general anesthesia. Recent study showed that more lymph nodes per patient and smaller lymph nodes were sampled more often when EBUS was performed under deep sedation or general anesthesia. In addition, on-site cytology evaluation was used more frequently when general anesthesia was used. However, several reports indicated no difference in patient satisfaction, yield, sensitivity, or specificity of the EBUS procedure when performed under moderate sedation versus general anesthesia.

Application of the Technique

Topical Anesthesia

Local anesthetics cause reversible block of the conduction of nerve impulses with subsequent sensory, motor, and autonomic blockade. Cocaine was the first topical anesthetic discovered, but it was soon found to cause topical irritation and psychological dependence. Subsequently, synthetic local anesthetics lacking such side effects were discovered. Procaine, the first synthetic local anesthetic, was introduced by Einhorn in 1905 and was followed by lidocaine, which was synthesized in 1943 by Löfgren. Synthetic local anesthetics have a lipophilic benzene ring linked via an amide or an ester bond to a hydrocarbon chain that is attached to a hydrophilic tertiary amine structure. Local anesthetics are classified according to the type of their linking bond to ester or amide local anesthetics. The nature of the linking bond affects the metabolism of the local anesthetic as well as its potential to produce an allergic reaction. Amide local anesthetics, which are commonly used in bronchoscopy, are metabolized by the liver microsomal enzymes and are also extracted through the lungs. The addition of epinephrine at 1:2,000,000 (5 μg/ml) concentration or 0.25% phenylephrine causes local vasoconstriction, which slows down the absorption of the local anesthetic, prolongs its duration of action, and decreases its systemic toxicity.

Side Effects of Local Anesthetics

Absorption of large amounts of local anesthetics from the application site or direct accidental intravascular injection of large dose can result in systemic toxicity, e.g., lidocaine plasma level of 5 μg/ml or greater than 8.2 mg/kg of lidocaine instilled in the airway can result in systemic toxicity. The toxic dose of benzocaine is 100 mg, and the toxic dose of tetracaine is 100 mg (but toxicity has been reported at 40 mg).

Central nervous system (CNS) toxicity initially present with symptoms of CNS excitation such as restlessness, vertigo, tinnitus, and slurred speech. The symptoms may progress to tonic–clonic seizure followed by CNS depression in the form of coma and possibly death. Seizures should be immediately treated with small doses of intravenous benzodiazepine (diazepam or midazolam), intravenous thiopental, or propofol. Hypoxemia should be treated with supplemental oxygen. Additionally hyperventilation with subsequent respiratory alkalosis causes hyperpolarization of

the nerve membrane, increases the threshold for seizure, and increases the amount of local anesthetic bound to protein, thus decreasing the delivery of free drug to the brain. If seizures continue despite treatment, intubation is warranted to protect the airway.

Cardiovascular toxicity due to blockade of the cardiac sodium channels can result in hypotension, long PR interval and widening of the QRS complex. More severe cardiotoxicity can present with severe hypotension, cardiac arrhythmias, and atrioventricular heart block.

Methemoglobinemia occurs when local anesthetic oxidize the iron molecule in the hemoglobin from the ferrous to ferric state. Hemoglobin with iron molecule in the ferric state is called methemoglobin and is characterized by its inability to release bound oxygen to tissue. Patients with methemoglobinemia present with cyanosis, chocolate-colored blood, stupor, coma, and death. Methemoglobinemia is easily treated by the administration of 1–2 mg/kg of methylene blue intravenously.

Allergic reactions to local anesthetics are rare but are more common with ester local anesthetic metabolite para-aminobenzoic acid (PABA). In addition, the preservatives used with either ester or amide local anesthetics (e.g., methylparaben) can be a source of allergic reaction. It is noteworthy that cross sensitivity does not exist between ester and amide local anesthetics.

Anesthesia of the Nasal Mucosa and Nasopharynx

Sensation to the nasal mucosa is provided by the middle division (V2) of the trigeminal nerve (CN V), the sphenopalatine ganglion, and the ethmoid nerve. The nasal mucosa and the nasopharynx can be topicalized using cotton-tipped applicators or pledgets soaked in a 1%, 2%, or 4%lidocaine solution with or without a vasoconstricting agent. The applicators are placed sequentially along the inferior turbinate, the middle turbinate, and the superior turbinate. Each applicator should be left in place for 5 min.

Anesthesia of the Mouth and Oropharynx

Sensation of the mouth and oropharynx is supplied by branches of the glossopharyngeal, vagus, and facial nerves. The lingual branch of the glossopharyngeal nerve provides sensation to the posterior third of the tongue, the vallecula, and the anterior surface of the epiglottis. The pharyngeal branch provides sensation to the posterior and lateral walls of the pharynx, and the tonsillar branch supplies the tonsillar pillars. The tongue can be anesthetized by placing a tongue blade coated with lidocaine gel on the tongue for several minutes. Oral and pharyngeal mucosa are anesthetized by inhalation of nebulized 4%lidocaine or 0.5%tetracaine or by using a Cetacaine atomizer spray (tetracaine and benzocaine combination). A gargle with 2–4 mL of viscous lidocaine for 30 s can provide additional anesthesia to the posterior pharyngeal wall.

Superior Laryngeal Nerve Block

The superior laryngeal nerve (SLN) is a branch of the vagus nerve that divides lateral to the cornu of the hyoid bone into internal and external branches. The internal branch passes under the greater cornu of the hyoid bone before piercing the thyrohyoid membrane and entering the pyriform recess where it provides sensory innervation to the base of the tongue, the superior epiglottis, the aryepiglottic folds, the arytenoids, and the laryngeal mucosa above the vocal cords. The external branch supplies motor innervation to the cricothyroid muscle.

To perform SLN block, the patient should be placed in a supine position with the head slightly extended, and the greater horn of the hyoid bone is palpated above the thyroid cartilage. The needle (size 22 or 23 gauge) is inserted towards the greater horn of the hyoid bone and then moved caudally until a pop is felt when the thyroid ligament is pierced at a depth of about 1–2 cm. Negative aspiration is then followed by injecting 2–3 ml of 2%lidocaine with epinephrine. Bilateral blocks should be performed (Fig. 4.2).

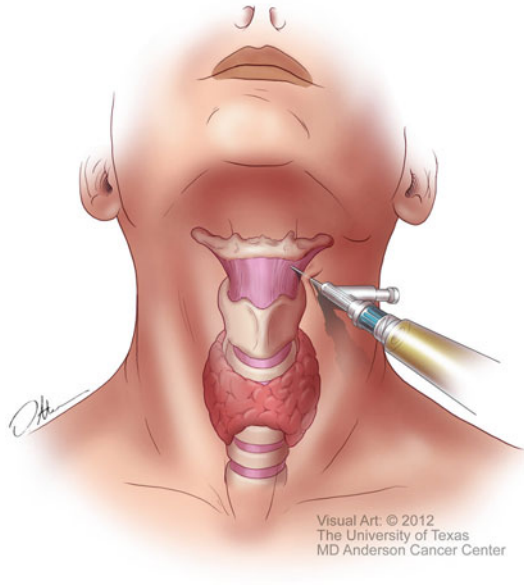

Fig. 4.2 Superior laryngeal nerve block

Recurrent Laryngeal Nerve Block

The recurrent laryngeal nerve provides motor innervation to the vocal cords and sensory innervation to both the trachea and vocal cords. In a supine patient with hyperextended neck, the skin over the cricothyroid membrane is anesthetized with lidocaine 1–2%with a 22-gauge needle. A 22-gauge IV catheter is then inserted through the cricothyroid membrane into the tracheal lumen at an angle of 45° caudally. Air should be aspirated to confirm intratracheal position. The needle should then be removed leaving the plastic catheter in the tracheal lumen. The patient is asked to take a deep breath followed by forced exhalation while 3–4 cc of 1–2%or 4%lidocaine is injected through the catheter. This maneuver's common result is cough that aids in spreading the local anesthetic over the vocal cords and the trachea.

Conscious Sedation

The American College of Chest Physicians has suggested in its consensus statement in 2011 that all physicians performing bronchoscopy should consider using topical anesthesia, analgesic, and sedative agents, when feasible. The advantages of conscious sedation are the reduction of patient anxiety, pain, airway reflexes such as cough and gag, and the dyspnea associated with the insertion of the bronchoscope. Amnesia from the procedure also increases patient satisfaction and willingness to undergo another bronchoscopic procedure. In addition, the ability of the bronchoscopist to adequately perform advanced diagnostic and therapeutic procedures in shorter duration improves with sedation.

Different drug regimens have been used, and they vary depending on the bronchoscopist's preference and experience. The most commonly used classes of drugs are benzodiazepines for anxiolysis and amnesia in combination with opioids for suppression of cough and pain. The combination of narcotics and benzodiazepines has an additive effect on the suppression of the respiratory drive and cardiovascular hemodynamics thus increasing the likelihood of apnea, desaturation, and hypotension. Therefore, these drugs should be titrated gradually to achieve the desired effect and avoid undesired side effects.

Benzodiazepines act primarily by enhancing the action of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) causing increased resistance of neuronal excitation. This translates clinically to anxiolysis, sedation, anterograde amnesia, centrally mediated muscle relaxation, and minimal depression of ventilation of the cardiovascular system. When compared with no sedation for bronchoscopy, benzodiazepine, as a single sedating agent, was associated with increased patient satisfaction and willingness to undergo another bronchoscopy. However, the post-procedure recovery time was longer in the benzodiazepine-treated patients without an increase in complication rates.

The three commonly used benzodiazepines for procedural sedation are midazolam, diazepam, and lorazepam. Midazolam is the most preferred benzodiazepine because of its water solubility, absence of pain with injection, rapid onset, short duration of action, and rapid clearance. The average dose of midazolam is 0.06–0.07 mg/kg with special consideration to use lower doses in elderly patients. Diazepam is a

Table 4.2 Pharmacodynamics of benzodiazepines

Drug	Dose (mg/kg)	Elimination half-life (h)
Midazolam	0.3–0.5	1–4
Lorazepam	0.05	10–20
Diazepam	0.15–0.3	21–37

water-insoluble drug that is dissolved in the organic solvent propylene glycol that causes pain on intravenous or intramuscular injection. Diazepam is metabolized by the liver into two active metabolites, desmethyldiazepam and oxazepam. The activity of these metabolites may cause prolonged sedation for 2–4 days in elderly patients and in those with impaired liver function. Lorazepam is an intermediate-acting benzodiazepine with a stronger amnestic effect and a delayed peak effect, making it the least favored benzodiazepine for procedural sedation (Table 4.2).

Flumazenil is the only known benzodiazepine antagonist. A dose of 0.2 mg IV every 1 min to a total dose of 1–3 mg per 1 h is commonly used. The onset of action is at 1–3 min, the peak is at 10 min, and the duration of action is 20 min. Additional doses may be required to maintain antagonism and prevent the recurrence of sedation by long-acting benzodiazepines. Side effects of flumazenil include nausea, vomiting, tachycardia, hypertension, headache, and rarely seizures.

Opioids are natural and synthetic substances that bind opioid receptors in the central nervous system and peripheral tissue, causing presynaptic inhibition of release of neurotransmitters (e.g., acetylcholine, dopamine, norepinephrine, and substance P). Activation of the opioid receptors mu, kappa, and delta results in varying degrees of analgesia and side effects such as depression of ventilation, urinary retention, constipation, miosis, and physical dependence. The natural-occurring opioid morphine and the synthetic opioids meperidine, fentanyl, sufentanil, alfentanil, and remifentanil have been used for bronchoscopic procedural sedation. Fentanyl is the most commonly used opioid for bronchoscopy sedation due to its rapid onset of action and short half-life. Although therapeutic bronchoscopy is not associated with significant somatic pain, opioids were found to cause suppression of airway reflexes in particular cough, tachycardia, and hypertension associated with bronchoscopy. See Table 4.3 for a comparison between the pharmacodynamics of different opioids. Noteworthy is that the combination of opioids and benzodiazepines is associated with better patient's tolerance of bronchoscopy when compared to each agent alone.

Monitored Anesthesia Care

MAC is defined as a specific anesthesia service in which an anesthesiologist has been requested to participate in the care of a patient undergoing a diagnostic or therapeutic procedure. However, MAC does not describe the depth of sedation. Under MAC the anesthesiologist can either provide sedation or general anesthesia and the post-procedure recovery care. Situations where MAC is valuable are:

1. When variable levels of sedation are needed to meet changes in the patient and the bronchoscopist needs during a procedure
2. Patients sensitive to small doses of sedatives where respiratory or hemodynamic complications can occur and resuscitation will be required
3. Patients who need transient period of general anesthesia

Therefore, the drugs of choice for MAC should be the ultrashort-acting anesthetics that are easily titrated to match the patient tolerance to the procedure with rapid return to baseline status at the end of the procedure, e.g., remifentanil, alfentanil, propofol, dexmedetomidine, and fospropofol. In addition, midazolam, fentanyl, and morphine can also be acceptable choices.

General Anesthesia

If general anesthesia is the chosen anesthesia technique for an interventional bronchoscopic procedure, an open discussion between the anesthesiologist and the bronchoscopist should take place before and throughout the procedure. The

Table 4.3 Pharmacodynamics of commonly used opioids

	Onset (min)	Peak (min)	Duration (h)	Elimination (h)	Context sensitive half-life (min)	Potency
Morphine	2–3	15–30	3	2–3		1
Meperidine	5	5–7	3	3–5		0.1
Fentanyl	1–2	3–5	0.5–1	3–6	260	75–125
Sufentanil	1–2	3–5	0.3	2–4	30	500–1,000
Alfentanil	1–2	1.5–2	0.2–0.3	1.4–1.5	60	10–25
Remifentanil	1–2	1.5–2	0.1–0.2	0.17–0.33	4	250

discussion should include procedure location (e.g., trachea vs. bronchi), degree of airway obstruction (e.g., complete vs. partial obstruction), depth of anesthesia needed (e.g., general vs. sedation), airway device options (e.g., none, endotracheal tube, laryngeal mask airway, or rigid bronchoscope), and the most suitable mode of ventilation (e.g., spontaneous ventilation, non-invasive positive pressure, assisted ventilation, mechanical ventilation, or jet ventilation). In addition, the anesthesiologist should be familiar with the step-by-step plan the bronchoscopist has to manage the airway pathology and possible complications.

Total intravenous anesthesia (TIVA) is the anesthetic technique of choice for interventional bronchoscopic procedures when compared to inhalation anesthesia. Inhalational anesthetics have multiple disadvantages, including the variable levels of anesthetic gas delivered because of frequent suctioning during the procedure and the contamination of the operating room air by inhalation agents. However, it is important to emphasize that inhalation agents can be a better choice in cases of bronchospasm or in patients with an anterior mediastinal mass, where maintenance of spontaneous ventilation is essential. The following medications are commonly used for TIVA.

Propofol, similar to benzodiazepines, acts to facilitate the inhibitory effect of GABA. When used for sedation for airway procedures, propofol has been shown to be superior to midazolam due to its short onset time of 30 s, metabolism independent of organ function, and rapid recovery time of 15 min after a 2 h infusion. In addition, propofol has been shown to result in significantly better neuropsychometric recovery than midazolam. When compared to inhalation anesthetics, propofol has been shown to reduce coughing and the depression in ciliary function as well as the release of cytokines and the stress hormone response.

Propofol infusion rates of 100–150 μg/kg/min can be used for anesthesia induction while maintaining spontaneous ventilation. The bispectral index monitor (BIS) can be used to titrate the propofol infusion rates to achieve and sustain an appropriate depth of anesthesia.

Remifentanil is a short-acting narcotic with duration of action of 3–10 min and a rapid onset of action at 1 min. After interventional bronchoscopic procedures, patients do not suffer from post-procedure pain thus eliminating the need for the use of long-acting narcotics. Remifentanil is ideal for blunting airway reflexes during the procedure with no residual effect in the recovery room.

Ketamine is a general anesthetic that induces a dissociative state in which sensory stimuli are blocked from reaching the cerebral cortex, causing amnesia and analgesia. Although ketamine is an old drug, its use has been revived because of its profound analgesic property. Ketamine-induced analgesia makes it a good adjunct to propofol that lacks any analgesic properties. Ketamine is particularly valuable for bronchoscopic procedures because of its bronchodilating properties and absence of respiratory depressant effect.

Dexmedetomidine is an α-2 agonist that inhibits norepinephrine release causing its unique ability to provide sedation and analgesia without respiratory depression. Dexmedetomidine has also been found to offer cardioprotective benefits

during surgery by lowering perioperative oxygen consumption and the stress response.

Muscle relaxants, such as succinylcholine, rocuronium, or cisatracurium, can be used safely during general anesthesia to prevent laryngospasm and coughing associated with the insertion of the bronchoscope in the airway. The use of muscle relaxation for therapeutic bronchoscopic procedures has many advantages. These include facilitating the insertion of airway devices (e.g., LMA, endotracheal tube, and the rigid bronchoscope), better lung compliance during positive pressure ventilation or jet ventilation, providing the bronchoscopist with a still field when precise targeting of lesions adjacent to major vessels and the heart is needed, and maintaining the glottis aperture open during multiple insertion and removal of the bronchoscope and other instruments thus minimizing trauma to the vocal cord.

On the other hand, indiscriminate use of muscle relaxant in interventional bronchoscopy can be associated with severe complications. For example, there are several reports of loss of the airway patency after muscle relaxant was given in patients with large anterior mediastinal mass. Pneumothorax and/or pneumomediastinum can develop in patients with tracheoesophageal fistulas, bronchoesophageal fistulas, or airway tears when muscle relaxant is given and positive pressure ventilation is used. In addition, prolonged unwanted muscle relaxation has been reported in patients with lung cancer and paraneoplastic Lambert–Eaton myasthenia syndrome.

In the event that muscle relaxation is deemed unsuitable, instillation of lidocaine on the vocal cords and the proximal airway is a better alternative to the use of muscle relaxation prior to insertion of the rigid bronchoscope or other airway devices.

Fraction of inspired oxygen (FiO_2) should be continuously adjusted to maintain patient oxygen saturation >90%during interventional bronchoscopic procedure. FiO_2 of 100%is commonly needed during an advanced bronchoscopic procedure especially in patients with advanced lung pathology, poor baseline oxygen saturation, and/or the use supplemental oxygen. In addition, FiO_2 of 100%is valuable when periods of complete airway occlusion and/or inability to provide mechanical ventilation are anticipated, e.g., during deployment or extraction of stents, balloon dilation of the airway, removal of a tumor mass where positive pressure ventilation can force the excised tumor down the airway causing acute obstruction, or during exchange of one rigid bronchoscope to a different type or size of rigid bronchoscope.

It is important to note that low FiO_2 of less than 40%is required during electrocautery, laser, and argon plasma coagulation (APC) in order to avoid airway fire.

Monitoring the Depth of Anesthesia

Processed electroencephalograms can be used to monitor the depth of anesthesia and in combination with the patient's clinical signs can guide the titration of intravenous anesthetics to achieve adequate depth of anesthesia. Consequently, adequate sedation without undesired side effects, such as respiratory failure or cardiovascular instability associated with increased depth of anesthesia, is more likely to be attained.

Description of the Equipment Needed

Interventional Bronchoscopy Suites

Interventional bronchoscopic procedures are commonly performed in an interventional bronchoscopy suite or the operating room. In most centers, the choice of the location of the procedure depends on the available resources and the anesthesia technique required. Interventional bronchoscopic procedures requiring local anesthesia and/or conscious sedation are usually performed in an interventional bronchoscopy suite where conscious sedation is administered by a trained bronchoscopy nurse under the supervision of the bronchoscopist. Meanwhile, rigid bronchoscopy or procedures that require general anesthesia are commonly performed in the operating room. In recent years, interventional bronchoscopy departments that

perform a large number of procedures on a daily basis have designed interventional bronchoscopy suites in collaboration with the anesthesiologist at their practice to be a replica of an operating room. This has allowed the bronchoscopists to perform more procedures under MAC or general anesthesia in the bronchoscopy suites. Interventional bronchoscopy suites have been operational for several years with great success in several centers in the USA and Europe.

Airway Devices

Procedures performed under conscious sedation or MAC require no invasive airway devices. However, the patient's oxygenation should be monitored by pulse oximetry, and supplemental oxygen should be delivered to maintain patient saturation above 90%during the procedure and in the recovery area.

- Laryngeal mask airway (LMA)
- The LMA was first introduced more than 20 years ago and is still used today, with a consistently low incidence of complications. The LMA is an ideal airway device for advanced bronchoscopic procedures. The large diameter of the shaft of the LMA makes it easy to insert large therapeutic bronchoscopes without compromise to the ventilation (Fig. 4.3). The LMA also allows the bronchoscopist to inspect the entire length of the airway from the vocal cords to the distal large bronchi. Additionally, the LMA allows free mobility of the bronchoscope in the airway when compared to an ETT. A bite block needs to be inserted around the LMA. Alternatively, the I-gel version of the LMA has a built-in bite block. The disadvantages of the LMA are the lack of protection against aspiration and the inability to seat the LMA in patients with oral, pharyngeal, or laryngeal deformity or pathology or those who have received radiotherapy. It is important to note that the LMA was originally designed for spontaneously ventilating patients; however, mechanical ventilation can be performed, with a limitation on the maximum airway pressure of 20 cm H_2O in order not to overcome the tone of the lower esophageal sphincter and insufflate the stomach with oxygen.
- Endotracheal tube (ETT)
- Although an ETT is the most definitive and most reliable airway device in patients undergoing general anesthesia, an ETT has challenges when inserted in a patient with central airway obstruction undergoing a therapeutic bronchoscopic procedure. Insertion of the ETT does not allow the bronchoscopist to examine the vocal cords and the upper part of the trachea for pathology. The large external diameter of the therapeutic flexible bronchoscope requires the insertion of an ETT with an internal diameter of 8.5 mm or 9 mm in order to deliver adequate ventilation around the bronchoscope (Fig. 4.4). The length of the ETT projecting from the patient's mouth limits the length of the flexible bronchoscope available for insertion into the airway, and the proximal end of the ETT is commonly cut off. Insertion of an ETT in a patient with preexisting tracheal or bronchial stents carries a risk of dislodging or deforming the stents, which can potentially result in airway compromise.
- Rigid bronchoscope
- The rigid bronchoscope is an ideal airway device in complicated interventional bronchoscopic procedures where instruments and stents are inserted in the airway. The distal end of the rigid bronchoscope is beveled to allow for lifting of the epiglottis and safer insertion through the vocal cords. The proximal end of the rigid bronchoscope can remain open to air to allow for simultaneous insertion of multiple instruments. Leak of the ventilating gas through the open end of the rigid bronchoscope makes jet ventilation or spontaneous ventilation the only possible mode of ventilation. Alternatively, when a cap is placed to seal the proximal end of the rigid bronchoscope, positive pressure ventilation from anesthesia ventilator can be used. Leak is overcome by inserting a throat pack and Vaseline gauze to occlude the nostrils. A short stainless steel cylinder attached to the proximal end of the rigid bronchoscope has multiple side ports to

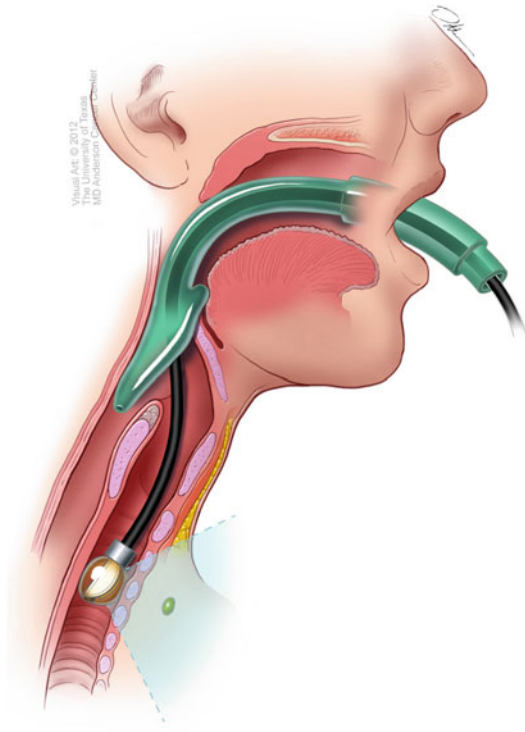

Fig. 4.3 EBUS bronchoscope introduced through LMA

accommodate a jet ventilator, an anesthesia circuit, and bronchoscopic instruments.

- The rigid bronchoscope has many advantages over the flexible bronchoscope. These include the ability to provide positive pressure ventilation during lengthy airway procedures and the ability to insert instruments with a large diameter into the airway such as the microdebrider, large suction catheter, and the deployment device for silicone stents. The rigid bronchoscope can also be used as a coring device to debulk airway tumors, dilate stenotic areas, stent the airway open in the case of external airway compression by an anterior mediastinal mass, and tamponade airway bleeding.

Modes of Ventilation

- Spontaneous ventilation
- Spontaneous ventilation is necessary in cases when the integrity of the airway is compromised, such as tracheoesophageal fistulas, bronchoesophageal fistulas, and iatrogenic tears in the airway. In such cases, positive pressure ventilation can result in leakage of the ventilating gas (oxygen and/or air) to the mediastinum, the thoracic cavity, and possibly the peritoneum. Anterior mediastinum mass is another indication for spontaneous ventilation because of multiple reports of worsening of the compressive obstruction of the central airway by the mass after a muscle relaxant was given. In addition, spontaneous ventilation is valuable during pleuroscopy, when collapse of the lung on the side of the procedure is essential for visualization.
- Spontaneous ventilation can be easily achieved under conscious sedation, MAC, or general anesthesia. Inhalation anesthetics or intravenous anesthetics with adequate topical anesthesia can be used, without the muscle relaxant, for the insertion of the rigid bronchoscope, LMA, or the ETT. Alternatively, a small dose of the short-acting muscle relaxant succinylcholine can be used for the intubation with rapid regain of spontaneous ventilation.
- Assisted ventilation
- In a patient with an airway device in place, ventilation can be assisted by multiple modalities to overcome hypoxia and/or hypercapnia associated with spontaneous ventilation under general anesthesia. For example, intermittent hand -bag ventilation with a large tidal volume, pressure support, or synchronized intermittent mandatory ventilation can be used to overcome atelectasis and improve saturation and CO_2 elimination during bronchoscopic procedures.
- Noninvasive positive pressure ventilation (NIV)
- NIV, commonly used for patients with sleep apnea, has been described as beneficial in hypoxemic patients undergoing bronchoscopy with anesthesia. Modified nasal or full-face masks, with a special adaptor to allow for the insertion of the bronchoscope, can be used. NIV should be considered when endotracheal intubation and mechanical ventilation are suspected to carry an increased risk to the patient undergoing

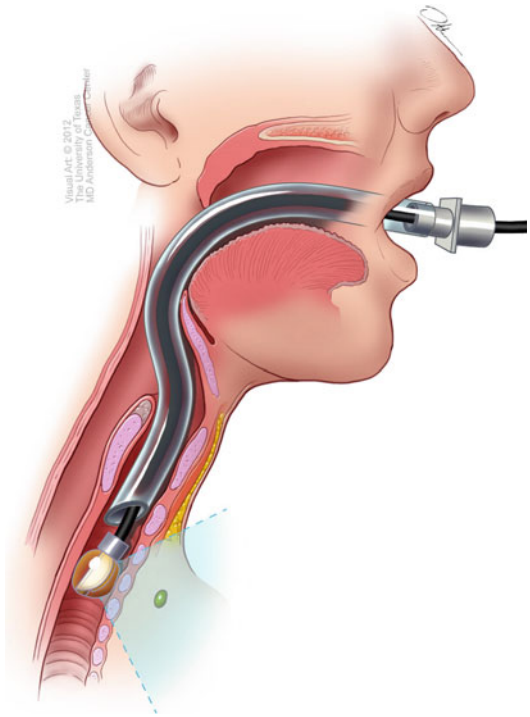

Fig. 4.4 EBUS bronchoscope introduced through ETT

bronchoscopy. The use of NIV ventilation was shown to improve oxygenation and reduce the risk of acute respiratory failure after bronchoscopy in patients with impaired baseline oxygenation, such as chronic obstructive pulmonary disease (COPD) patients with pneumonia or immunocompromised patients.

- Positive pressure-controlled mechanical ventilation
- Patients undergoing interventional bronchoscopic procedure that require muscle relaxation need mechanical ventilation. Mechanical ventilation can be delivered through the LMA, ETT, or rigid bronchoscope. When the LMA is the airway device of choice, the peak airway pressure should be kept below 20 CmH_2O to avoid opening the lower esophageal sphincter and inflating the stomach. Mechanical ventilation through the rigid bronchoscope is associated with leak around and through the rigid bronchoscope. To overcome such leak, insertion of a throat pack, occlusion of the nostrils with Vaseline gauze, capping of the rigid bronchoscope ports, and high oxygen flow rates with high tidal volumes are needed.
- Jet ventilation
- Jet ventilation can be performed using a handheld device through which 100%oxygen is injected into a port at the proximal end of the rigid bronchoscope. The pressure of the injected oxygen can be adjusted with a dial; the frequency of ventilation is left to the operator to select and frequently ranges from 8 to 20 breaths per minute. Jet ventilation should be performed only when the proximal end of the rigid bronchoscope is open to air, to avoid barotrauma. Air is entrained at the open proximal end of the rigid bronchoscope, causing variation in the delivered FiO_2.
- Electronic mechanical jet ventilation
- The mechanical jet ventilator (Acutronic Medical Systems, Hirzel, Switzerland) has many advantages over the simple handheld jet ventilator. The user can control the FiO_2, the frequency of ventilation (up to 150 breaths per minute), and the driving pressure of ventilation (up to 40 mmHg). The inspired oxygen can be humidified up to 100%, enabling prolonged jet ventilation without the risks of airway mucosal dryness and necrosis or damage to ciliary function. In addition, the mechanical jet ventilator has two alarms to protect against barotrauma and will discontinue ventilation if the set maximum airway pressure limit is reached.

Post-procedure Care

After interventional bronchoscopic procedures, patients should be transported to a standard designated recovery area with well-trained nursing staff. The recovery unit is generally equipped with wall oxygen, vital signs monitors, crash carts, and emergency intubation equipment. In patients who have undergone general anesthesia or who remain deeply sedated at the end of the procedure, supplemental oxygen should be continued via a face mask or a nasal cannula and weaned off gradually. Patients should be observed until they meet discharge criteria (i.e., for

30–45 min). Residual muscle relaxation or post-procedure respiratory failures for a variety of reasons are possible complications that may require intubation, unplanned hospital stay, and/or likely ICU admission.

Upon discharge, all patients should be advised in writing and verbally not to drive, sign legally binding documents, or operate machinery for 24 h after the procedure. The patient should be accompanied home by a responsible adult.

Summary and Recommendations

Conclusion

The field of interventional bronchoscopy has been evolving and is becoming more sophisticated, as has the field of anesthesiology. As a result, the older techniques of local anesthesia may not be as well suited for new, complex, prolonged bronchoscopic procedures. Communication between interventional bronchoscopy departments and anesthesiology departments is necessary to delineate when anesthesia services are needed and where certain bronchoscopic procedures should be performed. Recent advances in the field of anesthesiology render both conscious sedation and general anesthesia for interventional bronchoscopy safe, and the use of these advances is invaluable for the continued growth of the field of Interventional Bronchoscopy.

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Evaluating Outcomes After Interventional Procedures

5

Teruomi Miyazawa and Hiroki Nishine

Interventional Procedure

Inoperable central airway stenosis due to a malignant tumor is a relatively common condition and may be life threatening. Because of the poor prognosis, palliative methods are needed to maintain airway patency. In patients with severe malignant airway stenosis, interventional bronchoscopy is considered as a method of maintaining airway patency [1].

Flow limitation during forced expiration is affected by the relationship between transmural pressure (P_{tm}) and the cross-sectional area (A) of the airway. The wave speed is dependent on the stiffness of the airway wall, i.e., dP_{tm}/dA, and on the cross-sectional airway itself [2, 3]. The flow-limiting segment (FLS) occurs originally where the cross-sectional area of the airway is the narrowest. On the basis of wave-speed concepts of maximal expiratory flow limitation, stenting at the FLS improved expiratory flow limitation by increasing the cross-sectional area, supporting the weakened airway wall, and relieving dyspnea [4, 5].

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Assessment of Flow–Volume Curve

The location of the FLS is assessed using flow–volume curves. Analysis of the flow–volume curve can be used to define the nature of the stenosis and provide reliable information on the efficacy of stenting [5–10]. In patients with tracheal stenosis, the flow–volume curve shows a marked reduction of the expiratory flow (fixed narrowing patterns) with a plateau. In patients with bronchial stenosis, the flow–volume curve shows decreased flow with expiratory choking (initial transient peak flow followed by acute flow deterioration and consecutive low flow, and dynamic collapse patterns). In patients with carinal stenosis, the flow–volume curve shows a descending expiratory limb with a plateau and choking (combined fixed and dynamic patterns). In patients with extensive stenosis from the trachea and carina, extending to the bronchi due to tumor and/or mediastinal lymphadenopathy, the flow–volume curve shows severe reduction of the expiratory flow (complex patterns containing elements of all the former).

In a patient with *fixed intrathoracic stenosis* due to malignant lymphoma, CT showed extrinsic compression of the trachea (Fig. 5.1a). Bronchoscopy revealed the stenosis was caused by compression of an extrinsic tumor (Fig. 5.1b). Stenting was performed using intravenous anesthesia using a laryngeal mask. After stenting, stent deformities were seen at the most narrow

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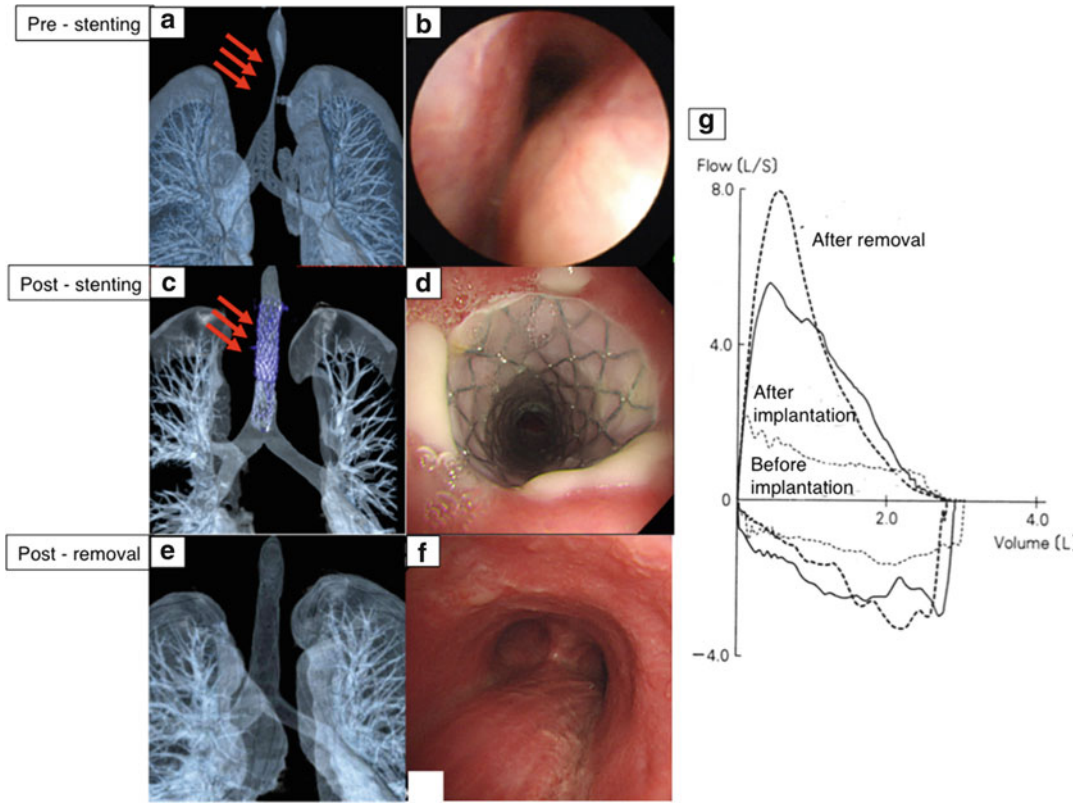

Fig. 5.1 Changes of the flow–volume curve after interventional bronchoscopy in *fixed intrathoracic stenosis* due to malignant lymphoma (before treatment: *panels* **a**–**b**, after stenting: *panels* **c**–**d**, after stent removal: *panels* **e**–**f**). *Red arrows* indicate the area of stenosis. After each treatment, the flow–volume curve showed a stepwise improvement over the interventional procedures. See text for further explanation

points of the lesion and carina (Fig. 5.1c, d), and after anticancer chemotherapy, tracheal patency was maintained and stent removal was performed (Fig. 5.1e). One week after removal, mild granulation was observed; however, no complications such as mucosal damage occurred (Fig. 5.1f). Before stenting, the flow–volume loops showed a marked reduction of the expiratory flow with a plateau (Fig. 5.1g), and the flow–volume loops after stenting showed immediate improvement of flow limitation (Fig. 5.1g). After stent removal, the flow–volume loops returned to near normal patterns (Fig. 5.1g). The patterns of the flow–volume curve showed a stepwise improvement over the interventional procedures.

Dyspnea

The degree of dyspnea depends on the degree of airway obstruction and becomes severe when well over 70% of the tracheal lumen is obstructed [11]. In cases with 50% *tracheal obstruction*, the highest velocities are in the jet, which is generated by glottic constriction. In cases with over 70% *tracheal obstruction*, peak velocities are generated at the stenosis and exceed velocities in the glottic area. Pressure differences changed dramatically from 70% *tracheal obstruction*.

The relation between the baseline degree of tracheal obstruction and the changes in MMRC (ΔMMRC) is shown in Table 5.1. Any patient

Table 5.1 Relation between the baseline degree of the tracheal obstruction and the change in MMRC after interventional bronchoscopy

Degree of tracheal obstruction	ΔMMRC[a]					Responders[b]
(%)	0	1	2	3	4	(%)
50–60			1	1		10/17 (58.8%)
61–70		2	1	1		
71–80	1	4	4	2		
81–90	1	1	5	1	3	11/13 (84.6%)
91–100			2			

[a]ΔMMRC = change in MMRC scale
[b]ΔMMRC responder = improvement in MMRC scale of two or more

with an improvement in the MMRC scale of 2 or more was considered to be a clinical responder. The clinical responder rate was 84.6% for obstructions above 80% and 58.8% for obstructions between 50% and 80%. Pre-operation measures by the baseline degree of tracheal obstruction could be used to predict the post-operation impact on dyspnea [12].

Assessment of Lateral Airway Pressure

Analysis of the flow–volume curve could be used in defining the nature of the stenosis. However, flow–volume curves cannot identify the precise location of the lesion where airway resistance increases nor can it immediately define the outcome of stenting.

With use of airway catheters in dogs [13–15] and in human subjects [16–18], the FLS could be located by measuring lateral airway pressure (P_{lat}) during induced flow limitation generated by either an increase in pleural pressure or a decrease in downstream pressure. Healthy subjects have relatively uniform pressure drop down the bronchial tree during expiration. In patients with airway stenosis, the major pressure drop occurs across the stenosis. By measuring P_{lat} on each side of the stenosis, we could detect the pressure difference between two sites (proximal and distal) of the stenotic segment [12].

After intubation, a double-lumen airway catheter was inserted into the trachea during bronchoscopy. P_{lat} was measured simultaneously at two points during spontaneous breathing with light general anesthesia before and after intervention. P_{lat} at the two points was plotted on an oscilloscope [pressure–pressure (*P–P*) curve]. The angle of the *P–P* curve was defined as the angle between the peak inspiratory and expiratory pressure points and the baseline of the angle. If the cross-sectional area (CSA) was small, then the angle was close to 0°; however, after intervention, the CSA significantly increased and the angle was close to 45°.

In healthy subjects, no pressure difference between the carina and trachea was observed during tidal breathing, and the angle was close to 45°. In patients with tracheal obstruction, dyspnea scale, pressure difference, and the angle changed significantly beyond 50% obstruction. After stenting, the pressure difference disappeared and the angle was close to 45°. The degree of tracheal obstruction was significantly correlated with the pressure difference and the angle [12].

This approach identified a need for additional treatment during interventional bronchoscopy. In a patient with *fixed intrathoracic stenosis* due to esophageal cancer, bronchoscopy showed an endoluminal stenosis at the lower trachea (Fig. 5.2a). Before treatment, a considerable pressure difference between the upper trachea and carina was noted (Fig. 5.2b), and the angle of the *P–P* curve was 1.9° (Fig. 5.2c). The flow–volume curve shows marked reduction of the expiratory and inspiratory flows (Fig. 5.2d). After balloon dilation, bronchoscopic image revealed greater patency for the trachea (Fig. 5.2e). However, the pressure difference only decreased from 23.2 cmH_2O to 3.69 cmH_2O (Fig. 5.2f), and the angle of the *P–P* curve only increased from 1.9° to 10.5° (Fig. 5.2g). Subsequently, a silicone Y stent was implanted from the upper trachea to the both main stem bronchus. After stenting (Fig 5.2h), pressure differences disappeared (Fig. 5.2i) and the angle

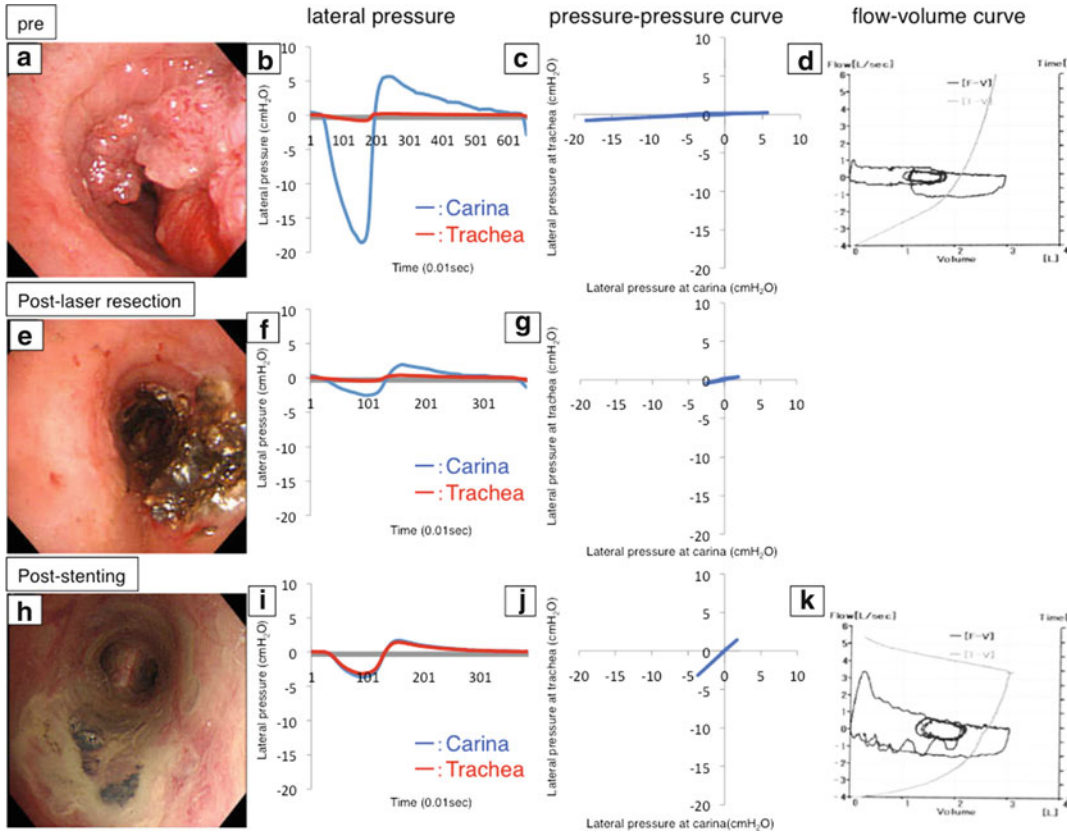

Fig. 5.2 Lateral airway pressure (P_{lat}) measurements during interventional bronchoscopy with balloon dilation and silicone Y stent implantation in *fixed intrathoracic stenosis* due to esophageal cancer (before treatment: panels **a**–**d**, after balloon dilation: panels **e**–**g**, after stenting: panels **h**–**k**). P_{lat} was measured simultaneously at two points (upper trachea and carina). *Blue line* shows P_{lat} at carina and red line indicates P_{lat} at upper trachea (**b**, **f**, **i**). After each treatment, the pressure difference and the angle of *P–P* curve improved. See text for further explanation

of the *P–P* curve increased from 10.5° to 42.9° (Fig. 5.2j). The MMRC scale decreased from 2 to 0, and flow–volume curve returned to a near normal pattern (Fig. 5.2k). Measuring lateral airway pressure could estimate the need for additional procedures better than bronchoscopy alone. The direct measurement of the pressure difference and the angle of pressure–pressure curve is a new assessment modality for the success of interventional bronchoscopy.

Analysis of Pressure–Pressure Curve

Central airway stenosis can be divided into four major types: *fixed, variable*, *extrathoracic*, and *intrathoracic stenosis*. In *fixed stenosis*, the CSA at the site of the lesion does not change during the respiratory cycle, and the *P–P* curve was linear. In *variable stenosis*, the configuration of the stenotic lesion changes between phases of respiration. Airway narrowing occurs during expiration in *intrathoracic stenosis*, whereas airway narrowing occurs during inspiration in *extrathoracic stenosis*. In *variable extrathoracic stenosis*, the angle of the *P–P* curve during inspiration is smaller than during expiration, and in *variable intrathoracic stenosis*, the angle of the *P–P* curve during expiration is smaller than during inspiration.

In a patient with *fixed extrathoracic stenosis* due to exuberant granulation tissue, MDCT showed a weblike stenosis at the endotracheal tube cuff site (Fig. 5.3a). Before balloon dilation, a considerable pressure difference between the

upper trachea and carina was noted (Fig. 5.3b). After resection using the tip of a rigid bronchoscope and balloon dilation, MDCT showed restored patency of the trachea (Fig. 5.3d), and the pressure difference disappeared (Fig. 5.3e). After treatment, the flow–volume curve returned to an almost normal pattern (Fig. 5.3c). Before dilation the *P–P* curve was linear, and the angle of the *P–P* curve was small during inspiration and expiration (Fig. 5.3f).

In a patient with *fixed intrathoracic stenosis* due to choriocarcinoma, MDCT showed an extrinsic compression at the metastatic lymph nodes (Fig. 5.3g). Before stenting, there was a considerable pressure difference between the upper trachea and carina (Fig. 5.3h). After implantation of a self-expandable metallic stent, the trachea was clearly patent (Fig. 5.3j) and the pressure difference disappeared (Fig. 5.3k). After stenting, the flow–volume curve improved (Fig. 5.3i). Before stenting, the *P–P* curve was linear and the angle of the *P–P* curve was small during inspiration and expiration (Fig. 5.3l).

In a patient with *variable extrathoracic stenosis* due to esophageal cancer, MDCT showed a dynamic airway collapse caused by excessive bulging of the left airway wall covered with a titanium mesh after tracheoplasty (Fig. 5.4a). Before stenting, there was a considerable pressure difference between the upper trachea and carina (Fig. 5.4b). After implantation of a self-expandable metallic stent, the trachea was patent (Fig. 5.4d) and that the pressure difference disappeared (Fig. 5.4e). After stenting, the flow–

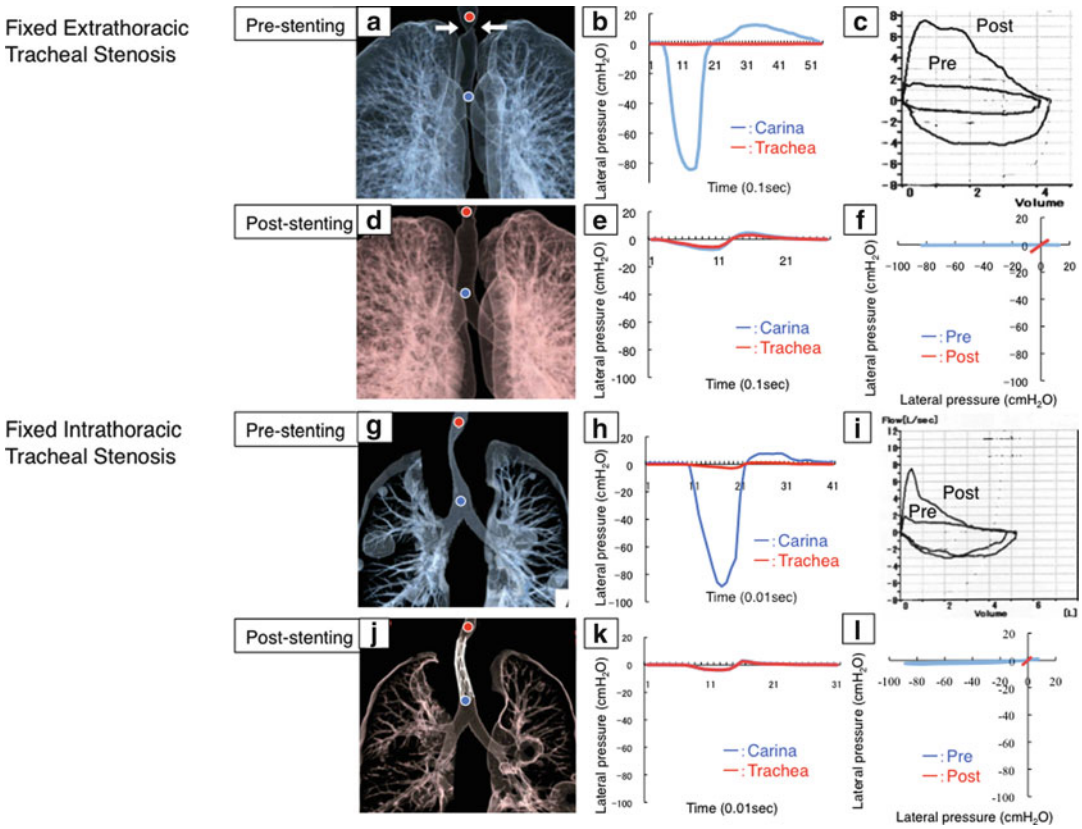

Fig. 5.3 Patterns of lateral airway pressure (P_{lat}) measurement before and after interventional bronchoscopy for *fixed tracheal stenosis* (**a–f**: *fixed extrathoracic stenosis*, **g–l**: *fixed intrathoracic stenosis*). *White arrows* indicate the area of stenosis. P_{lat} was measured simultaneously at two points (upper trachea and carina). *Blue lines* show P_{lat} at carina and *red lines* indicate P_{lat} at upper trachea. The pressure–pressure curve represented by the *blue line* shows the result before procedure, and the *red line* shows the result after procedure. See text for further explanation

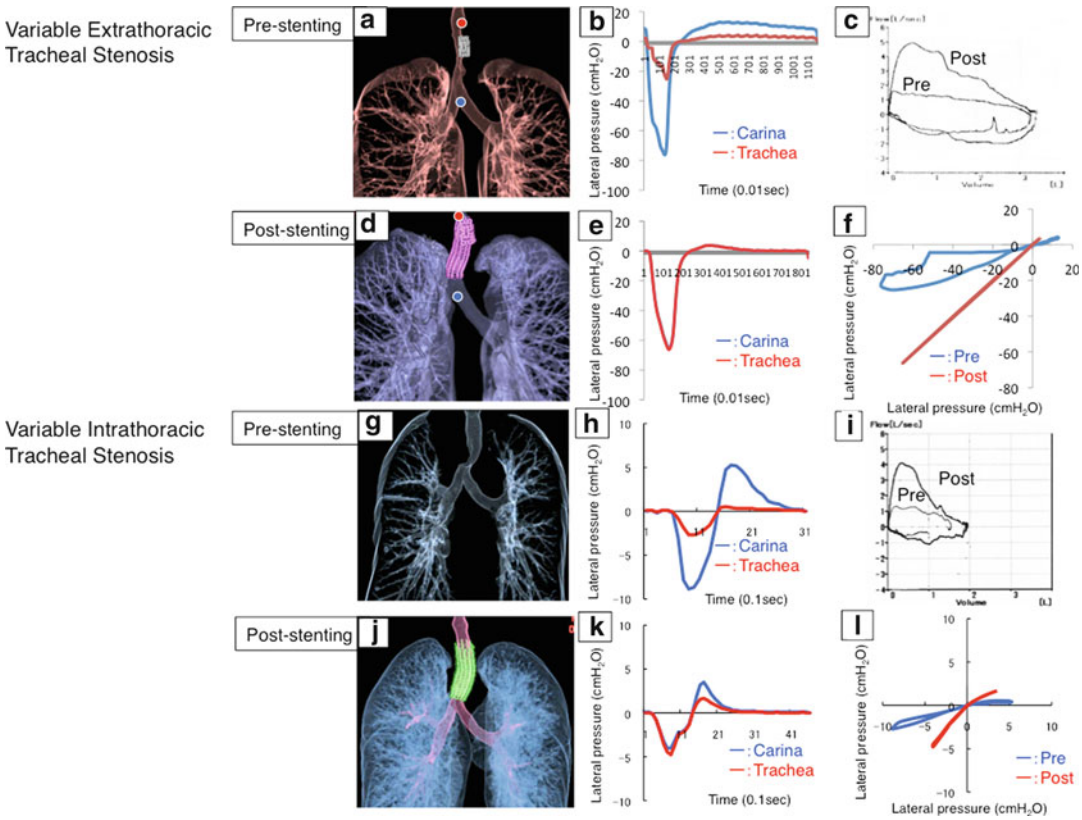

Fig. 5.4 Patterns of lateral airway pressure (P_{lat}) measurement before and after interventional bronchoscopy for *variable tracheal stenosis*. P_{lat} was measured simultaneously at two points (upper trachea and carina). *Blue line* shows P_{lat} at carina and *red line* indicates P_{lat} at upper trachea. The pressure–pressure curve represented by the blue line shows the result before procedure, and the red line shows the result after procedure. See text for further explanation

volume curve improved (Fig. 5.4c). Before stenting, the angle of the *P–P* curve during inspiration was smaller than during expiration, and the *P–P* curve appeared loop shaped during the inspiratory phase (Fig. 5.4f). After stenting, the angle of *P–P* curve increased with a linear shape (Fig. 5.4f).

In a patient with *variable intrathoracic stenosis* due to colon cancer, MDCT showed compression from an extraluminal tumor on the right side (Fig. 5.4g). Before stenting, a considerable pressure difference between the upper trachea and carina was noted (Fig. 5.4h). After implantation of a self-expandable metallic stent, the trachea was patent (Fig. 5.4j) and the pressure difference decreased (Fig. 5.4k). After stenting, the expiratory flow increased (Fig. 5.4i). Before stenting, the angle of the *P–P* curve during expiration was smaller than inspiration and appeared loop shaped (Fig. 5.4l). After stenting, the angle of the *P–P* curve increased and a linear shape was seen (Fig. 5.4l).

Conclusions

Placement of the stent at the flow-limiting segment (FLS) provided the greatest functional benefit to patients with central airway stenosis [4, 5]. Although bronchoscopic image showed that tracheal patency was restored after procedures, the angle of *P–P* curve did not always improve. It is

difficult to estimate the outcome of interventional procedures by bronchoscopy alone. When the location of the FLS is assessed using flow–volume curves, the pressure difference and the angle of pressure–pressure curve are able to immediately estimate the outcomes of interventional bronchoscopy in real time.

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Bronchoscopy Education: New Insights

6

Henri G. Colt

Tell me and I'll forget; show me and I may remember; involve me and I'll understand.

Chinese Proverb

Background

I have always been amazed that medical education involved learning "on" patients as well as from them. Many years ago, surrounded by other medical students, I positioned myself so as to stand directly beside my senior resident as he prepared to perform a lumbar puncture. Erect in our long white coats, leaning inwards with anticipatory curiosity and awe, we marveled at the way he told the patient what he was going to do before ordering her to turn onto her side. After prepping the skin, he inserted the spinal needle effortlessly. We cringed collectively, however, as it was repositioned, causing the patient to cry out in pain. We sighed with relief when a clear fluid suddenly appeared, and the procedure finished, we admired the authoritative tone with which our resident informed this small, frail and frightened 18-year-old girl with sweat-drenched hair and a poorly fitting hospital gown that uncovered her bare buttocks and lower back, that she must lay quietly for several hours and that everything was going to be fine. As we followed the resident out of the room (the ward had several patients, all of whom had been watching us), we felt important in our white coats. Like a swarm of flies around a picnic table covered with food, we excitedly spoke about how cool the resident had been and how easy the procedure seemed. Later that afternoon, I recalled that we had never been told the patient's name, nor been introduced to her as she lay passively on her bed. We were not given much of an explanation about the procedure either, and I had not yet had the opportunity to watch others before I was told the very next morning to "go tap that patient in bed 3".

Until very recently, medical training has followed guidelines established by Flexner and Halsted in the early twentieth century [1]: A stepwise postgraduate training program is designed within a "see one, do one, teach one" paradigm, with patients serving as teaching material. Trainees gradually achieve independence from faculty supervision as they progress through their years of apprenticeship. Competency is often presumed based on numbers of procedures performed, and objective measures of knowledge (high-stakes tests) are used for licensure and certification purposes [2].

Today, "see one, do one, teach one" is no longer an acceptable paradigm of procedure-related medical instruction, so patients need no longer suffer the burden of procedure-related training. Furthermore, teachers need no longer devote hours to enumerating facts and figures related to medical illnesses because educational media are

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increasingly accessible, with information at the fingertips and on the computer screens of health care providers and patients alike [3]. Using inanimate and computer-based platforms, technical skills can be practiced independently or under supervision; structured curricula help assure a foundation of knowledge regardless of the diversity and variability of the clinical setting, and new norms and expectations governing professionalism help guide physician behaviors that promote respect for patient autonomy and shared-decision making.

These early twenty-first century learning environments empower both teacher and learner. Benefitting from a bidirectional learning process they are able to explore together many new and exciting roles. Computer simulation allows students to practice procedures before ever going to the patient's bedside, and, as new delivery systems for instructional materials replace conventional textbooks, enhancing the portability, access, and design of information, both learners and teachers can devote more time to learning *how to think* or *how to teach*, rather than on rote memorization and content development [4]. The availability of web-based instruction, use of interactive case-based exercises, role-playing sessions, opportunities for individualized instruction, and an open forum where teachers serve more as coaches or wise elders frees teachers from their podiums. Low-stakes assessment tools and self-assessments can be used to identify areas that warrant remedial training, as well as to document one's progress towards competency and proficiency because at the bedside and in the classroom, the implementation of new models of instruction allows educators more time to build personal relationships with learners. Learners benefit from this because face-time with instructors can be used to encourage learning through positive reinforcement, provide key insights into a procedure or management decision, enhance intrinsic motivation, and discover fun in learning. Learning curves may thus be climbed with greater confidence and comfort in a truly caring education environment.

Taking the liberty to depart from a conventional chapter including science and literature review, my objectives in the following paragraphs, are instead to (1) address major elements of curricular structure and delivery, (2) provide an example of how a structured curricular approach using a combination of onsite and online materials such as those provided in the Bronchoscopy Education Project might facilitate learning, (3) describe how assessment tools might help guide the educational process and assure procedure-related competency, and (4) discuss how an ethics of teaching underlies and justifies the paradigm shift occurring in today's world of medical procedural education. While flexible bronchoscopy and airway procedures are used as models for discussion, much of what I write is applicable to other areas of procedure-related medicine.

Curricular Structure and Delivery

Bronchoscopy is performed by a variety of medical and surgical specialists including Pulmonologists, Thoracic Surgeons, Ear, Nose and Throat specialists, Anesthesiologists, and Intensivists. Indications vary from simple inspection to diagnosis of lung and airway disorders, assistance with intubation, and therapeutic procedures to remove foreign bodies, restore airway patency, treat emphysema, asthma or cancer to name but a few. There does not appear to be a universally accepted convention by which to teach the technical skills required to perform this procedure, nor to introduce learners to the complexities of a bronchoscopy-related consultation.

In many institutions, the bronchoscopy learning experience is variable, in part because of diverse practice patterns and patient referrals, but also because of different teaching interests, methodologies and time committed to the educational process [5]. In fact, despite its existence since the late 1960s, many questions remain regarding the clinical practice of flexible bronchoscopy. The variability of equipment used and resources available for teaching further complicates matters when contemplating a global approach to the educational process. Videobronchoscopes, for example, are used in most prosperous areas of North America, Europe and the Middle East, whereas flexible fiberoptic bronchoscopes are still

the workhorses of South Americans and many developing countries in Asia. Techniques are also controversial: Should the scope be held in the left or the right hand? Where should assistants stand? Should the procedure be performed from the head or from in front of the patient? Should the patient be supine or semi-erect? What kind of sedation, if any should be used? Are universal precautions, including gown, gloves and protective eyewear always necessary, and how should equipment be cleaned? Finally, who should be considered able and competent to perform the procedure? Could it be performed by nonphysician providers in specific settings such as an intensive care unit or as part of a lung donor eligibility assessment, or should bronchoscopy remain a physician-only performed procedure? Should training and certification processes be different depending on medical specialty? Should bronchoscopy privileges extend to all types of procedures, or should only certain specialists perform certain types of procedures? How many procedures should one perform to be deemed competent, and if numbers are used as a metric, how many must be performed each year to maintain competency? If they are not used as a metric, what assessment and testing tools might be employed to assure that procedures are performed safely and competently?

What is a Bronchoscopy Curriculum?

In most countries, there is no fixed curriculum pertaining to bronchoscopy education. It is assumed that physicians in various specialties become competent in the procedure as a result of their subspecialty training. In the United States, where more than 500,000 bronchoscopies are performed each year, there is no uniform structure for bronchoscopy training other than learning during residency or fellowship [6]. Nor is there a standardized method by which technical skills and procedure-related knowledge are assessed. In fact, very few questions (usually <5) are devoted to bronchoscopy on subspecialty board examinations, even though it is the major minimally invasive procedure performed by chest physicians.

Surveys pertaining to flexible bronchoscopy in countries as diverse as Singapore, Great Britain, India, Poland, Egypt and the United States consistently identify variations in practice and training [7–9]. This diversity derives from a lack of uniform requirements, paucity of structured curricula, absence of validated measures of competency and proficiency, unequal access to learning materials, variability of patient-based learning experiences, and differences in skill, interest and teaching abilities of medical practitioners designated as bronchoscopy instructors. Furthermore, the lack of a uniform competency-based framework for bronchoscopy education makes it difficult for physicians already in practice to acquire new skills.

A curriculum (noun, plural of which is curr-ric-u-la or curr-ric-u-lums), can be defined as a group of related courses, often in a special field of study (http://www.thefreedictionary.com/curriculum, downloaded May 25, 2012). As such, it pertains to the purpose, content, activities, and organization inherent to an educational program [10]. There are many challenges that must be overcome, however, as one contemplates curricular structure [11]. Some of these are related to conceptualizing the instructional process and defining meaningful learning experiences. Others relate to tradition, availability of resources, variability of deeply held beliefs and teaching styles, and the paucity of bronchoscopy-education related research.

Instructional Process and Defining Meaningful Learning Experiences

John Dewey (born 1859–1952), probably one of America's most influential philosophers, wrote "the belief that all genuine education comes about through experience does not mean that all experiences are genuinely or equally educative" [12]. For healthcare providers, being obliged to perform what might be for the first time, albeit with guidance, a procedure in a patient is both discomforting and anxiety-provoking. A social mandate for accountability and truly informed consent will make it increasingly difficult for practitioners

to learn by doing. In addition, such a learning environment creates an ethical dilemma for the competent instructor being asked to advocate for efficient, evidence-based, cost-effective quality of care, and who knows that he or she can perform the procedure more quickly, more efficiently, and with greater patient comfort than the learner. These arguments justify a more widespread use of simulation-based bronchoscopy training.

Changes in the perception of the educational process have resulted from modifications of medical education systems. In the United States, for example, The Accreditation Council of Graduate Medical Education currently advocates a competency-based training model that replaces one based on process and number of cases performed [13]. Great emphasis is placed on objective measurements of competency, including elements of professionalism, systems-analysis, and healthcare team development. In designing a bronchoscopy curriculum, therefore, one must consider how learning processes reach beyond technical skill development to involve the cognitive, affective, and experiential forms of knowledge, as well as how knowledge acquisition and retention might be assessed both during and after training [14]. These arguments, in my opinion, justify recommending reading assignments, case-based and problem-based learning exercises [15], low-stakes assessments to document progress along the learning curve [16], and outcome metrics [17] to study the effectiveness of postgraduate courses on individual and groups.

From a learner-centric perspective, therefore, bronchoscopy education should entail elements of critical thinking, problem-solving, ethical values and behaviors, mastery of critical facts and figures, mastery of certain technical skills unique to each type of procedure being performed, self-realization, self-esteem and emotional stability, safety, and an ability to effectively and efficiently integrate procedural practice into one's institution-based medical practice. From a teacher's perspective, these curricular elements should be developed in a manner that is time and cost-efficient, nonalienating, and conducive to individualized and collective learning, standardized to the extent that a generally accepted foundation of facts and philosophies are imparted, and integrated into various individual and group educational venues (clinical setting, online or computer-based programs, postgraduate seminars, online and onsite courses). Furthermore, as new concepts, learning materials, and techniques are introduced, faculty development programs are warranted to enhance teaching skills, assure continuity and growth, and to share experiences regarding the advantages and challenges of moderating small group learning sessions, using interactive presentations and audience participation software, and integrating video or other media, including real time decision trees, instant messaging or Twitter, tablet PCs and writing boards into educational programs (Figs. 6.1 and 6.2).

While a mentor's behaviors, good or bad, might be readily emulated after observation, to expect that an ability to teach effectively comes naturally to all runs contrary to assumptions in other fields and professions (i.e., public education, hobbies, or sports), and, in my opinion, represents a significant shortcoming of our academic philosophy. The purpose of faculty development programs, often referred to as train the trainer seminars, therefore, is to help motivate, stimulate, inspire, and teach professionals interested in serving as role models, mentors or instructors of various educational techniques and methodologies, and to provide and study resources that can be incorporated in whole or in part into various training curricula.

Tradition, Teaching Styles, and Beliefs

There seems to be a grand tradition in bronchoscopy education. This tradition is twofold. In the first instance, it is assumed that learners will learn bronchoscopy during the course of their specialty training [18], and that learning will be satisfactory because learners are exposed to different faculty members who might each perform bronchoscopy in a different way (set-up, positioning, sedation and medication use, techniques, etc.). With this is the idea that the complexities of a bronchoscopy-related consultation can be learned as part of a routine specialty consultation service,

and that all of the items pertinent to such a consultation will be satisfactorily addressed, even if they are not explicitly reviewed with the attending faculty (indications and informed consent, procedure-related strategy and planning, technique and expected results, response to complications, post-procedure management and follow-up). The second tradition pertains to the popularity of 1- and 2-day postgraduate courses devoted until recently and for the most part to physicians already in-practice. For bronchoscopists, this tradition comes from decades of hands-on learning that began with patient-based instruction in rigid bronchoscopy by Gustav Killian and Chevalier Jackson. The expert bronchoscopist lectures on a topic while the learner group listens attentatively. Speakers each prepare their lectures with little guidance or fixed-in-advance common purpose destined to integrate their lecture with the content of other lectures being given during the course. Sometimes, live transmissions of cases are included in the program, with either the operator or other faculty member interacting with the audience to discuss indications and procedural techniques.[1]

During these programs, learners are expected to have learned by simply being present: usually no preliminary or postcourse assessments are performed, and little attempt is made to individualize the learning process. Popular hands-on sessions are organized using animal models and equipment loaned from equipment manufacturers. More recently, computer-based simulation and inanimate models have been introduced. Learners rotate from station to station, listening to experts tell them about a procedure or technique, then watch as he (until recently, most bronchoscopy experts have been male) demonstrates the technique. Then one after another, learners take the scope in hand and do something, some less well than others.

[1] Live transmissions carry many challenges not the least of which are that cases may be selected based on the expectant participants, intraoperative decisions might be made solely on the basis of educational or theatrical need, and the operator may be distracted by questions or other interactions with the audience.

The realities of these programs are that (1) little reward is provided to faculty who devote much of their time and energy to teaching bronchoscopy, (2) the complexities of bronchoscopy-related instruction and consultation are increasing in view of the rapid expansion of interventional pulmonology, (3) time constraints, accountability, concerns for cost-effectiveness and a mandate for enhanced patient safety and respect make patient-based instruction increasingly problematic, (4) passive learning from listening to a speaker giving a lecture is not as effective as when learners are actively engaged, (5) critical thinking and problem-solving are rarely addressed, yet are a major component of procedure-related competency, (6) educational content and the effectiveness of its delivery depends on who prepares the lecture and how it is delivered, (7) active engagement time (the time the learner is actually devoting to learning by doing) is minimal, consisting of, for example only 3–5 min per person for a group of five people during a 30-min station session, (8) specific tasks are often not made explicit at each hands-on station, decreasing the chance that a specific skill will actually be acquired at the station, (9) substantial time is spent listening to lecturers during both the didactic and hands-on sessions, and (10) little or no attempt is made to assess the baseline knowledge or skill levels of the course participants, making individualized training difficult.

Because there are no studies, to my knowledge pertaining to the effectiveness, or lack thereof of this traditional method of bronchoscopy education, it has been challenging for educators to step out of the box and view these traditional educational processes differently. It is equally challenging to introduce and potentially justify changing an educational modality. The new reality is, however, that (1) different modalities are and can be complementary, (2) many lectures can be accessed off-site though the use of the internet, (3) well-edited videos can replace long periods of watching a transmitted “live” case, without jeopardizing patient care, (4) not all experts are good teachers or good lecturers, (5) not all lectures provide a foundation of knowledge useful or required by learners, (6) active engagement time

Fig. 6.1 Example of instructor led small group discussion in Peru. Participants are debating the advantages of using BSTAT (Bronchoscopy skills and task assessment tool in background) quiz to develop a common language for airway secretions and mucosal abnormalities (*courtesy of Henri Colt, M.D.*)

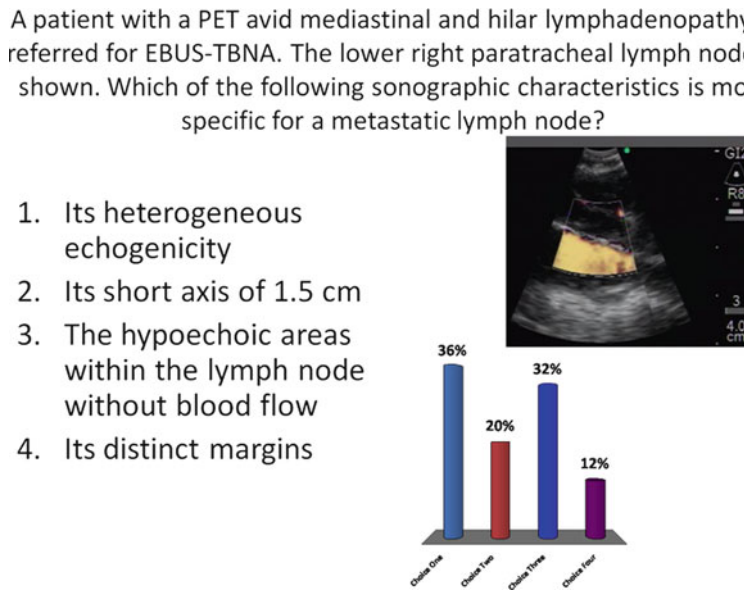


Fig. 6.2 Example of using audience participation software during an interactive question/answer session. In view of the wide variety of responses shown on the graph, the instructor will provide insight regarding each of the possible answers (*courtesy of Henri Colt, M.D.*)

can be maximized when experts devote less time to demonstrating, and more time to assisting learners perform specific skill sets of a procedure, (7) problem-solving and critical thinking needs to become a standard part of bronchoscopy courses because they are essential to the safety, effectiveness, and efficiency of bronchoscopic practice, (8) animals, veterinary services, cadavers

and animal laboratory usage are costly, also prohibiting courses in hotels or other venues, (9) the unnecessary sacrifice of live animals can almost always be avoided by using inanimate models and computer-based simulation, and (10) metrics will be needed to help ascertain knowledge and skill acquisition as well as program effectiveness as part of a competency-oriented program of procedure-related learning.

These *reality lists* are obviously not exclusive, and many other elements are important in rethinking traditional methods of bronchoscopy education. Agents of change are necessary to develop and implement different teaching strategies and methodologies across the globe. Industry support is essential to educational programs, and professional societies may need to work together, rather than compete, in order to foster a foundation of information and assure a greater democratization of knowledge. Finally, either/or debates and opposing points of view, rather than be eternalized by experts resistant to change, may need to be synthesized in a manner that promotes learning and choice, acknowledging both points of view in the context of a broadened educational process [19] (Fig. 6.3).

Bronchoscopy-Education Related Research

The bronchoscopy-related literature is gradually supporting the paradigm shift whereby patients will no longer bear the burden of procedure-related training. In a review pertaining to the use of simulation for bronchoscopy education [20], we noted that simulation helps learners improve procedural efficiency and economy of movement, thoroughness and accuracy of airway examination, and decreases airway wall trauma [21]. In addition to increasing learner satisfaction and interest, simulation allows tasks to be practiced repeatedly without jeopardizing patient safety, and training scenarios can be individualized. Both low- and high-fidelity simulation have been shown to enhance competency in procedural skills while saving time and improving the learning curve [22, 23]. Furthermore, skills acquired through practice on simulators are transferable to the clinical setting [24]. Objective assessment identifies errors and provides opportunities for remedial training [25, 26].

High-fidelity simulation platforms using three-dimensional virtual anatomy and force feedback technology can be used to teach conventional and EBUS-guided transbronchial needle aspiration (TBNA), although less expensive, low-fidelity models comprised of molded silicone, excised animal airways, and ultrasound phantoms are also effective [27]. We demonstrated the efficacy of a low-fidelity hybrid airway model made of a porcine trachea and a plastic upper airway for learning transcarinal and transbronchial needle aspiration [28]. This model gave learners an opportunity to practice needle insertion, positioning, safety measures, and communication with ancillary personnel. This model has since been modified so that a plastic airway is used, obviating the need for discarded animal parts, and making the use of such training materials possible in hotel conference centers and non-hospital facilities. Models can also be used to teach scope manipulation and airway anatomy, foreign body removal, bronchoscopic intubation, EBUS-guided TBNA, and other interventional techniques, some of which can also be practiced using high-fidelity computer based simulation[2] (Fig. 6.4). New, portable computer-based bronchoscopy simulation is becoming available using laptop computers and proxy bronchoscopes.[3]

Demonstrating improvements in technical skill complete only part of the picture [29]. The increasing emphasis on competency-oriented education warrants that bronchoscopy courses also use competency-based measures to assess the efficacy of course curricula and training modalities [30]. Outcome measures might take the form of high or low-stakes testing in the various cognitive, technical, affective, and experiential elements of procedure-related knowledge [31–33]. Using quasi-experimental study design and a series of pre-test/post-test assessments with

[2] See for example, http://simbionix.com/

[3] See for example, http://www.orsim.co.nz/, and http://www.anesthesia.utoronto.ca/edu/cme/bronch.htm.

EITHER	OR	BOTH-AND SYNTHESIS
Scope handling with the left hand	Scope handling with the right hand	Both are correct and impact positioning of bronchoscopy assistants and handling of ancillary equipment. Operator comfort and teaching traditions with influence choice.
Operator position from the head of the patient	Operator position from in front of the patient	Both are correct and should be learned because either may be necessary depending on procedural setting and indication.
Tests	Assessments	Both are important in improving learning. How should competency be ascertained? Is there a role for Mastery learning? What kind of remedial training may be warranted? How can both be used in the setting of physicians-in-training as well as for physicians already in practice?
Teacher-centered instruction	Learner-centered learning	Teacher-learner relationships are important and allow teachers to assume various roles. New technological platforms create greater opportunities for independent study, collaboration, and long-distance learning.
Apprenticeship-style learning	Competency-oriented learning	Both are important as learners take on greater responsibilities. Using new technologies and educational methodologies are likely to help accelerate the learner's progress along the learning (experience) curve, enhance quality patient care and safety, and allow a more rapid introduction of new procedures and techniques into the patient care arena.
Face-to-face instruction	Online learning	Both are important. Face-to-face instruction and active engagement time, especially during hands on training, takes on even greater value when learners learn using online resources. Face-to-face time can occur through videoconferencing as well as during onsite seminars, and of course at the patient's bedside or in the simulation center.
Learning on patients	Learning using simulation	Both are important. All facets of bronchoscopic knowledge and skill, including elements of professionalism, physician behaviors, procedural techniques, response to complications, and management decision making can be improved upon using inanimate models, computer-based simulation, and by helping learners work through the decision-making process during indvidual or group learing sessions. These can occur prior to or concurrent with patient-based experiences.
Reading conventional textbooks and articles	Media and technology	Both are important. Reading conventional textbooks may still be helpful, but media and technology are changing the way learners can interact with reading, both online and in print. Videos and interactive images and text (such as patient-centered exercises and clinical pathways) enliven the learning process and help learners analyze their performance. Articles are easily retrieved today using online informational databases, and can be used to justify decision-making and enhance evidence-based quality care practice.
Competency determined based on single institution subspecialty training	Competency determined based on completing a core curriculum that might be applicable in part or in whole in many	Both are necessary. For example, a curriculum similar to one proposed in the Bronchoscopy Education Project and modified based on institutional needs or medical practice setting (see Figure 4) assures objective monitoring of trainees who attend onsite learning programs, complete specific reading assignments, patient-centered exercises, and clinical pathways, experience the advantages of simulation, and demonstrate skills using checklists and assessment tools in both the simulation and patient-care environment.

*Inspired from reference #20: Chen M, Education Nation pg 23-24.

Fig. 6.3 Examples of turning either/or debates into both/and syntheses (*courtesy of Henri Colt, M.D.*)

calculations of absolute, relative and class-average normalized gain, we have demonstrated the efficacy of a 1-day structured curriculum including didactic lectures, workshops, and hands-on simulation-based training in both flexible bronchoscopy and thorac oscopy [34, 35].

Assessment tools that objectively measure skill and knowledge acquisition will also need to

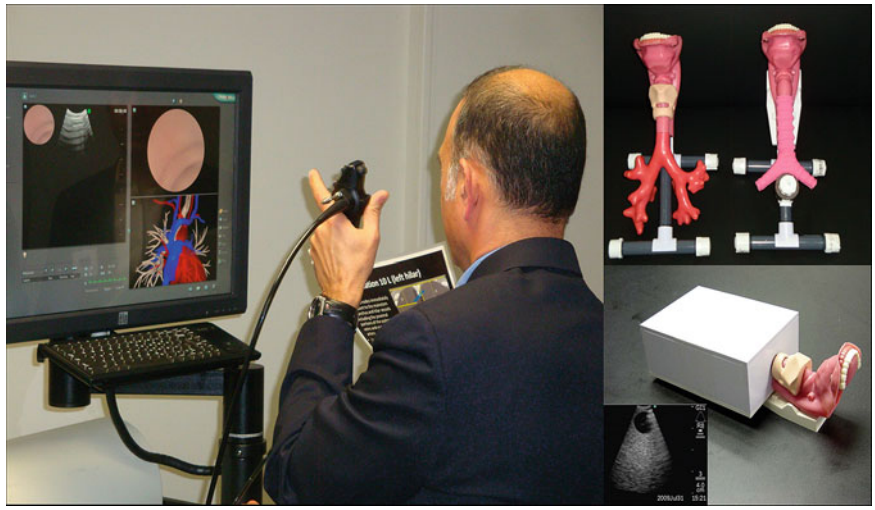


Fig. 6.4 Examples of inanimate and computer-based simulation platforms for learning bronchoscopy. Shown are the Symbionix Bronch mentor (EBUS module) and inanimate models assembled by Bronchoscopy International: bronchoscopy airway inspection model using bifurcated normal airway from CLA, Germany, transbronchial needle aspiration model using silicone airway from Sawbones Seattle WA, USA, and inanimate EBUS model using Laerdal Laryngeal structure and ATS laboratories ultrasound phantom with bifurcated airway and simulated lymph nodes at levels 2, 4, and 7 (ATS laboratories, Bridgeport, CT) (*courtesy of Henri Colt, M.D.*)

be designed and validated in various learning settings and medical environments [36]. Finally, as faculty development programs are integrated into curricular structures, it will become necessary to study their impact on teaching and learning. As new curricular platforms are introduced, education-related research will need to be designed in order to assess their impact on learning methodologies and results.

The Bronchoscopy Education Project

Developed by Bronchoscopy International,[4] The Bronchoscopy Education Project (BEP)[5] has been officially endorsed by several international bronchology and interventional pulmonology societies. Its aim to provide bronchoscopy instructors and training program directors with competency-oriented tools and materials in order to help train bronchoscopists and assess progress along the learning curve from novice to competent practitioner. These include The Essential Bronchoscopist™ series of eBooks [37, 38], Fundamentals of Bronchoscopy© series of training manuals [39], an encyclopedia of Practical Approach© patient-centered exercises that integrate cognitive, affective and experiential knowledge pertinent to bronchoscopy-related consultation, Bronchoscopy step-by-step© lessons, a problem-oriented BronchAtlas™ video series,[6] and a set of Bronchoscopy Assessment Tools and Checklists. Material can be integrated in whole or in part, as needed by each program. Learning is based on individual and group study of training manuals, participating in didactic and interactive lecture programs delivered onsite and

[4] A transnational group of educators and agents of change devoted to the dissemination of bronchoscopy-related knowledge.

[5] The BEP is a work in progress with materials constantly being added. For more information, visit HONcode certified website at http://www.Bronchoscopy.org and the BronchOrg page on YouTube.

[6] For example, video found at: http://www.youtube.com/watch?v=–MP-WdVcCxY

online, viewing instructional videos on social media sites such as YouTube and Facebook, and participating in deliberate hands-on practice sessions during postgraduate programs and in the course of subspecialty training. Faculty development programs are being conducted across the globe to help an international group of experts, early adopters, and agents of change use learning materials, improve their presentation skills, and develop new concepts that will strengthen future educational programs. A brief description of some of the BEP resources, built on the philosophy of using frequent, repeated group and individual exposures to multimedia rather than single medium instruction [40] is found below:

- As part of the Essential Bronchoscopist™ Series of eBooks The *Essential Flexible Bronchoscopist*© and The *Essential EBUS Bronchoscopist*© are comprised of specific reading materials, learning objectives, and post-tests. Each module contains 30 question-answer sets with information about major topics relating to bronchoscopic procedures. The aim of these modules is not to replace the apprenticeship model, but to complement in-hospital subspecialty training and to encourage open dialogue between learners and faculty.
- A *Bronchoscopy Step-by-Step*© and *EBUS Step-by-Step*© series of graded exercises help learners acquire technical skills necessary to perform these procedures.[7] Instructional videos are readily viewable on desktop computers as well as hand-held devices, IPADs, or cell phones. Specific training maneuvers help the learner practice incrementally difficult steps of bronchoscopy and EBUS-guided TBNA.[8] Steps are designed to enhance the development of "muscle memory" by breaking down complex moves into constituent elements and practicing the separate elements repeatedly before gradually combining them into more complex maneuvers.
- *The Introduction to Flexible Bronchoscopy* and *Endobronchial Ultrasound and EBUS-Guided TBNA* series of PowerPoint lectures and interactive slide presentations are, in part available online and provided as part of regional training programs. As part of the Fundamentals of Bronchoscopy© Curriculum, specific training manuals are available in hard copy as well as in the form of eBooks that contain program materials, simulation scenarios, recommended reading assignments, patient-centered practical approach exercises, checklists, and procedure-specific assessment tools.
- *BronchAtlas*™ includes a series of PowerPoint presentations and the BronchAtlas™ Video Series, a group of concise problem-oriented text files and short, hyperlinked videos designed to address specific issues encountered in daily bronchoscopic practice. Each text (PDF) file enunciates the problem (for example, bronchoscopy in patients with obstructive sleep apnea), and uses bullet lists to describe the problem with greater detail before providing solutions, a video, and a handful of relevant references. Files can be downloaded onto IPADs and mobile devices for rapid review.
- An encyclopedia of *Practical Approach patient-centered exercises* using a four-box approach to bronchoscopy-related consultation (includes elements from the initial evaluation, procedural strategies, techniques and results, and long-term management). Specific scenarios and case resolutions can be used for purposes of individual and group study, assessment, or as content for didactic or interactive lecture sessions.
- A series of *Bronchoscopy Assessment Tools*© designed as learning instruments provide objective measures of knowledge acquisition. Fixed numeric scores are attributed to learners based on performance of technical skills that include dexterity, accuracy, anatomic recognition, navigation, posture and position, economy of movement, atraumatic instrument manipulation, pattern recognition, and image analysis (Fig. 6.5a, b).

[7] Colt HG. *Bronchoscopy Lessons*. Instructional video pertaining to various aspects of bronchoscopy You Tube (posted 2010): http://www.youtube.com/watch?v=phRv73Ik7fI&feature=related.

[8] For example, video found at http://www.youtube.com/watch?v=Z9FdgVx_xrM

EBUS-STAT 10 Point Assessment Tool

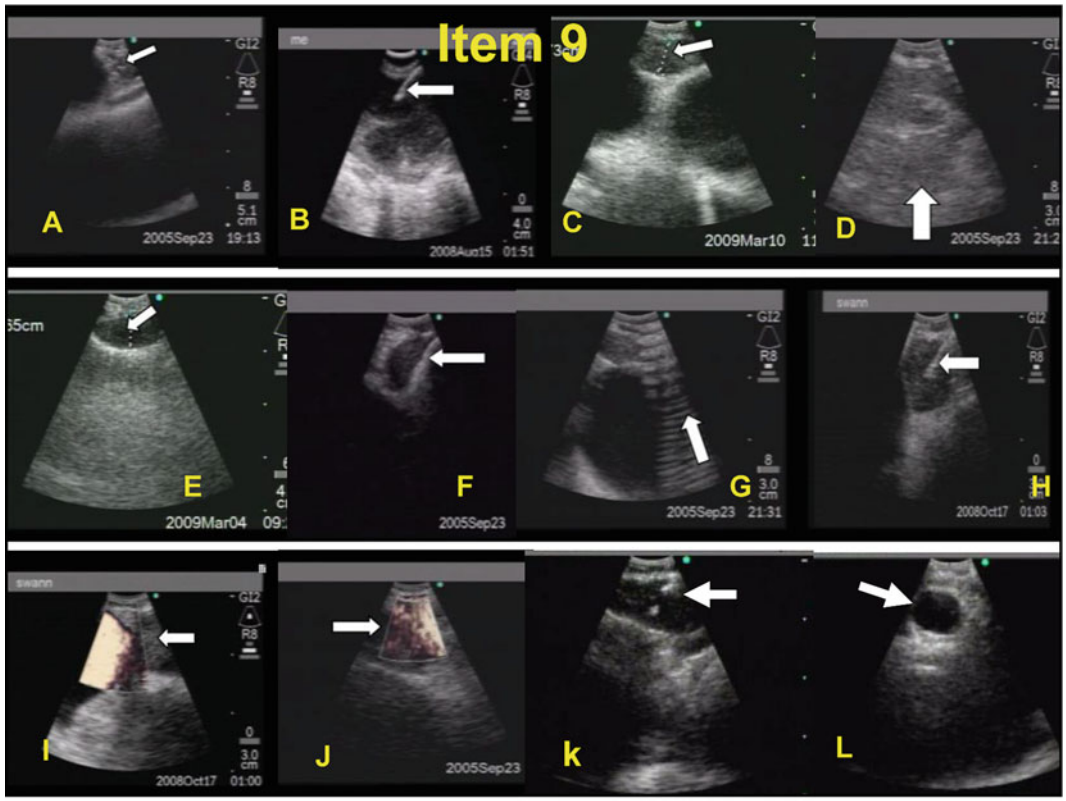
Learner: _____ Year of Training _____
Faculty _____ Date _____

Educational Item* Items 1-10 each scored separately	Satisfactory Yes/No
1. Able to maneuver the scope through upper airway into trachea, without trauma or difficulty (5 points for single item tested) □ Mouth and Vocal cords □ ET Tube □ Laryngeal mask airway	Yes / No Score ____/5
2. Able to maneuver scope using white light bronchoscopy within tracheobronchial tree without trauma (4 points, no partial points) □ Scope centered in airway lumen avoiding airway wall trauma	Yes / No Score ____/4
3. Ultrasound image obtained without artifacts (5 points, no partial points) □ Absence of artifacts on image, any target	Yes / No Score ____/5
4. Identify major mediastinal vascular structures (4 points per item) □ Aorta □ Pulmonary artery □ Superior vena cava □ Azygos vein □ Left atrium	Yes / No Score ____/20
5. Identify lymph node station (Select 3 targets, 5 points each) □ 2R □ 2L □ 4R □ 10R □ 7 □ 4L □ 10L □ 11L □ 11Rs □ 11Ri	Yes / No Score ____/15
6. Able to operate EBUS processor (2 points each item) □ Gain □ Depth □ Doppler	Yes / No Score ____/6
7. Performance of EBUS-TBNA (1 point each, target 15 points) □ Advance needle through working channel (neutral position) □ Secure needle housing by sliding the flange □ Release sheath screw □ Advance and lock sheath when it touches wall □ Release needle screw □ Advance needle using jab technique □ Visualize needle entering target node □ Move stylet in and out a few times □ Remove stylet □ Attach syringe □ Apply suction □ Pass needle in and out of node 10-15 times □ Release suction □ Retract needle into sheath □ Unlock and remove needle and sheath	Yes / No Score ____/15
8. Image analysis: CT scans (1 point each, target 10 points) □ Image 1 □ Image 2 □ Image 3 □ Image 4□ Image 5 □ Image 6 □ Image 7 □ Image 8 □ Image 9 □ Image 10	Yes / No Score ____/10
9. Image analysis: EBUS views (1 point each, target 10 points) □ Image 1 □ Image 2 □ Image 3 □ Image 4□ Image 5 □ Image 6 □ Image 7 □ Image 8 □ Image 9 □ Image 10	Yes / No Score ____/10
10. Decision-making tasks: (2 points each, target 10 points) □ Image 1 □ Image 2 □ Image 3 □ Image 4 □ Image 5	Yes / No Score ____/10

* The combined use of the 10 items tests competencies needed to climb the learning curve from novice to advanced beginner to intermediate to competent bronchoscopist able to independently perform EBUS-TBNA.

FINAL GRADE PASS FAIL **SCORE** _____/100

Fig. 6.5 Example of EBUS-STAT (checklist and one component of the EBUS-STAT image quiz), an assessment tool for endobronchial ultrasound and EBUS-guided transbronchial needle aspiration (STAT = Skills and Tasks Assessment Tool) (*courtesy of Henri Colt, M.D.*)



ITEM 9: Match the photo (A-L) to the corresponding 10 EBUS views (Only one response per description)			
_____ Station 4R adjacent to pulmonary artery superior vena cava and ascending aorta	_____ Needle penetrating through and through	_____ Needle missing target node	_____ Station 4L adjacent to aorta and pulmonary artery
_____ Station 4L adjacent to pulmonary artery	_____ Needle within lymph node	_____ Normal lung	_____ Reverberation artifact
_____ Station 7 adjacent to left atrium	_____ Hilar node adjacent to normal lung	NO RESPONSE	

Fig. 6.5 (continued)

Using Assessment Tools to Guide the Educational Process

Whether learning to play a musical instrument, participate in a sporting activity, or perform a medical procedure, learning requires acquisition of technical skill, facts (cognition), experience, and an understanding about how we relate emotionally to what we are doing (affect). The effectiveness of the learning process depends, in part, on the frequency, variety, quality and intensity of the learning encounter, as well as on the presence, quality, interest, skill and demeanor of the teacher. One's natural talents and predisposition, motivation, and personality come into play, as do the various written, passive, visual, aural, interactive ways that are used to present learning materials.

Just as tasting is a prerequisite to good cooking, assessments are a fundamental part of learning. In health professions education, written tests, performance tests, clinical observation, and other methods of evaluation such as chart reviews and oral examinations are used as a high-stakes tests for certification[9] or licensure, but are also valuable when used as low-stakes assessments[10] that are part of the learning process during the learner's quest for competency[11]. In this case they help document progress along the learning curve,[12] identify gaps in knowledge warranting remedial or individualized training, uncover strengths and weakness of an educational program, may help identify different knowledge levels among a group of trainees or course participants in order to design a more individualized sequence of training, and help determine congruence with self-assessments performed by learners as part of a feedback or debriefing session [41].

When cognitive knowledge is assessed using standardized tests with written multiple-choice questions or oral interviews, questions should ideally be validated using specific criteria that include testing for difficulty and internal reliability. This may not be absolutely necessary when designing assessment tools where learning is the major objective. Assessments, contrary to tests, have the primary purpose of giving feedback to both teachers and learners about gaps in knowledge and how to improve learning. Technical skill assessments, however, to be valuable across a broad range of learners, should probably use measures that are validated in various learning settings, be reliable,[13] and have a strong correlation to the procedure being taught. Checklists can be used to ascertain progress towards competency in various components of a procedure such as ability to obtain informed consent or safe use of fluoroscopy. Checklists also democratize

[9] *Certification* is defined as a process that provides assurance to the public that a medical specialist has successfully completed an educational program and undergone some type of evaluation, which almost always includes a high-stakes written examination that is designed to test the knowledge, experience, and skills requisite to the provision of high-quality care in that specialty (see ACGME—Accreditation Council for Graduate Medical Education).

[10] *Low-stakes* testing usually does not have pass-fail thresholds or carry significant consequences. Such assessment would be consistent with an educational process that emphases a quest towards professionalism and competency (progress along the learning curve), but does not measure skill or knowledge with significant consequences. A *high-stakes* assessment, on the other hand, usually carries significant consequences, such as licensure or pass/fail certification.

[11] *Competency* is the ability gained from knowledge and skills, which forms a basis for performance. To be competent means being able to activate and utilize that knowledge when faced with a problem.

[12] In medicine, a learning curve, also called an *experience curve*, applies to a process where performance improves as a function of practice. This curve may be more or less steep depending on the learner's skill and knowledge, circumstances, experience, and on whether the procedure being learned is new or established. We increasingly tend to differentiate learners into novices, beginners, intermediate learners (also referred to by some as advanced beginners), experienced, and experts, but simpler delineations of beginner, intermediate, and competent practitioner might also be used. Progress along the learning curve usually occurs in steps, with learners remaining, or choosing to remain on a particular plateau that itself may have its occasional dips and peaks.

[13] Reliability is defined as the proportion of reproducible data to random noise recorded by the assessment instrument. Using criterion-referenced testing, concrete criteria are established and the individual is challenged to meet them. This explores what proportion of specific content of knowledge and skills the learners know or are able to perform, as opposed to norm-referenced tests that compare an individual's performance to the performances of a group (see http://www.valparint.com/CRITERIO.HTMreference downloaded May 25, 2012).

knowledge and have the potential to improve safety and quality of care [42].

It is noteworthy that validity evidence refers to the data and information collected in order to assign meaningful interpretation to assessment scores or outcomes designed for a specific purpose and at one specific point in time [43]. Hence, validity refers to score interpretations and not to the assessment itself [44]. While validity has been traditionally divided into *construct*, *content*, *criterion* and *face validity*, Downing and others consider construct validity (a test measuring what it is supposed to measure) as the whole of validity, and validity evidence as both case and time specific.[14]

The Bronchoscopy Education project stresses the importance of using a Mastery training paradigm whereby the eventual expected score on an assessment reflects 100% correct responses because each and every operator should be able to master each of the constituent elements of a safe and effective procedure in order to achieve and document competency. The main variable that distinguishes different learners is the slope of the curve, i.e., the time each learner requires to reach this educational goal [45]. The program's core curriculum, which contains many components of bronchoscopic practice extending from fundamentals of bronchoscopy to endobronchial ultrasound, bronchoscopy in the intensive care unit, and interventional bronchoscopy, can be integrated in part or in whole into ongoing training programs. A program completion checklist helps document a learner's participation in specific components of the curriculum as shown in this example pulled from the Introduction to Flexible Bronchoscopy Program (Fig. 6.6).[15]

[14] In other words, the evidence presented to support or refute the interpretation assigned to assessment that can be used for one test administration and is not necessarily applicable to a different test administration (see Downing and Yudkowsky [44], pp. 22–23).

[15] While user instructions, checklists, and assessment tools are provided in the Bronchoscopy Education Project Faculty Development Training Manual, they can also be obtained from various professional societies (such as the ASER and WABIP) and at http://www.Bronchoscopy.org

The Ethics of Teaching

"We're Doctors" proclaims actor Harry Connick Jr., portraying Dr. Dennis Slamon[16] in his plea for continued research funding in the Lifetime television movie *Living Proof* (Dan Ireland, 2008), about the discovery of epidermal growth factor Her2 and subsequent development by Genentech of the antibreast cancer drug Herceptin. Perhaps this simple statement, more than any other, justifies taking a new look at how bronchoscopy is both taught and learned.

As medical practitioners dedicated to the health and well-being of our patients, it is paradoxical that for the past 40 years, patients have suffered the burden of bronchoscopy-related training. As availability to technology and computer-based learning increases around the world, however, and the cost of using alternative learning materials such as instructional videos, training models, and simulation decreases, educational processes and philosophies will inevitably change. Learners are already less dependent on rote memorization, referring frequently to web-based instruction, digital textbooks, electronic information delivery systems, and social communication media available through their computers and hand-held mobile devices.

Educators interested in the advantages of "scaffolding", a process by which instructional techniques, materials, and other educational resources are used to structure programs that are conducive to the learner's more rapid ascent of the experience curve, will therefore need to revisit how educational materials are packaged and delivered. Furthermore, a health professional's education will need to reflect society's desire for provider competency, accountability, professionalism, and expert medical procedural practice in a world that is rapidly becoming a global village.

Undoubtedly, much of the intrinsic value physicians accord to medical education is derived from knowing that a job is well done and that a patient has been well served. In this sense, both consequentialist (to reduce suffering and

[16] Currently Director of clinical/translational research, UCLA Jonsson Comprehensive Cancer Center.

Introduction to Flexible Bronchoscopy Program Program Completion Checklist

Educational Item*	Completed Yes/No	Assessment Item	Pass/Fail/Incomplete
1. Participation in regional introductory course	Yes / No	Post-test scores Target 12/20 (60% correct) Score _____%	Pass / Fail / Incomplete
2. Assigned reading: *The Essential Flexible Bronchoscopist*	Yes / No	Post-test scores Target 7/10 (70% correct)	Pass / Fail / Incomplete
Module 1	Yes / No	Score _____	Pass / Fail / Incomplete
Module 2	Yes / No	Score _____	Pass / Fail / Incomplete
Module 3	Yes / No	Score _____	Pass / Fail / Incomplete
Module 4	Yes / No	Score _____	Pass / Fail / Incomplete
Module 5	Yes / No	Score _____	Pass / Fail / Incomplete
Module 6	Yes / No	Score _____	Pass / Fail / Incomplete
3.*Sedation module*	Yes/No	Score _____	Pass / Fail / Incomplete
4. *Fluoroscopy Module*	Yes/No	Score _____	Pass / Fail / Incomplete
5. Informed consent, patient safety, and procedural pause simulation workshops	Yes / No Yes / No Yes / No	IC 10-pt Checklist Target 100% Score _____% on each	Pass / Fail / Incomplete
6. Informed consent, patient safety, and procedural pause patient-based scenarios	Yes / No Yes / No Yes / No	IC 10-pt Checklist Target 100% Score _____% on each	Pass / Fail / Incomplete
7. Practical Approach interactive workshop	Yes / No	Subjective scores Target Pass	Pass / Fail / Incomplete
8. Flexible bronchoscopy simulation workshop	Yes / No	Target scores 100% BSTAT _____% TBLB/TBNA ____%	Pass / Fail / Incomplete
9. Flexible bronchoscopy patient-based scenario	Yes / No	Target scores 100% BSTAT _____% TBLB/TBNA ____%	Pass / Fail / Incomplete
10. Proctored case bronchoscopy checklist	Yes / No	FB 10-pt Checklist Target 100% Score _____%	Pass / Fail / Incomplete

*When completed, learners are assumed to be able to perform flexible bronchoscopy independently. Programs may still require observation and faculty presence based on training regulations and preferences.

Fig. 6.6 Program completion checklist from the bronchoscopy education project's introduction to flexible bronchoscopy curriculum (*courtesy of Henri Colt, M.D.*)

avoid retribution) and nonconsequentialist ethical arguments (duty, obligation, and the respect of principles such as beneficence or justice) enhance intrinsic motivation and prompt learners freed from the classroom and the patient's bedside, to improve their skills and knowledge by accessing educational resources using new technologies. Resistance to this shifting paradigm is futile, because learners cannot be denied such access, nor be restrained from obtaining varying points of view regarding a certain procedure or technique in light of the increasing availability of learning materials on the internet. Because many are free, teachers, rather than being fearful of their loss of power and control, should view them as short-cuts to the learning process. By embracing the digital age and encouraging learners to access these resources that might foster dialogue and debate,[17] faculty can use one-on-one time with learners more productively to enhance understanding, rectify erroneous interpretations, and teach how to *think* and *process* information.

Curiously, however, doctors are unfairly expected to be good mentors and effective instructors without ever having learned to teach. As mentioned earlier, this presumption is, for the most part, absent in other fields such as public school, sports, or music education, and represents, in my opinion, a significant shortcoming of our academic institutions and profession. Very few bronchoscopists have been offered seminars specifically designed to teach educational methodologies [46], team dynamics, communication techniques, leadership, presentation skills, or conflict resolution, and even fewer have taken classes in behavioral psychology or learned how to evaluate and relate to students with different individual propensities for learning.[18]

When Learners Teach: The Journey from Novice to Mastery and Back Again

For those interested in teaching, an exciting and fascinating journey lies ahead Physicians already expert at various bronchoscopic interventions, but less knowledgeable about education can experience the thrill as well as the insecurity of becoming novices again. In addition to renewing interests in bronchoscopy-related knowledge and techniques, we can familiarize ourselves with social media in order to facilitate communication with a new generation of learners at a time that is most convenient for both. We can become skillful using programs and devices for editing audio and video files, creating ebooks, constructing learning platforms, and delivering educational materials. We might also explore websites like Cool-math, SuccessMaker, and Kahn Academy to experience how interactive online programs effectively encourage learning.[19] Throughout this journey, we will become increasingly knowledgeable of five structural elements crucial to the educational process: curricular design, content development, instructional methodology, teaching techniques, and flexible assessment tools that accurately measure what is learned and identify what remains to be taught.

> In learning you will teach, and in teaching, you will learn
> From *Son of Man* (1999), lyrics by Phil Collins

[17] Tinsley and Lebak expanded on Vygotsky's contructivist theories, describing a zone of reflective capacity in which adults increased their ability for critical reflection through feedback, analyses, and evaluation of one another's work in a collaborative environment (see Lebak K, Tinsley R. Can inquiry and reflection be contagious? Science teachers, students, and action research. J Sci Teach Educ 2010;21:953–70).

[18] Fenstermacher and Soltis describe a humanistic teaching approach, whereby teachers strive to impart knowledge within an environment in which learning has personal meaning for the learner. By adopting various teaching techniques; facilitator (*coaching*), executive (*modifying the curriculum based on review of assessment results*), or liberationist (*fostering discovery and creativity*); for example, liberationist educators might alter their teaching methods on the spot according to the medical learning environment and to fit the many different ways individual learners learn (italics are mine).

[19] David Ausubel (1918–2008) in his meaningful reception theory where, contrary to rote memorization or discovery learning based on problem-solving, one's knowledge of new material is enhanced if the material is related to relevant ideas within the learner's existing cognitive structure (http://tip.psychology.org/ausubel.html, downloaded December 27, 2010).

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Part II

Tracheobronchial Obstructions

7 Reopening the Airway: Fast Methods—Laser-Assisted Mechanical Resection, Electrocautery, and Argon Plasma Coagulation

Michela Bezzi

Introduction

Central airway obstruction can occur secondary to a number of lung primary, adjacent, or metastatic malignancy and benign processes. It may be extrinsic or intrinsic. Interventional options for central airway obstruction are subject to the availability of experienced personnel and equipment. In addition, the degree of obstruction and severity of symptoms, the nature of the underlying problem, and the patient's overall prognosis and quality of life impact the choice of intervention [1–5].

Endobronchial therapy for malignant tumors is purely palliative and should only be performed in nonsurgical cases. Surgical resection is feasible only in about 25% of patients with lung cancer, and <30% of these survive longer than 5 years. Thus, more than 90% of these patients require palliative treatment. Thirty percent of lung cancers cause obstructions of the trachea and main bronchi [6] with consequent respiratory distress, bleeding, and infection. The technique of endobronchial coagulation and disobstruction plays a pivotal role in all these situations, since conventional treatment with chemo- and radiotherapy is often performed with unsatisfactory results with regard to the endobronchial component of the tumor [7, 8]. Endoscopic coagulation and debulking allow restoring of airway patency, palliation of symptoms, and improvement of quality of life. However, palliation with endoscopic techniques is to be reserved to inoperable obstructive central tumors in symptomatic patients (Fig. 7.1a).

Airway obstruction due to a benign lesion may also be amenable to laser resection. Such lesions include benign tumors, inhaled foreign bodies, stenoses due to granulation tissue, intubation injuries, post-radiation strictures, complications of tracheal or bronchial resection and reanastomosis, or weblike strictures from inhalation injury and also benign exophytic disease with either mucosal infiltration or circumferential narrowing due to granulomatosis with polyangiitis, amyloidosis, or tuberculosis.

If exclusively endoluminal, endoscopic laser resection (laser-assisted mechanical resection, see further) anticipates the acronim LAMR should be the first therapeutic choice for central benign tumors. Surgery should be limited to those cases with partial or exclusive extrabronchial growth.

The advent of endoscopic therapy has also deeply modified the approach to the management of *inflammatory tracheobronchial strictures*. Candidates for bronchoscopic laser resection include those who are not eligible for open resection (because of age, overall medical status, fear of surgery, severity of other underlying disease, or the extent, location, and degree of the stricture), but also severe, dreadfully symptomatic

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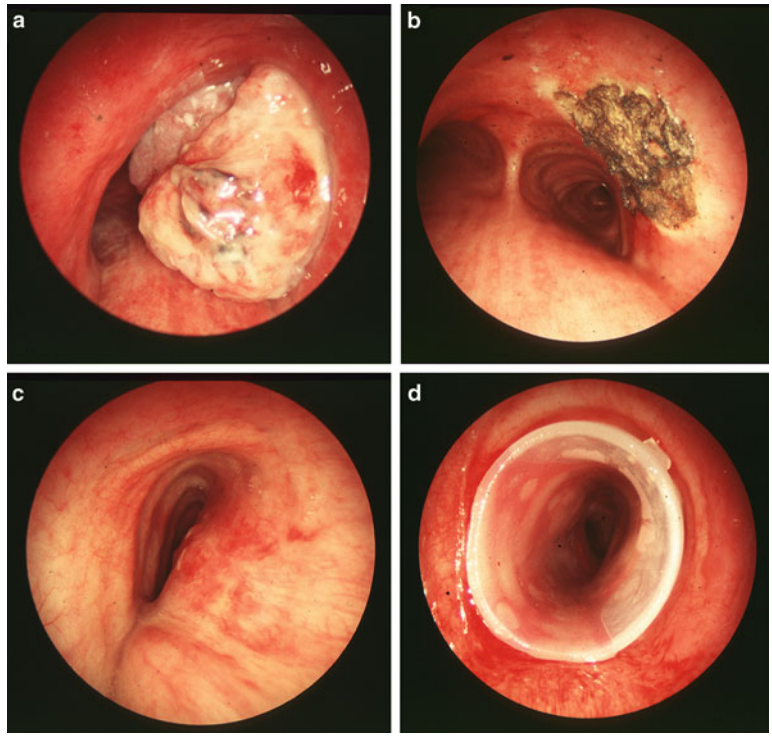

Fig. 7.1 (**a**–**d**) Extrinsic/intrinsic stenosis before and after treatment

stenoses. Interestingly, most simple stenoses (e.g., weblike stenoses or stenoses without cartilage involvement) can be successfully dilated through laser-assisted mechanical dilation, and surgery may no longer be necessary [9].

Clinical Presentation

Central airway obstruction may cause a variety of symptoms, from shortness of breath to respiratory failure and death. The hallmark of severe airway obstruction is impairment of oxygenation and ventilation. Patients may develop symptoms suddenly or more gradually; the onset and progression of symptoms depend upon the nature of the problem (acute with foreign bodies, slowly progressive with an expansive goiter) and the location of the lesion (tracheal vs. bronchial). Symptoms and signs develop when airflow impairment reaches a critical threshold. Patients complain of shortness of breath, which is often constant and unresponsive to bronchodilators. Monophonic wheezing may be present and can be unilateral if the lesion is distal to the carina. Stridor is a sign of severe subglottic or tracheal obstruction. Breathing becomes labored in advanced phases and heralds impending respiratory failure. In the decompensated patient, immediate restoration of ventilation and oxygenation is of vital importance. Patients with minor obstruction are often asymptomatic, since airflow limitation is mild. However, rapid deterioration may occur if swelling or secretions increase the degree of luminal impingement during a respiratory tract infection. It is not uncommon for patients with subcritical lesions to be misdiagnosed as suffering from an exacerbation of asthma or chronic obstructive pulmonary disease (COPD), while the true etiology is anatomic airway obstruction. Patients with airway obstruction also frequently present with pneumonia; if symptoms

and/or radiographic infiltrates do not resolve within 4–6 weeks, bronchoscopy should be considered.

A number of studies are employed to confirm the presence of central airway obstruction and estimate its magnitude: plain chest radiographs are rarely diagnostic. If an airway lesion is suspected and time permits, a high-resolution chest computed tomography (CT) can prove helpful [1]. In a stable patient, spirometry can show the characteristic flattening of the curve on flow volume loops, frequently before abnormalities in the spirometric volumes are noted. Direct bronchoscopic visualization is the gold standard for confirming the presence of airway obstruction and also aids in discerning its underlying etiology. Often, the differentiation of endobronchial or extrinsic lesions can be accomplished only at bronchoscopy (Fig. 7.1a–d).

Management of central airway obstruction requires initial stabilization of the patient with secure access to the airways to guarantee ventilation. Airway interventions can then be considered.

In a stable patient, imaging studies and pulmonary function tests should be obtained as mentioned above. A patient with severe tracheal or bronchial obstruction and marginal lung function requires initial stabilization to secure ventilation and oxygenation. Flexible bronchoscopy can be performed after the airway has been secured (orotracheal tube/deep sedation or general anesthesia) and appropriate gas exchange documented. During the bronchoscopic examination, the airway is inspected, lesions are assessed, distal secretions are suctioned, and diagnostic tissue is obtained if needed. This information is used to plan further interventions aimed at opening an airway and maintaining patency. After the patient has been stabilized, he or she should be transferred to a specialized center where a dedicated airway team is available. In case of severe tracheal obstruction, use of the open ventilating rigid bronchoscope is the preferred method of airway control. The rigid bronchoscope not only provides a secure airway during visualization but also is a therapeutic tool. In emergent cases, the rigid bronchoscope is the preferred instrument for unstable patients and when significant bleeding is expected. The airway can be dilated with the barrel of the scope [2]. During this procedure, the patient is intubated with the instrument under general anesthesia. The optical telescope is advanced through the stenotic airway opening and the barrel then pushed through the obstruction in a rotating motion. Bleeding is usually minimal due to compression of the lesion by the rigid instrument (Fig. 7.2). In one session, using the rigid bronchoscope under general anesthesia, immediate good results can be achieved: bronchial recanalization with improvement of ventilation and/or drainage of post-stenotic secretions. Dilation is immediately effective for intrinsic and extrinsic lesions, but the results are usually not sustained. For this reason, multimodality approaches featuring a combination of several interventions are preferred for their mucosal sparing effects and long-term success over dilation alone [1–3]. The number and scope of therapeutic options have increased dramatically, and a given intervention must be chosen carefully in the context of an individual patient's situation. They can be divided into "slow methods" such as photodynamic therapy, cryotherapy, and brachytherapy or fast methods: laser, argon plasma coagulation, and electrocautery. Fast methods will be the topic of this chapter, whereas slow methods are described elsewhere in this book.

Laser therapy normally integrates rigid bronchoscopic resection; this procedure is worldwide known as laser-assisted mechanical resection (LAMR) and represents the safest and more effective way to obtain all potential effects of laser in bronchoscopy. Some authors use laser with the flexible bronchoscope with limited safety and efficacy if compared to LAMR. The tissue–light interaction leads to thermal tissue damage with vaporization, coagulation, resection, or incision of obstructing lesions [10, 11].

Laser therapy was originally indicated for short endobronchial central airway lesions with a visible distal lumen. Bronchoscopists who become familiar with the technique will use it even in complete stenoses where the distal bronchial tree can only be reached using the suction

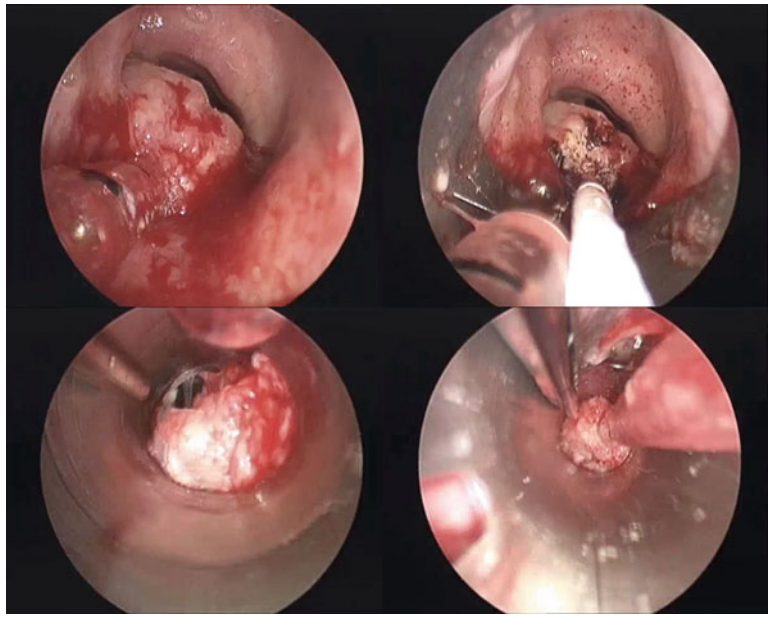

Fig. 7.2 Tumor resection with the rigid bronchoscope

tube and the rigid bronchoscope basing upon precise knowledge of the anatomy and preferably with support from CT scan images. In these cases, the combination of rigid bronchoscopy and laser firing is crucial. The technique is most commonly applied in cases of malignant intrinsic airway obstruction or in postintubation tracheal stenosis. The effects upon airway lumen size are usually immediate and accompanied by excellent control of bleeding.

Electrocautery and argon plasma coagulation also rely on thermal tissue destruction. With electrocautery, a high-frequency current is applied to the lesion with bipolar probes. When the current is directly applied to the tissue, heat develops and leads to tissue necrosis. Electrocautery is traditionally defined as "the poor man's laser," since it can mimic the effects of laser firing when vaporization or resection is needed with a less expensive equipment.

Argon plasma coagulation is a related therapeutic intervention. Argon gas is emitted through a flexible Teflon tube. This gas is ionized because of exposure to high-frequency current, and an electrical arc is formed which allows for desiccation and tissue destruction. It is a valuable tool in treating superficial bleeding and debulking granulation tissue and tumors.

Indications, equipment, application, and outcomes of these techniques will be extensively discussed hereafter.

Laser-Assisted Mechanical Resection

History and Historical Perspectives

Until the early 1980s, the endoscopic treatment of central airway obstructions was hazardous and often inadequate. Mechanical resection was performed using the rigid bronchoscope and rigid biopsy forceps with high risk of bleeding. Even when successfully managed, it often provided only short-term results. Endoscopic electrosurgery and cryotherapy were then introduced to reduce the risk of bleeding and prolong palliation. Nonetheless, these methods provided only delayed recanalization also carrying an unpredictable risk of damage to adjacent healthy tissue. The advent of laser immediately proved very

useful in reducing hemorrhages. Once an appropriate technique for the treatment of the implantation base was developed, laser coagulation in depth proved also quite effective in prolonging palliation in central airway obstruction due to lung cancer. Bronchoscopic mechanical resection turned then into laser-assisted mechanical resection (LAMR).

Indications and Contraindications

Bronchoscopic laser resection (LAMR) can relieve malignant and benign intraluminal tumors, particularly exophytic proximal airway lesions, but it has no role when the obstruction is caused by extrinsic compression [12, 13]. Laser is also useful in the treatment of benign diseases such as cicatricial tracheobronchial stenoses.

Benign and Malignant Tumors

Although rare, benign tumors are the best indication for laser therapy. If exclusively endoluminal, endoscopic laser resection should be the first therapeutic choice for such tumors, as they are usually polypoid and rarely recur if the tumor base can be well photocoagulated with the laser. Surgery should be limited to those cases with partial or exclusive extrabronchial growth.

Airway obstruction from bronchogenic carcinoma is the most frequent indication for laser resection. It is typically employed in patients who have exhausted their therapeutic options, although some may be eligible for salvage chemotherapy, brachytherapy, or surgical resection [2, 3, 14].

Other malignant causes of central airway obstruction that have been managed by laser resection include not only the so-called low-grade malignancy such as adenoid cystic carcinoma, mucoepidermoid carcinoma, and bronchial carcinoids but also endobronchial metastases from melanoma and colon, kidney, and breast cancer [15, 16].

The major aim of laser therapy in malignant central airway obstruction is to recanalize the tracheobronchial tree and restore adequate ventilation and/or drainage of post-stenotic secretions. It is the location and macroscopic appearance of a tumor, rather than its histological type, which determine whether or not laser therapy can be carried out. Because of accessibility, the best results are obtained in tumors located in the trachea or main bronchi which are also where obstruction causes the greatest respiratory distress. On the contrary, tumors obstructing segmental bronchi do not impair ventilation to the degree that severe symptoms are produced. Furthermore, reduced accessibility with the laser fiber and the thin walls of these bronchi increase the difficulty of laser delivery and the risk of perforation. The sole indications for laser disobstruction of segmental bronchi are drainage of distal purulent secretions (postobstructive pneumonia) and cure of benign tumors.

It is very important for the endoscopist to identify the base of the obstructing endobronchial tumor. Polypoid tumors are easy to remove and often completely resectable (Fig. 7.3a and b). Intraluminal tumors which also infiltrate the bronchial wall cannot be treated completely. Though if the airway lumen is not seriously reduced by tumor infiltration, ventilation is usually not impaired appreciably and laser resection may not be necessary.

For occluding endobronchial tumors with an extraluminal component or with significant mediastinal growth, laser treatment alone is frequently unsuccessful. Although the endoluminal growing component may be initially successfully removed, the airway is quickly re-obstructed as a result of further growth, extrinsic compression, and endoluminal migration of the tumor. In these cases, laser treatment is to be considered as preliminary to stenting or, if the extraluminal component is only peribronchial, to brachytherapy. Pure extrinsic compression is a major contraindication for endoscopic laser treatment.

Regardless of impact on ventilation, location, or macroscopic appearance, vascular tumors producing hemoptysis represent a good indication for laser bronchoscopy. Although the tumor is often not completely resected, short-term reduction or ceasing of bleeding occurs systematically after laser coagulation.

In all of the previous conditions, endoscopic resection allows a precise assessment of the

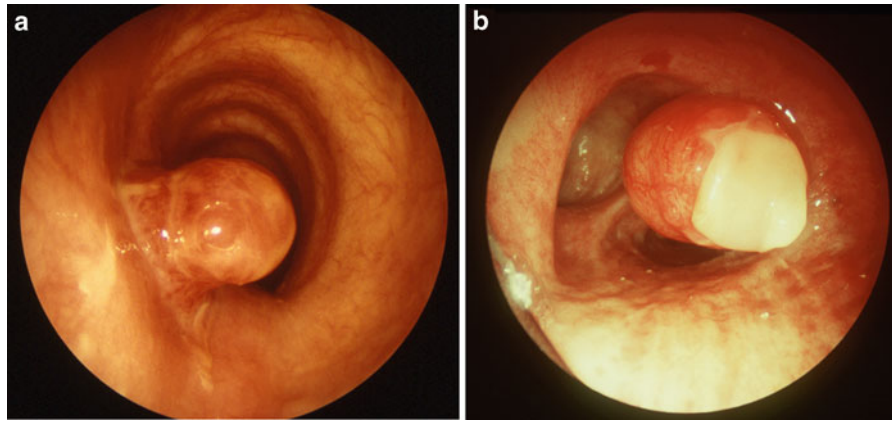

Fig. 7.3 (**a**, **b**) Polypoid lesions

extent of the tumor, shifting to surgery patients originally considered to have inoperable disease or allowing lung-sparing resections [17].

The combination of endobronchial laser therapy with other palliative therapies is possible and can be extremely advantageous. The addition of radiotherapy is particularly useful by either external beam radiation or endobronchial brachytherapy, with extension of the palliation. When indicated, laser resection will be performed before radiotherapy, because preventive laser recanalization of obstructed airways allows improved functional status. Furthermore, it is well known that radiotherapy and chemotherapy are poorly effective on the endoluminal component of the tumor [7, 8]. Similar therapeutic algorithms for the management of central airway neoplastic obstructions have been described by different authors [18–20].

Here is how we proceed (Fig. 7.4).

Tumors with Uncertain Prognosis

Tumors with uncertain prognosis lump together several tumors characterized by slow growth and rare tendency to metastasize; among these carcinoid tumors, adenoid cystic carcinomas and mucoepidermoid carcinomas are the most common. The same histological type can present with different grades of malignancy. As for malignant tumors, laser therapy is mainly palliative or in some cases useful for a better surgical assessment.

Local cure may be achieved when the tumor has a small and localized base and a low-grade malignancy. This different therapeutic approach in relation to the different tumoral characteristics is to be considered for typical carcinoid tumors. Atypical carcinoids, i.e., well-differentiated neuroendocrine carcinomas, deeply infiltrate the bronchial wall and produce an appearance similar to the bronchogenic carcinoma. In most cases, the tumor cannot be removed completely, and recurrence after laser resection is almost always expected. On the contrary, typical carcinoids can be considered as more benign lesions; their macroscopic and microscopic aspect is similar to benign neoplasms, i.e., central well-differentiated neuroendocrine tumors, normally growing exclusively inside the bronchial lumen as polyps with a narrow base. In these cases, laser-assisted mechanical resection may be curative (Fig. 7.5) [21, 22].

Inflammatory Disease

Airway obstruction due to an inflammatory lesion may also be amenable to laser resection. Such lesions include inhaled foreign bodies, stenoses due to granulation tissue, intubation injuries or

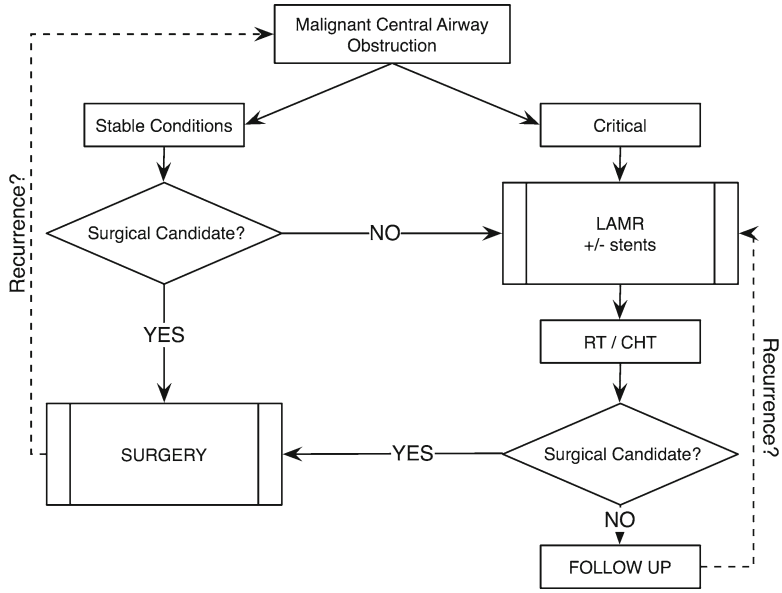

Fig. 7.4 Algorithm for the management of malignant central airway obstruction

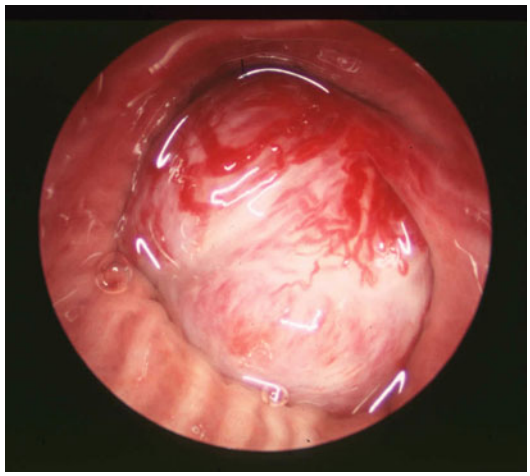

Fig. 7.5 Carcinoid tumor

post-radiation, lung transplantation, post-resection and reanastomosis strictures, benign exophytic disease with either mucosal infiltration or circumferential narrowing due to granulomatosis with polyangiitis (formerly called Wegener's granulomatosis), amyloidosis, tuberculosis, or endometriosis [23]. Generally speaking, patients who have inflammatory airway strictures due to causes other than infection should always be considered for open surgical resection [2, 3]. Candidates for bronchoscopic laser resection include those who are not candidates for open resection because of age, overall medical status, fear of surgery, severity of other underlying disease, or the extent, location, and degree of the stricture. However, the advent of endoscopic therapy has deeply modified the approach to the management of iatrogenic tracheobronchial strictures [24, 25]. In particular, immediate laser recanalization must be considered as the first-choice treatment in painfully symptomatic and ingravescent close stenosis, with risk of death for the patient, allowing to avoid urgent tracheotomy which could produce further problems. It is always possible to obtain a rapid and immediate good result, independently of the type of stenosis. Once the emergency has been handled, there is more time to consider the best treatment strategy (Fig. 7.6a and b). In case of relatively indolent stenoses without severe ventilation impairment, endoscopic therapy should be considered as an alternative to open surgery when the latter is contraindicated. Even patients eligible

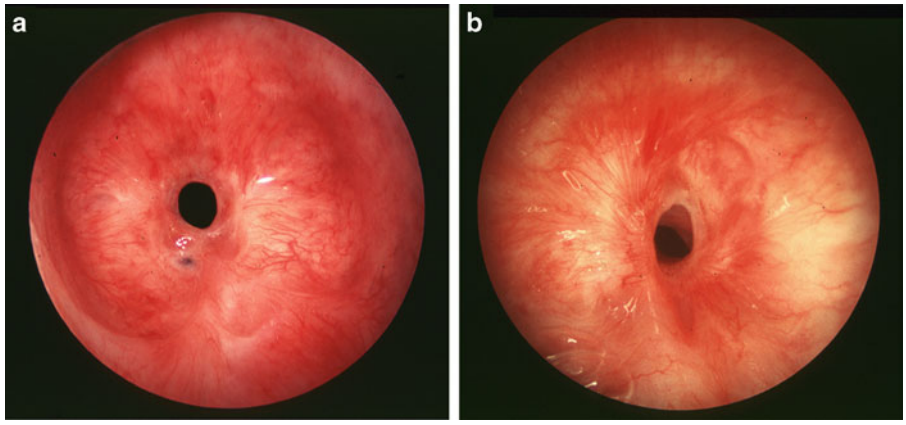

Fig. 7.6 (**a**, **b**) Severe tracheal stenoses

for resection could benefit from a preliminary endoscopic treatment, to allow stenosis stabilization and precise delimitation. Complications to open surgery such as granulomas or restenosis can be effectively treated endoscopically. In some selected simple stenoses (e.g., weblike stenoses or stenoses without cartilage involvement), stable good results can be achieved after laser-assisted mechanical resection, and surgery could no longer be necessary [25–27].

Description of the Equipment Needed

The word LASER is the acronym of light amplification of stimulated emission of radiation. The main components of a laser are the laser cavity, the pumped material, and the pumping system. The cavity is a reflecting cylindrical camera with mirrors at each extremity, one of which is partially reflective. When, inside the camera, an active substance is electrically or optically stimulated, it spontaneously emits photons which are reflected by the mirrors through the active substance itself producing new photons with the same wavelength (and energy) and direction. The result of this stimulated radiation is a laser beam. The wavelength depends on the nature of the active material that is stimulated. For example, Nd:YAG laser emits in the infrared range at 1.064 nm.

The main characteristics of a laser beam are:

- Coherence (the waves emitted are in phase)
- Collimation (the waves are parallel to each other)
- Monochromaticy (the waves are all of the same length)

These properties allow concentration, without loss of power, of the laser beam on a small target. When using laser, one should always have a precise knowledge of a few physical aspects:

- *Laser power* is the power erogated by the laser machine and can be exclusively regulated through the laser equipment. It is measured in watts (W):

$$\text{Laser Power} = \text{Watts (W)}$$

- *Laser energy* is affected by the time of exposition in a physically determined manner:

$$\text{Laser Energy (Joule)} = \text{Power (Watts)} \times \text{time (s)}$$

- *Laser power density* is strongly dependent on the extension of the impact surface:

$$\text{Power Density (Watts / cm}^2\text{)} = \frac{\text{Laser Power (Watts)}}{\text{Surface (cm}^2\text{)}}$$

Releasing high power density can cut and vaporize living tissue. A lower power density laser can rather coagulate tissue determining necrosis or hemostasis without loss of substance. The interaction between laser and living tissues also depends on many other factors, such as wavelength, distance from fiber to target, angle of incidence, color of impact surface, exposure time, absorption, and penetration in depth of the radiation. The thermal effects are the best known and the most used.

With regard to temperature, below 50°C, we obtain tissue necrosis and inflammation, and at a higher temperature, vaporization is observed. Power density is inversely proportional to square distance. Penetration, which is inversely proportional to absorption, depends on the frequency of the radiation, tissue color, and its vascularization. There are many types of biomedical lasers, including the carbon dioxide (CO_2) laser, neodymium–yttrium–aluminum–garnet (Nd:YAG) laser,neodymium–yttrium–aluminum–perovskite (Nd:YAP) laser, argon ion laser, excimer laser, potassium titanyl phosphate (KTP) laser, alexandrite laser, diode lasers, pulse dye lasers, and the most recent thulium laser. CO_2 laser was the first laser used in bronchoscopy. It is invisible (10,600 nm in infrared range) and is transmitted to the tissue through an articulate arm composed of mirrors. These characteristics limit its application in bronchial endoscopy. Biologically, tissue vaporization is precise and efficient because of low penetration in depth; yet low penetration determines poor hemostasis. The laser that is most commonly used for bronchoscopic laser resection is the Nd:YAG laser. Its energy is delivered through flexible quartz fibers that are inserted through either a rigid or flexible bronchoscope. The wavelength of this laser (1,064 nm) is invisible; thus, a red helium–neon beam is used to indicate where the laser energy will be applied. It delivers sufficient power to vaporize tissue, also producing a good coagulating effect. The active substance is a crystal of yttrium–aluminum–garnet doped with neodymium. A 1,320 nm Nd:YAG laser is also available with greater cutting and vaporization effects, especially in low-vascularized tissues with high water content.

Coagulation and vaporization are produced by a thermal effect which is not limited to tissue surface: the laser beam can be transmitted as deep as 1 cm. This radiation is differently absorbed by tissues, depending on the color of the surface and laser power density. The beam can pass through a pale and low-vascularized tissue without a visible effect, but it will be absorbed by a dark surface limiting penetration in depth.

Diode laser is a newly conceived laser exploiting a semiconductor diode technology. When electrical current passes through a diode, it emits a laser radiation. Diode technology reduces problems related to the laser cavity complexity, allowing the design of portable, compact, and high-power air-cooled lasers. It is available in different wavelengths (808, 940, 980, and 1,470 nm). The 808 nm and 940 nm is exclusively absorbed by hemoglobin, making this laser very useful for treating highly vascularized tissues, but absolutely indolent if fired on a white surface. The 980 and 1,470 nm is also well absorbed by water, so very effective when treating white tissues too.

Nd:YAP laser: the active substance is yttrium–aluminum–perovskite, with a wavelength of 1,340 nm, which is absorbed by water 20 times more than the 1,064 nm of the Nd:YAG, thus providing a better effectiveness/power ratio. Coagulation is particularly good.

Thulium laser has recently been considered for endobronchial application. The 2 μm wavelength emitted by Cyber™ (thulium) laser is strongly absorbed by water, resulting in an outstanding coagulation and aerohemostatic effects with preservation of the surrounding tissue. Since 2 μm laser wavelength is strongly absorbed by water which is ubiquitous in all tissues, the speed of cutting and vaporizing will remain relatively constant regardless of tissue vascularization. Energy from the thulium laser penetrates only a fraction of a millimeter of the tissue, with a high degree of control and substantially reduced risk of inadvertent injury.

In practice, the ideal laser in bronchoscopy should be transmissible by fiber, safe, easy to set up and use, cheap, and portable. It should produce many and sometimes opposite specific

effects: excellent coagulation so as to control bleeding and different resecting modes according to clinical occurrence. For cicatricial stenosis, mainly postintubation tracheal stenosis, lasers should be as precise as a scalpel to spare the surrounding tissues; on the contrary, for endoluminal neoplastic masses, a vaporizing effect on large volumes is needed. More importantly, high penetration of energy without loss of substance, producing deep thermal damage and consequently a cytocidal effect, is required to treat the tumor base in depth and delay (malignant tumors) or even prevent recurrences. This is the principle for cure in benign, strictly endoluminal tumors, typical carcinoids, carcinoma in situ, and early cancers. All these characteristics do not perfectly coexist in the same laser, so the interventional pulmonologist has to choose the best compromise or use more than one tool.

Application of the Technique

Most bronchoscopic laser resection will be performed via rigid bronchoscopy in the operating room with general anesthesia [28–30]. In fact, laser therapy normally integrates rigid bronchoscopic resection; this procedure is worldwide known as laser-assisted mechanical resection (LAMR) and represents the safest and more effective way to obtain all potential effects of laser in bronchoscopy. Some authors use laser with the flexible bronchoscope with limited safety and efficacy if compared to LAMR. It is performed in a specially equipped bronchoscopy suite with topical anesthesia and conscious sedation. LAMR is performed using general anesthesia; the patient's oxygenation and ventilation are supported through the rigid bronchoscope by spontaneous-assisted ventilation or jet ventilation [11, 17, 31]. Intermittent negative-pressure ventilation (poncho) is associated with lower incidence of complications such as acidosis due to hypercapnia (Fig. 7.7) [32]. Muscle relaxants and paralytic agents can be helpful during general anesthesia because they prevent the patient from coughing during resection and they facilitate insertion of the rigid bronchoscope. The four main effects laser can provide are *coagulation*, *resection*, *vaporization*, and *incision* (Table 7.1).

Laser resection is generally facilitated by the use of the rigid scope in the so-called laser-assisted mechanical resection already mentioned before. It follows *laser coagulation* which involves directing the laser at the target lesion, devitalizing the lesion via photocoagulation of the feeding blood vessels, so that the devitalized tissue can be more easily removed with the beveled edge of the bronchoscope, forceps, or suction minimizing the risk of bleeding. Coagulation is possible because laser penetrates tissue to a depth of up to 10 mm in an inverted cone fashion and provides reliable photocoagulation at this depth. Its power density can be altered by moving the laser closer to or farther from the target tissue. *Laser vaporization* is possible because energy from laser is relatively well absorbed by water. It involves aligning the laser parallel to the bronchial wall and aiming at the edge of the intraluminal lesion (the laser should never be discharged perpendicular to the airway wall because of an increased risk of perforation). It can also be performed through the flexible scope; in this setting, laser pulses of only one second or less are used to vaporize the tissue to prevent thermal injury to the scope and airways. On the contrary, when performed in rigid bronchoscopy, laser can be used for longer periods of time reaching higher temperatures with higher power densities. This is possible because laser debris and smokes can be effectively suctioned by the suction tube inserted through the scope minimizing the risk of injury. Laser vaporization applied using a fiber-optic bronchoscope should be limited to small non-bleeding lesions, to refine and complete treatments previously performed with the rigid scope and, through a tracheal tube, for treating neoplasms in the upper lobe bronchi, in distal locations, and for distal tracheobronchial toilette.

The channel of the rigid bronchoscope is wide enough to ensure ventilation and passage of telescopes, suction tubes, and laser fiber. Simultaneous laser coagulation of a bleeding site and suction of blood and clots is very important when dealing with airway hemorrhage. In addition, the rigid bronchoscope allows mechanical resection of

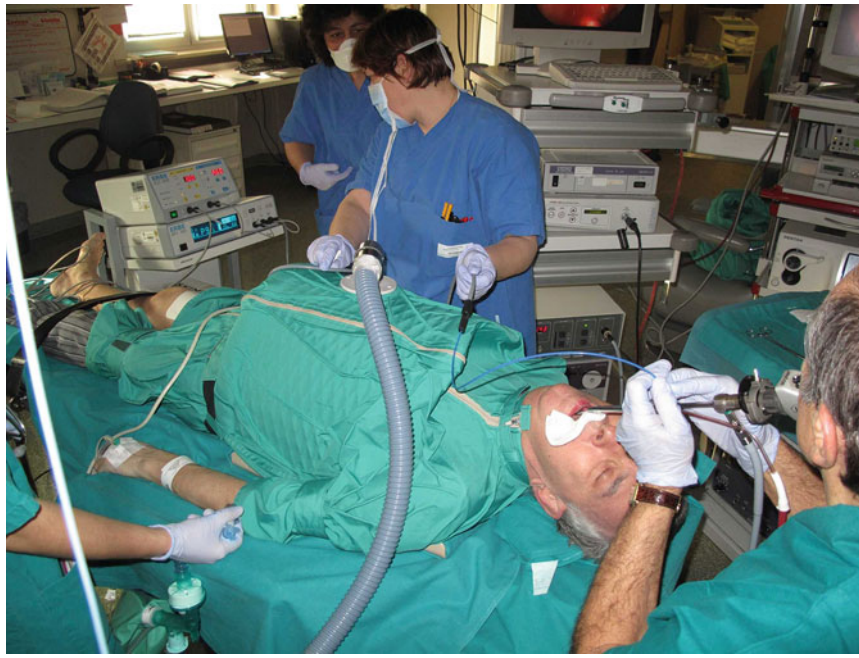

Fig. 7.7 Intermittent negative-pressure ventilation (poncho)

Table 7.1 Laser techniques

Techniques		
Laser vaporization	Flexible bronchoscope	Up to 90% of cases. Time consuming but can be effective
	Rigid bronchoscope	Rare; for control of bleeding and vaporization of tumor remnants after mechanical resection
Laser resection	Rigid bronchoscope (LAMR)	To reduce risk of bleeding during tumor debulking
Laser coagulation	Rigid bronchoscope	To prevent bleeding before mechanical resection To treat implant base in depth (up to 5 mm) and delay recurrence
Radial incision	Flexible/rigid	Performed to reduce tension of cicatricial stenoses (before dilation if rigid scope is used)

polypoid tumors, previously coagulated with laser, which saves considerable time over laser vaporization. For all these reasons, most bronchoscopists prefer rigid bronchoscopy, although a flexible bronchoscope is to be available if the airway abnormality is within a distal segmental bronchus and also to remove blood and debris from the distal airways. In the treatment of cicatricial tracheal stenosis (e.g., postintubation web-like stenoses), laser is used in contact mode to perform radial incisions before a mechanical dilatation is obtained with rigid bronchoscopes of progressive caliber. The radial incisions permit to reduce tension with minimum heating of the adjoining tissue, thus limiting recurrence [33–35]. Other authors described a different technique with repeated small radial incisions in contact mode through the flexible bronchoscope [36].

Most laser resection teams are comprised of a bronchoscopist, an anesthesiologist experienced with interventional pulmonology techniques and airway management, an endoscopy nurse familiar with the equipment, and a second endoscopy nurse who assists the bronchoscopist and controls

the laser settings. General anesthesia is usually more comfortable for both the patient and the operator; it allows maximal control of ventilation and immediate management of complications. Anesthetic agents that are rapidly eliminated or readily reversed should be used so that the patient can be rapidly reawakened and postoperative mechanical ventilation can be avoided. Regardless of the type of anesthesia, the laser endoscopist and the anesthesiologist need to work in close agreement throughout the procedure, adapting to mutual needs.

For endobronchial tumors, the most common indication for laser treatments, the use of a rigid bronchoscope is crucial since the most evident part of the maneuver, i.e., the obstructing mass removal, is mechanically performed. In this setting, laser is more efficiently used to coagulate the endoluminal mass before the mechanical resection to avoid or reduce bleeding and to treat in depth the implantation base of the tumor in order to delay recurrences or to achieve cure in case of benign tumors, selected typical carcinoids, early cancers, and carcinoma in situ.

A proposed technique for laser treatment of endobronchial tumors consists in initial low-power Nd:YAG laser firing (<30 W) to coagulate the tumor followed by removal of the endoluminal portion of the lesion with the tip of the rigid bronchoscope, the biopsy forceps, and the suction tube. High-power settings (50–60 W) are then employed to vaporize the residual endoluminal tumor. At the end of the procedure, the base of the lesion is exposed to low-power settings with long pulses (20–30 W for 4–5 s; 2,000 J/cm^2) to obtain a cytocidal effect in depth within the airway wall. Dark-colored tissues (e.g., charred or hemorrhagic tissue) and large lesions require special consideration. With respect to dark tissues, laser coagulation in depth is limited because the dark color enhances tissue absorption, limits deep tissue penetration, and reduces deep photocoagulation. To avoid charring and vaporization due to radiation absorption on the surface and to obtain coagulation in depth, the laser fiber must be kept at a sufficient distance from the tumor surface and directed a little bit more tangentially to the bronchial wall, thus obtaining, because of the divergence of the beam, an increase of the diameter of the spot and therefore a reduction of the power density.

With respect to large lesions, firing with laser in full tumor is not advisable. It is time consuming and uselessly risky to reduce the whole endoluminal mass by charring and vaporizing it with laser. Bronchoscopic laser resection should only be performed by bronchoscopists who have advanced training and experience. Bronchoscopists and team members should remain familiar with techniques, potential complications, and necessary precautions [37]. To minimize the risk of combustion:

- The fraction of inspired oxygen should be kept below 40% during laser firing [38].
- Power settings should not exceed the maximum recommended for the laser being used (60 W for the Nd:YAG laser).
- Flammable materials (including silicone stents) should be kept far away from the operating field.
- Adequate suction must be available to remove the combustible laser plume (the smoke caused by vaporization of tissues) [39].
- If a flexible bronchoscope is employed, the laser must be kept a sufficient distance beyond the tip of the bronchoscope.

Video systems allow all personnel to observe the procedure, which makes it easier for assistants to anticipate the needs of the bronchoscopist and the patient. Many bronchoscopic laser resection procedures are performed in <1 h [40].

Evidence-Based Review

Outcome data regarding bronchoscopic laser resection are sparse. However, it appears to be a rapid and safe method to relieve airway obstruction. A case series that included 2,610 laser resections in 1,838 patients with malignant airway obstruction found that airway patency improved and symptoms were palliated in over 90% of patients [17]. In this series, the rigid bronchoscope was used in 92% of the treatments that were performed almost always under general anesthesia. The fiber-optic bronchoscope—alone—was used

in <10%. In 93% of the patients with endobronchial malignant obstruction, Nd:YAG laser therapy allowed the patency of the central airways and avoided the most distressing symptoms of the disease, enhancing the patient quality of life. The location and macroscopical appearance of the lesion play the greatest role in determining the success of the procedure: for tumors involving the trachea and main bronchi, immediate results were almost always excellent (>95%). The median time between a first and second palliative treatment was 102 days. Mortality was <1% within 7 days of the procedure.

Smaller series have reported similar results [11], while a larger series reported that death occurred in only 15 out of 5,049 patients (0.3%) and serious complications occurred in only 119 out of 5,049 patients (2.4%) [41].

In 38 typical carcinoids and in more than 150 benign tumors, in which the base of the lesion was reached, laser therapy was curative. These results were achieved in exclusively endoluminal polypoid tumors in which coagulation of the lesion and mechanical resection were followed by a systematic treatment of the base of the tumor with low-power setting and long exposure time, avoiding tissue loss while still obtaining a cytocidal effect in depth. Overall mortality rate was 0.25% [42].

In benign stenoses and particularly in postintubation tracheal stenoses, laser-assisted mechanical dilation can guarantee cure in up to 66% of cases, 100% when only cicatricial weblike stenoses are considered [9].

Complications of bronchoscopic laser resection are infrequent, but they include hypoxia, hemorrhage, airway wall perforation, airway wall necrosis, and fistula formation. Hypoxia, whether due to general anesthetic or to major bleeding, may lead to irreversible cardiovascular complications and thus must be corrected promptly by bleeding suction and ventilation control. Adequate control of hemorrhage and ventilation can only be assured with the rigid bronchoscope. Other possible complications include perforation of the airway with resulting mediastinal emphysema, pneumothorax, or infection. Perforation is unlikely if the procedure is performed by experienced endoscopists familiar with rigid bronchoscopy. Airway fires have been reported, particularly when flexible fiber-optic instruments are used. Fortunately, this complication is quite rare. Arterial air embolism has been anecdotically reported as a complication of bronchoscopic laser resection. Studies of laser procedures performed during continuous transesophageal echocardiographic monitoring suggest that air emboli may be caused by coolant gas (which exits the bronchoscope under high-flow and high-pressure conditions to cool the laser probe) entering the pulmonary venules and gaining access to the systemic circulation [43]. The frequency of this complication may be reduced by maintaining the laser fiber coolant airflow at the minimum level and avoiding direct contact between the laser probe and tissue.

Summary and Recommendations

- Bronchoscopic laser resection has to be considered as a part of a more complete treatment called "laser-assisted mechanical resection/dilation—LAMR/LAMD." It is rapid, effective, and repeatable and may be complementary to other therapies.
- Bronchoscopic LAMR/LAMD is used to relieve malignant or benign intraluminal airway obstruction. It has no role when the obstruction is caused by sole extrinsic compression.
- In malignant stenoses, LAMR consists of (a) firstly laser coagulation, (b) then mechanical resection, and (c) finally low-power laser treatment in depth of the implantation base.
- The type of laser that is most commonly used for LAMR is the neodymium–yttrium–aluminum–garnet (Nd:YAG) laser. It relieves airway obstruction by either resecting or vaporizing the obstructing lesion.
- Bronchoscopic laser resection should only be performed by bronchoscopists who have advanced training and experience.
- Complications are infrequent, but they include hemorrhage, airway wall perforation, airway wall necrosis, fistula formation, and air embolism.

Endobronchial Electrocautery and Argon Plasma Coagulation

Introduction and Definition of the Procedure

Several techniques are available for the bronchoscopic treatment of obstructing tissue in the tracheobronchial tree. Of these options, only laser-assisted mechanical resection (LAMR, already discussed above), argon plasma coagulation (APC), and electrocautery produce rapid tissue destruction in a single session and are therefore appropriate to treat lesions that are producing acute respiratory distress or hemoptysis. The neodymium–yttrium–aluminum–garnet (Nd:YAG) laser is commonly used in this situation, but expense limits the availability of laser equipment in many parts of the world. Endobronchial electrocautery and argon plasma coagulation (APC) are alternative modes of thermal tissue destruction that may be used via the flexible or rigid bronchoscope. Electrocautery could be called "the poor man's laser," because it also produces rapid thermal destruction of tissue but does so relatively inexpensively by means of electric current rather than laser light [44, 45]. Argon plasma coagulation (APC) is also an electrosurgical technique used to resect an obstructing lesion and/or to achieve hemostasis [46, 47]. The history, principles, equipments, and techniques of endobronchial electrocautery (also referred to as electrofulguration, diathermy, electrocoagulation, thermocoagulation, or electrosurgery) and argon plasma coagulation (APC) will be reviewed here. In addition, their indications, contraindications, and complications are presented.

History and Historical Perspective

Electrocautery was first used in the 1930s to treat rectal cancer [48]. Endoscopic electrocautery subsequently has found wide use in the treatment of gastrointestinal lesions, such as colonic polyps, bleeding vessels, and biliary stenoses.

Initial reports of the potential utility of electrocautery in the treatment of tracheal and bronchial tumors also appeared in the 1930s [49–51], but complications such as burns, tracheal perforation, and fatal hemoptysis dampened enthusiasm for the technique [52]. Refinements of the electrodes and other hardware and the use of more sophisticated generators of high-frequency current have improved the efficacy and safety of bronchoscopic electrocautery and have led to a renewed interest in the technique. Nonetheless, the literature describing palliative electroresection is limited, and most pulmonologists remain unfamiliar with its use.

A relatively new development is the noncontact mode of argon beam coagulation or argon plasma coagulation (Fig. 7.8). It was meant to improve surgical hemostasis. Its use gradually expanded in the early 1990s when a flexible probe was introduced that could be used via a flexible scope. Since then, APC has been used during bronchoscopic procedures to debulk malignant airway tumors, control hemoptysis, remove granulation tissue from stents or anastomoses, and treat a variety of other benign disorders [44–50].

Indications and Contraindications

Electrocautery and APC are used to treat central endobronchial benign or malignant airway lesions [46, 47, 53–56]. The most common indication for these techniques is resection of an obstructing airway lesion that is associated with dyspnea, hemoptysis, cough, or postobstructive pneumonia. Treatment may be curative or palliative. Characteristics of lesions that are associated with improvement of a patient's quality of life following palliative resection include polypoid shape, large endobronchial component, location in the trachea or mainstem bronchus, and a short length. It is also favorable if the airway lumen can be visualized beyond the lesion and the distal lung is still functional.

Malignant tumors—Symptomatic airway obstruction caused by bronchogenic carcinoma is the most common indication for endobronchial electrocautery and APC in patients who are not

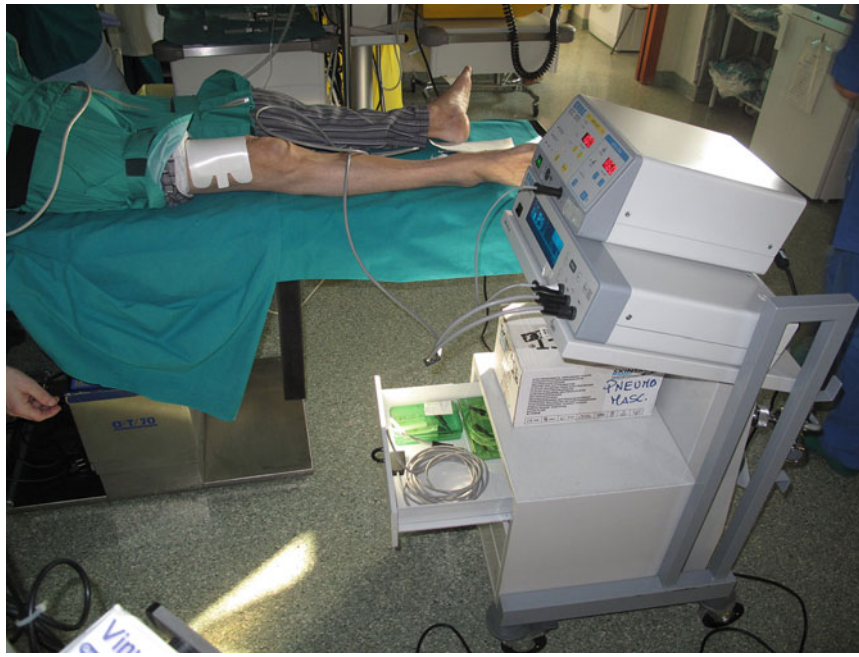

Fig. 7.8 Argon plasma coagulation

operative candidates [57–60]. Endobronchial electrocautery has been used to treat other causes of malignant airway obstruction as well, including endobronchial metastases. Such resections are only palliative if the lesion is malignant. Indolent malignant tumors such as bronchial carcinoids are less common but may also be treated effectively with endobronchial electrocautery [54–57] as well as radiographically occult intraluminal microinvasive lung cancer. Whether APC can cure early lung cancer is not fully established. The fact that endobronchial electrocautery has been shown to cure early lung cancer suggests that APC may do the same.

Benign lesions—Endobronchial electrocautery can be used to treat benign obstructing lesions of the central airways such as granulation tissue, hamartomas, papillomas, and lipomas. Another setting in which endobronchial electrocautery is used to treat benign disease is when there is granulation tissue obstructing metal or hybrid stents. Indications for APC include benign polyp removal, hemostasis, and debridement of granulation tissue around endobronchial stents. The penetration depth of the argon plasma is reliably 2–3 mm, which makes APC a valuable tool in treating superficial bleeding.

Endobronchial lesions may cause hemoptysis or postobstructive pneumonia, both of which can be successfully treated with endobronchial electrocautery. Treatment (and prevention) of postobstructive pneumonia requires the restoration of at least partial airway patency. This can be achieved using endobronchial electrocautery.

Extrinsic compression of the airway is a contraindication to electrocautery and APC. In this circumstance, there is no endobronchial tumor to remove, and these techniques can produce a hole in the bronchus. Electrocautery with unipolar electrodes can deprogram cardiac pacemakers or implanted defibrillators and should be undertaken with caution in such patients [61].

Description of the Equipment Needed

Similar to laser tissue destruction, the effect of both endobronchial electrocautery and APC is

determined by heat and tissue interaction and is fairly rapid. Heat is created through the application of high-frequency electric currents to coagulate or vaporize tissue. The difference between the two procedures centers on the fact that APC is a noncontact mode of tissue coagulation. Dedicated operators use argon plasma as the medium to conduct the electric current in APC rather than using the contact probe as a medium to conduct the electric current as electrocautery does. In addition to the equipment needed for the flexible or rigid bronchoscopy, a dedicated operator needs a high-frequency electrical generator in combination with insulated probes. Different types of probes in terms of shape as well as polarity (monopolar vs. bipolar) are available. For patient and staff protection, proper insulation precautions need to be observed. Insulated flexible equipment is also available.

Electrocautery electrodes—Unipolar electrodes are most commonly used and may be rigid or flexible. The rigid blunt electrode is 70 cm long and 2.5 mm in diameter, while flexible devices are 190 cm long and 2 mm in diameter. Electrodes are available in several configurations: blunt probe, knife, forceps, or wire snare. Rigid probes are more effective for debulking large tumors, while flexible probes permit treatment of small tumors, particularly in the upper lobes.

Electric current flows through the desired instrument, tissues, and a grounded neutral plate electrode attached to the patient. The neutral electrode must have a sufficiently large contact surface with the patient to prevent a cutaneous burn at its point of attachment.

Endoscope—Rigid electrocautery probes are used with a rigid bronchoscope, while flexible electrodes can be used through the working channel of a fiber-optic bronchoscope. The ability of an electrode to deliver electricity depends in part on its diameter; for this reason, a fiber-optic bronchoscope should be selected with as large an operative lumen as possible. The operative lumen of a rigid bronchoscope must have a diameter large enough for both the electrode and the rigid optic system. Most bronchoscopes in current use are not grounded, and there is a risk of the endoscopist receiving a shock if there is not a suitable low-resistance pathway for current to pass through the patient to the neutral electrode. In addition, burns of the tracheobronchial tree may result if the bronchoscope makes contact with the patient near the point of electrocautery.

High-frequency current generator—Most presently available generators are not configured in a manner that permits precise control of the power delivered to a lesion. Standard generators usually have power output settings that are graduated from 1 to 10; estimates about the actual power delivered at a given setting are often inaccurate, and the delivered voltage is variable. In addition, the resistance characteristics of a given tissue change as it is cauterized, and charring can foul the electrode. This promotes adhesion to the tissues, and the charring serves as an insulator that prevents coagulation from progressing. Newer high-frequency generators are regulated with a microprocessor and a voltage stabilizer, which allow precise control of the thermal coagulation process. Most of these generators switch off automatically at 100°C in order to prevent the production of exploding steam pockets that can cause tissue perforation, rupture, and hemorrhage (the "popcorn effect"). Additional safety features, such as isolated outputs and precise control of delivered power (in watts), are also included.

For APC, a dedicated operator needs a special catheter allowing for the argon gas and the electrical current flow. This catheter is not used in electrocautery where there is direct tissue contact. The argon gas is emitted through a Teflon tube that can be passed through a flexible bronchoscope. This gas is ionized because of exposure to high-frequency current, and an electrical arc is formed which allows for desiccation and tissue destruction without direct contact.

Application of the Technique

Endobronchial electrocautery and APC are thermal tissue-destructive modalities that use electricity to generate heat. They differ in the fact that APC does not make contact with the tissues it destroys and has a penetration depth of just a few millimeters. For these reasons, it is more suitable

for the treatment of superficial and spreading lesions. Once gas is released through the catheter tip, it is ignited through electrical current; an arc is formed if the probe is close enough to the mucosal surface, causing heat destruction and desiccation of the tissue. The arc can be moved back and forth (painting) and can even be aimed around bends, making it very suitable for hard-to-reach lesions. When electric current flows through human tissue, a *thermal* effect is observed due to the resistance of the tissue to the flow of electrical current. The rise in temperature is proportional to the square of the applied electrical current times the intrinsic resistance of the tissue; the latter is largely a function of vascularity and water content, with bone and fat having a higher resistance than skin and muscle [62]. Resistance and thermal effects are also increased by reducing the area of contact between the electrical probe and the patient, since the same quantity of current must then flow through less conducting tissue. The temperature rises at different rates in different areas within a given tissue due to inhomogeneity of tissue density and the irregular distribution of electrical current. As a rule, the density of the electric current is largest, and the rise in temperature greatest, in the contact area between the coagulation electrode and tissue, and decreases with greater distance from this point. Thermal destruction of tissue can be used to effect coagulation or resection.

Coagulation—Thermal coagulation (or "white coagulation") is caused by the relatively slow heating of tissue to approximately 70°C. Above this temperature, the glucose-containing coagulum dehydrates and carbonizes. Three different coagulation modes are differentiated: soft coagulation, forced coagulation, and spray coagulation.

Soft coagulation—Soft coagulation is produced when no electric arcs pass between the coagulation electrode and the tissue; this prevents the tissue from becoming carbonized. The unipolar or bipolar electrode is brought into direct contact with the tissue to be coagulated, and <200 V is employed. This mode is used when coagulation is needed solely to stop bleeding.

Forced coagulation—Forced coagulation results when electric arcs are generated between the coagulation electrode and the tissue in order to obtain deeper coagulation than is achieved with soft coagulation. The electrode is kept in contact with the tissue, a minimum of 500 V is used, and cutting effects are avoided. This mode is used for vaporization of tissue.

Spray coagulation—Spray coagulation is characterized by the intentional generation of long electric arcs between a spray electrode and tissue without any direct contact between electrode and tissue. High voltages are necessary, and tissue destruction and carbonization are readily accomplished. This mode is used when a large area is to be cut and vaporized.

Resection—Tissue can only be cut when the voltage between the electrode and the tissue is sufficiently high to produce an electric arc, effectively concentrating the electric current onto specific points of the tissue. The temperature produced at the points at which electric arcs contact the tissue is so high that the tissue is immediately evaporated or burned away.

Electric arcs cannot be triggered and tissue cannot be cut if <200 V is used. Higher voltages are sometimes required, depending on the resistance characteristics of the tissue to be resected. General precautions are required to prevent electrical injuries to the patient, clinician, and support staff. The patient should not have any contact with metal from the table, and sheets should be dry. The neutral plate electrode must be placed in its entirety on the patient. If the contact surface is not sufficient, the current will pass from the patient through smaller contact points which, by virtue of their lesser area and consequently higher resistance, may cause burns. At a minimum, cardiac rhythm and oxygen saturation should be continuously monitored and blood pressure frequently assessed during the procedure. Routine intraoperative monitoring protocols are generally used if the electrocautery is performed under general anesthesia. The procedure usually lasts between 20 and 60 min if performed through a rigid bronchoscope and longer if a flexible fiberoptic scope is used.

Anesthesia—General anesthesia is usually required if endobronchial electrocautery is performed through a rigid bronchoscope, although dissociative anesthesia with sedatives and neuroleptics is occasionally employed. Local anesthesia and conscious sedation can be used when the procedure is performed through a fiber-optic bronchoscope with flexible electrodes.

The fraction of inspired oxygen should be kept at the lowest level required to maintain adequate patient oxygenation in order to reduce the risk of tracheal fires. The maximal fractional concentration of inspired oxygen for use with electrocautery is 0.4.

Procedure—The fiber-optic endoscope can be introduced by either the nasal or oral route. The procedure is carried out under direct vision, with the electrode introduced within the tube of the rigid bronchoscope beside the optical system or in the operating channel of the fiber-optic bronchoscope. The operator assesses the lesions to be treated, noting their position and the extent of stenosis or extrinsic compression, whether they are projecting or infiltrating and whether they are hemorrhagic or bland. The electrode must protrude from the end of the bronchoscope by about 2 cm and is then placed in contact with the lesions to be destroyed. The high-frequency generator is adjusted to automatic control of soft coagulation, with a power setting generally between 40 and 60 W, or is adjusted to the visible coagulative effect if a first-generation machine is used. Other modalities, such as forced or spray coagulation or cutting mode, are used as required, and different electrodes (e.g., blunt electrode, wire snare, forceps, or knife) are selected as needed. It is necessary to clean the tip of the electrode frequently, because buildup may damage the electrode and/or reduce the delivered power.

Two main methods of electrocautery are used: debulking of tissue by means of a cutting loop or direct electrodestruction of tissue. Both techniques are effective and provide good results, but smoke needs to be suctioned during resection, and an unpleasant burnt tissue smell is given off. Treatment is continued until sufficient patency of the airway lumen is restored and/or bleeding arrested.

Resection of tissue generally is accomplished by the use of a unipolar wire snare apparatus similar to that used to excise colonic polyps. The technique is most suitable for narrow-based lesions causing incomplete bronchial obstruction, such that the instrument can be passed distal to the tumor and the base snared. The device is passed either through the endotracheal tube alongside a fiber-optic bronchoscope or inside the operating channel of the fiber-optic or rigid bronchoscope, looped around the base of the tissue to be resected, and then energized [53, 58, 63, 64]. Debrided tissue fragments are often too large to be removed through the flexible bronchoscope and must be grasped and removed in conjunction with it.

Tissue can be directly destroyed with electrocautery to achieve an effect similar to that seen with Nd:YAG laser vaporization [63, 64]. A blunt cautery probe is directly applied to burn, desiccate, and vaporize obstructing tissue. Unipolar probes have generally been used for this purpose, but a bipolar flexible electrocautery probe (BICAP) has been adapted for use through the operating channel of a fiber-optic bronchoscope [65–67].

Prior to the procedure, a grounding pad should be placed on the patient's lower back or flank.

Once the patient is sufficiently sedated, flexible bronchoscopy is performed and the target lesion is identified. A flexible probe—which is usually 1.5 or 2.3 mm in diameter and 220 cm in length—is then passed through the instrument channel of the bronchoscope and advanced until the location of its tip is several centimeters beyond the bronchoscope's tip. This insures that the bronchoscope will not be burned. The probe tip should be within 1 cm of the target lesion and should not contact it. Argon gas is expelled from the probe, and then a high-voltage electric current is passed along the probe. Reasonable initial settings are power of 30 W and argon flow rate of 0.8–1 L/min. The operator may then advance up to an applied power of 80 W with an argon flow rate 0.3–2 L/min. When the electric current contacts the argon gas, the argon gas becomes ionized and conducts a monopolar current to the target lesion. The application time for each burst

is generally <2–3 s. The heat produced denatures protein and evaporates intra- and extracellular water. The net effect is tissue destruction and coagulation.

To debulk an obstructing lesion, the eschar is removed with forceps, and then APC is applied to the underlying fresh tissue. This is repeated until the tumor is debulked sufficiently. The depth and volume of tissue impacted depend on the voltage applied to the gas (i.e., the applied power) and the duration (i.e., the application time). As an example, the depth of penetration is <5 mm when the applied power is between 40 and 120 W and the application time is ≤2 s. When brisk bleeding complicates the procedure, increasing the argon flow rate may blow blood away from the source, thereby providing better visualization of the culprit lesion. An endotracheal tube may sometimes be necessary to provide better airway control for patients who are tenuous or whose procedure may be complicated.

Evidence-Based Review

No controlled trials have been published that compare the various modalities that can perform endobronchial procedures. As a result, current practice is based upon local influences, available resources and equipment, the bronchoscopist's training and preferences, and uncontrolled studies. Endobronchial electrocautery and APC are frequently seen as a less expensive alternative to laser therapy with similar effects and as such similar indications. These treatment modalities are indicated for any benign or malignant tissue destruction responsive to heat delivery. These indications include endobronchial malignancy, benign tumors, relief of postintubation stenosis, and, in the case of APC, treatment of stent-induced granuloma.

The impact of endobronchial electrocautery on malignant airway obstruction has been illustrated by case series. Generally speaking, in such patients, airway patency is restored in more than 80% of patients, and symptoms are relieved in more than 70% [13]. In one series of 17 patients with locally advanced tracheobronchial malignancies who underwent endobronchial electrocautery, 15 patients had immediate reopening of the airway (89%) [57]. Eleven of those patients had restoration of >75% of the normal airway diameter, although only four patients had objective improvement in their physiological parameters. There were no deaths resulting from treatment, but minor bleeding occurred in one patient, and aspiration pneumonia developed in another. Three patients required additional therapy. A prospective cohort study of 364 patients who underwent APC (482 procedures) reported a success rate of 67%, defined as hemostasis and/or full or partial airway recanalization [68]. The most common indications were airway obstruction (51%) and hemostasis (33%), of which malignancy was the underlying cause in nearly 90%. Of note, rigid bronchoscopy was used in 90% of the interventions. In a retrospective cohort study of 60 patients who underwent APC (70 procedures), treatment was immediately successful in 59 patients [31]. All of the patients had either hemoptysis or airway obstruction, with treatment success defined as resolution of hemoptysis and/or decreased airway obstruction. Hemoptysis did not recur over a mean follow-up of 97 days, and improved dyspnea persisted over a mean follow-up of 53 days. Malignant disease existed in 95% of patients, and all of the procedures were performed with flexible bronchoscopy. A similar study of 47 patients reported a success rate of 92%, which was maintained over a mean follow-up of 6.7 months [46]. However, an average of more than three sessions per patient was required to achieve this result. Endobronchial electrocautery may also effectively treat indolent malignant tumors [56] as illustrated by a series of 11 patients with intraluminal bronchial carcinoid tumors [54]. Electrocautery eradicated lesions in eight of the patients (73%). The remaining three patients could not be completely treated because the lesions were in the upper lobe bronchi. Treatment of radiographically occult intraluminal microinvasive lung cancer is most likely to be successful in patients who have strict intraluminal disease, visible distal margins (detected using autofluorescence), no invasion of the bronchial wall (identified by bronchoscopy),

and no extraluminal growth (determined by high-resolution computed tomography) [69]. Endobronchial electrocautery proved useful in treating benign obstructing lesions of the central airways in a series of 38 patients who underwent endobronchial electrocautery [45]. Twenty-five patients had benign lesions, while 13 patients had malignant tumors. A total of 47 procedures were performed, of which 42 were deemed successful (89%). Also, APC has successfully treated benign disorders such as granulation tissue due to stents or airway anastomoses [47, 68, 70]. Both postobstructive pneumonia and hemoptysis due to the presence of an endobronchial lesion can be successfully treated with endobronchial electrocautery as well as APC. Treatment (and prevention) of postobstructive pneumonia requires the restoration of at least partial airway patency. APC is superior to electrocautery and laser photoresection in achieving hemostasis. Effective treatment of hemoptysis requires an accessible, visible lesion. In such circumstances, immediate hemostatic control is gained in approximately 75% of patients. Adequate visualization of the tumor is essential in this situation, and rigid bronchoscopy may allow more effective suctioning of briskly bleeding structures.

Complications—In addition to the risks associated with the rigid or flexible bronchoscopy, potential complications are similar to other thermal therapies and include airway fires (need to keep oxygen levels as low as possible, preferably <40%), hemorrhage, airway perforation, and stenosis. Endobronchial electrocautery is usually well tolerated, although there have been few large series that documented complication rates. Electrocautery can be performed safely as long as certain precautions are adhered to, including avoiding supplemental oxygenation, avoiding direct applications of energy onto stent covering, and keeping energy applications to a minimum. These precautions are necessary because electrocautery can ignite the lining of covered metal stents, as well as break metal stents [71, 72]. A number of complications of endobronchial electrocautery have been described [57, 59, 61, 63, 64, 66]:

- Application of deep electrocautery too close to the bronchial wall may result in perforation and pneumothorax. Cartilaginous rings may be destroyed, leading to a loss of structural support, tracheo- or bronchomalacia, and/or secondary stenoses.
- Electrocautery generates electric arcs and can cause tracheal fires or ignition of endotracheal tubes, fiber-optic bronchoscopes, or silicon endoprostheses. The risk of fire is increased if high fractions of inspired oxygen are used. The maximal fractional concentration of inspired oxygen for use with electrocautery (or bronchoscopic laser resection) is 0.4.
- Bleeding can result from penetration of the probe into the tumor but generally stops quickly due to thermocoagulation. Significant bleeding occurs in approximately 2% of cases and may be more common with vascular neoplasms such as carcinoid tumors and hamartomas.
- Aspiration pneumonia has been reported, either as a complication of anesthesia or due to aspiration of postobstructive pus into the contralateral lung immediately after debulking.
- Electrical shock and/or electrical burns to the patient or operator may occur if unipolar leads and a nongrounded apparatus are used.
- Ventricular fibrillation has occurred when electrocautery is used near the heart, and interference with the function of implanted cardiac pacemakers or defibrillators may occur.

Complications of APC are infrequent (<1% of procedures). They include airway burn and airway perforation, which can cause pneumomediastinum, subcutaneous emphysema, and pneumothorax [68]. Gas embolism has also been described in a case series, leading to three cases of cardiovascular collapse and one case of death [73]. In all of the cases, the argon flow rate was within the suggested range, but gas bubbles were seen in the left ventricle during transesophageal echocardiography. Ignition of a nonmetallic stent and electrical shock are theoretical complications of APC. Massive bleeding may occur during tumor resection, although this has not been reported. A burned bronchoscope has also been reported.

Limiting the inspired oxygen concentration, the applied power (<80 W), and the application time (<5 s) probably minimizes the risk of airway perforation or fire. Keeping the probe tip several centimeters away from any combustible material and from the bronchoscope tip likely prevents airway fire and similarly the bronchoscope from being burned. Placing a grounding pad on the patient and keeping the probe tip away from the bronchoscope tip may decrease the chance of electrical shock. Finally, maintaining the argon flow rate (<2 L/min) may lessen the chance of gas embolism.

Summary and Recommendations

Electrocautery is an effective and inexpensive technique that is most often used for palliative debulking of endobronchial lesions in the central airways. However, it also has the potential to cure some benign lesions.

A common indication for APC is resection of an obstructing airway lesion that is associated with dyspnea, hemoptysis, cough, or postobstructive pneumonia. Alternative indications include benign polyp removal, hemostasis, and debridement of granulation tissue around endobronchial stents.

Endobronchial electrocautery and APC are performed with local anesthesia using a fiber-optic bronchoscope. Advances in the design of electrodes, bronchoscopes, and generators may improve precision and safety. The technique can be very useful, particularly in centers where the cost of bronchoscopic laser equipment is prohibitive.

No controlled trials have been published that compare the various modalities that can perform endobronchial procedures. As a result, current practice is based upon local influences, available resources and equipment, the bronchoscopist's training and preferences, and uncontrolled studies.

Complications of endobronchial electrocautery and APC are infrequent, occurring in fewer than 1% of procedures. Strategies exist that may decrease the likelihood of a complication.

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Cryotherapy

8

Jose Pablo Díaz-Jimenez
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Introduction

Cryotherapy is an old method used in different fields of medicine taking advantage of the properties of cold. In pulmonary medicine, especially in endoscopic application, cryotherapy allows tissue destruction by applying cycles of freezing and thawing, producing tissue necrosis by local cytotoxic effect.

Compared to other endoscopic therapies, cryotherapy belongs to the so-called slow methods to treat intraluminal tumors along with brachytherapy and photodynamic therapy. New modalities of application for fast opening are under investigation.

Cryotherapy is a safe and low-cost method and has different capabilities that will be discussed in this chapter. It can be used as a single therapeutic method or as a palliative method or in conjunction with other treatment modalities such as laser and brachytherapy.

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History

The application of low temperatures on living tissues has been used successfully to treat a wide variety of injuries. History of cold application in medicine is very old and dates back to ancient Egypt. In Greece, Hippocrates considered it useful to treat injuries such as bleeding and inflammation. During the Russian war of 1812, Larrey used cold as an analgesic and hemostatic treatment during amputations. More recently, cold has been frequently used as an anesthetic agent [1]. The first catheter to deliver cold was manufactured during the second decade of this century, in France, for applications in dermatology, gynecology, and neurology.

The first case of endobronchial tumor treatment with cryotherapy was published in 1968 by Agge [2]. Later, Neal, DeSanto, and Sanderson [3] from Mayo Clinic published some cases of tracheal and bronchial stenosis treated successfully applying this method. In spite of this, cryotherapy felt into disuse until 1985 when the technique had a renaissance in Europe, particularly France, England, and Italy [4].

Currently, it is frequently used in several specialties such as pulmonary medicine, dermatology, urology, or surgical oncology.

The physical mechanism involved in the development of cryoprobes is based on temperature changes that take place in a gas when the pressure changes. When a gas expands, temperature may increase or decrease, depending upon

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the initial temperature and pressure. The gas used to apply cryotherapy is stored in a liquid state under high pressure and, when it is abruptly decompressed, passes from a liquid to a gaseous state producing an important fall in temperature (Joule–Thomson effect).

The cold thus produced when applied to tissues generates cryonecrosis, and destruction occurs, following a spherical model and respecting the collagen structures.

Cryotherapy gained popularity in some centers in the treatment of head and neck malignant tumors, early and advanced airway tumors, benign tracheobronchial stenosis, and subglottic stenosis in adult and pediatric population [5].

However, as will be discussed below, it has not been found to be better than laser application in any of its indications. Even when most experts prefer laser over cryotherapy, they should not be considered competing therapeutic tool, since they have different indications and, in many situations, their use can be complementary. For instance, when cryotherapy is applied following laser resection of malignant tumors, it can eliminate areas of tumor implantation in depth. The same effect can be obtained combining both methods to treat early tumors with curative intention.

In 1970, Thomford et al. caused necrosis in a dog trachea through the external application of liquid nitrogen. Serial histological cuts later showed an early ulceration of the mucosa in the cryonecrosis region, followed by resurfacing with columnar epithelium after 72 h. The new epithelium lacked cilia and goblet cells. At 4 weeks, the epithelium had returned to normal [6].

In 1975, a new device was designed, allowing the endobronchial application of cryotherapy. It consisted on a rigid probe 57 cm long with different-sized tips that could be used with the standard cryosurgery equipment. A study in a canine model found that this technique could be applied through bronchoscopy. Currently, more modern devices following the same principles of cryotherapy application are used to treat in situ carcinoma and early stages of small cell bronchogenic tumors or in high-risk surgical patients whose respiratory reserve is inappropriate. It can also be used to reduce tumor mass as a palliative treatment in patients with advanced lung cancer [7].

Physical Principles and Mechanism of Action

The action of extreme cold causes freezing of the tissue. Initially, extracellular water is frozen, increasing its osmolarity. This generates a cellular dehydration and finally cytolysis if the situation persists or if the cyclic freezing–thawing is repeated long enough.

In addition to this mechanism, cold produces mechanical damage by ice crystals (particularly at an intracellular level, affecting mainly the mitochondria), which is more considerable when the freezing phase is rapid and the thawing phase is slow.

In a fast thawing, the cell is exposed to a high concentration of electrolytes and a high temperature too, which induces intra- and extracellular migratory recrystallization, either by crystal growing or by small crystal aggregation. A slow thaw produces this migratory crystallization phenomenon on a larger scale, which is very destructive to the intracellular organelles. In summary, the rapid freezing followed by slow thawing makes cold application most detrimental for the cell.

Six factors determine the cellular injury during this period: compression and deformation of the cell due to extracellular crystallization, intracellular crystallization, cell collapse due to intracellular dehydration, increase of intracellular solute concentration, membrane distortion, and thermal shock.

Mazur [8] described the physical events in suspension cells during freezing:

- At −5°C, the system is still liquid, although the cytoplasm freezes at −2.2°C. This phenomenon is called overcooling, and it occurs secondary to a reduced freezing point, due to the presence of different kinds of solutes in the suspension.
- Between −5°C and −15°C, extracellular crystallization takes place. The intracellular environment remains cold but not frozen, thanks to

the cellular membrane which acts as a barrier to the propagation of ice. In this state, the speed of freezing is critical. If the cell is frozen slowly, intracellular dehydration produces a redistribution of solutes in the cytoplasm, and it does not freeze. However, if the freezing process is fast, the intracellular water will not have time to pass through the cellular membrane, and deleterious crystals will develop inside the cell.

- Below −15°C, a transitional state takes place. Any increment in the solute concentration results in a lowering of the freezing point for the liquid remaining.
- Finally, a solid state or complete crystallization is obtained.

At tissue level, destruction is mainly due to changes in microcirculation. Blood flow is compromised by arterial and venous spasm and changes in the vascular endothelium. The result is an increment in capillary permeability, increased blood viscosity, decreased blood flow, platelet aggregation, and finally, intravascular thrombosis [9]. An additional immunological effect of cryotherapy has been described but is controversial [4].

Since tumors are not homogeneous, the application of cold generates different types of lesions. In the area located around the cryoprobe (around 3 mm radium), all cells will be destroyed homogenously. At 3–4 mm outside this area, cryolesion is less homogeneous affecting mainly blood vessels and perivascular cells.

The association of cryotherapy with other therapeutic modalities such as external radiation [10] and chemotherapy [11] can help eliminate residual tumor. Research studies have shown that around 15 days after cryotherapy, new blood vessels develop in the treated area that can increase the effects of radiotherapy. Likewise, after 1 h of cryotherapy, there is a higher absorption of bleomycin by tumor cells. It is postulated that bleomycin is trapped inside the tumor due to vascular disruption caused by freezing.

Many tissues are cryosensitive (Table 8.1), including granulation tissue, mucous membranes, and malignant cells.

Among the cryoresistant tissues, we find cartilage, fibrous tissue, and fat. The low water content of these cells is responsible for their cryoresistance. In the central airway, this fact provides an additional advantage: secondary wall perforation is almost impossible [12].

Table 8.1 Summary of cryotherapy-sensitive tissue

Cryosensitive tissues	Cryoresistant tissues (low cellular water content)
• Granulation tissue/ granuloma	• Cartilage
• Mucosal lesions	• Collagen
• Neoplastic tissue	• Fibrous tissue
	• Fat
	• Poorly vascularized tissues

Experimental studies have shown that the trachea is remarkably resistant to cryotherapy. Following the application of temperatures near −80°C for 60 s, the tracheal epithelium becomes ulcerated in 48 h, but it regenerates completely within 4 days, and after 6 weeks, it has a normal appearance. It was also noted that the affected respiratory mucosa heals without stenosis [13].

Equipment and Technique

Cryogenic Agents

Cryogenic agents are gases that, when stored at high pressures, they present in a liquid state. When they are suddenly decompressed and pass to gaseous form, the temperature abruptly falls, according to the physical principle of Joule–Thomson.

Various cryogens are available: chlorofluorocarbon substances, CO2, liquid nitrogen (N2), and nitrous oxide (N2O):

- Chlorofluorocarbon substances are used in industrial or domestic refrigeration, and they have no medical application.
- CO2 is a very effective cryogen (reaching temperatures of −79 °C) but can only be used with large probes since it generates carbonic snow that occludes cryoprobes. Therefore, it is not useful for application with the thin probe introduced through the working channel of fibro-bronchoscope (BF), but it can be applied for instance in superficial skin lesions.

- Liquid nitrogen (liquid N2) is readily available and also generates low temperatures reaching −196°C but has a slow action, and it is difficult to store.
- Nitrous oxide (N2O) has a fast action, is low cost, and is broadly available. It is currently the most common source of cold used since it is easy to handle. It can be stored at room temperature, generating acceptable temperatures (−89°C) at the tip of the probe. N2O produces a fast fall in temperature with an instantaneous freezing effect, which represents an important advantage when used as a therapeutic method.

Sources of Cold

Devices for cold production available in the market are DATE (DEVEL APPLIC TECH ENERGIE, La Motte d'Aveillans, France), ERBE (Tübingen, Germany), and SPEMBLY MEDICAL LTD (Andover, UK). All of them have a central console, a rod, a cryoprobe, and a gas cylinder. DATE and ERBE commercialize rigid, semirigid, and flexible rods, while SPEMBLY presents only a rigid rod.

They all use N2O as cold source, stored in a cylinder at 50 bar and reaching temperatures below −40°C at the tip of the probe. They generate temperatures of −30°C and −40°C at the level of the treated tissues (Fig. 8.1).

The temperature needed for a lesion to be destroyed is −40 to −20°C. To freeze a tissue, −40°C or less is needed, while at a rate of −100°C per minute, more than 90% of cellular death is achieved.

Cryoprobes

- Rigid or semirigid cryoprobe: It is only applied through the rigid bronchoscope and for treatment of large tumors. Probes are 60 cm long and 3 mm in diameter. The probe is coated with an insulating material except for the distal tip that contacts directly to the tissue and applies cold.

Fig. 8.1 ERBE cryotherapy console

- Flexible cryoprobe: It was designed for the use with the flexible bronchoscope to treat smaller lesions, requiring a working channel of 2.6–3.2 mm diameter. They are specially suited for the treatment of small lesions, even in bronchial divisions, not accessible to the rigid bronchoscope (Fig. 8.2).

Since most of the initial airway treatments were performed with a rigid bronchoscope, first designed cryoprobes were rigid and semirigid. The rigid bronchoscope is not affected by freezing, but the flexible instrument cools during the procedure and may be frozen with risk of damage.

Monitoring the Freezing

Until today, there is no reliable method to monitor the freezing process. The dedicated operator is well trained in evaluating signs such as tissue color changes, consistency of the tissue (that can be felt with the suction catheter), and extent of the treatment, but it remains an empirical process based on experience.

DATE and SPEMBLY machines provide indirect information through the introduction of a

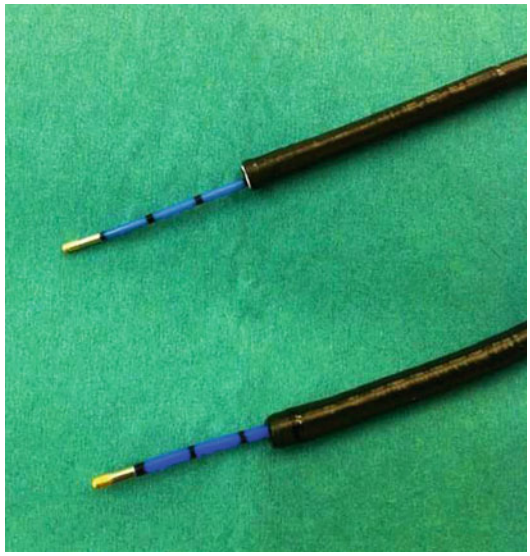

Fig. 8.2 Flexible cryoprobes: 1.9 and 2.4 mm diameter

detector at the end of the probe, which confirms that cold is being applied but do not give any information on tissue temperature (SPEMBLY). Another method more reliable and incorporated in DATE devices is tissue impedance. It is based on the fact that the complete extracellular crystallization is essential for producing tissue necrosis and that this change in the physical state of the extracellular substance modifies tissue impedance. A resistance between 200 Ω and 500 Ω indicates that thawing has been carried out correctly.

Technique

Cryotherapy can be applied with rigid or flexible bronchoscopy. The method used depends upon preference of the operator and availability. We recommend the use of the rigid bronchoscope for all airway resections, since the rigid bronchoscope allows complete control of the airway and easy removal of large pieces of tumor, among other benefits. Rigid bronchoscopy is discussed someplace else in this book. The patient should be evaluated for surgery or laser photoresection, including medical history, routine laboratory tests, coagulation profile, acid–base balance, electrocardiogram, chest radiography, and computerized tomography. Adequate information should be given to the patient and family, and informed consent should be signed.

The procedure can be performed under general anesthesia (rigid bronchoscope) or conscious sedation (flexible bronchoscope) by an anesthesiologist used to administer anesthesia for airway resection procedures. Vital signs should be monitored during the whole procedure (EKG, noninvasive blood pressure, pulse oximetry).

The patient will be intubated with the rigid bronchoscope as usually performed for rigid bronchoscopy resections. The rigid bronchoscope most commonly used is the Dumon–Harrell model. Once the patient is intubated and connected to assisted ventilation, treatment can be initiated by introducing the rigid, optic suction catheter and the cryoprobe through the rigid tube.

Cold application is extremely simple. After selecting the area to be treated, contact is made with the cryoprobe, and cold cycles are applied for 1 min. An ice ball is seen appearing in the treated site, about 15 s after initiation of treatment. One to three freeze–thaw cycles (approximately 30 s each) are applied at the same place. It is important to treat the entire surface of the tumor, and sometimes, 40 cycles or more are necessary.

Resulting cryothrombosis is delayed several hours, during which time, the tumor cannot be removed mechanically. For this reason, conventional cryotherapy does not achieve immediate opening of the airway and is considered a slow-opening method and should not be used in cases of acute dyspnea due to critical obstruction.

At 8–10 days of treatment, necrotic debris are expelled by coughing or removed by bronchoscopy. Usually, a second bronchoscopy is necessary to remove residual tumor.

Different from conventional cryotherapy where the cryoprobe is not removed immediately after stopping the application of cold allowing spontaneous thawing, during cryoablation, the probe is withdrawn at the end of the freezing cycle with a piece of tumor attached to it obtaining a fast opening of the airway. Given the vasoconstriction secondary to cold, there is no bleeding during treatments.

One advantage of cryotherapy is that since there is no risk of endobronchial fire, there is no need to reduce the fraction of inspired oxygen, and therefore, it can be applied to patients with respiratory insufficiency.

Application with flexible bronchoscope is substantially similar, but it is performed with conscious sedation and a flexible probe 2–3 mm in diameter. These rods have two disadvantages: they have less power than the rigid ones and thawing takes 30–45 s, which prolongs the procedure time. However, they have the advantage of being useful for treating small lesions and upper lobe disease. Same requirements prior to treatment and monitoring are applicable to this modality, similar to laser application with FB.

After therapy, the patient will be transferred to a recovery room for postoperative monitoring. We also perform a post-procedure chest radiograph, which is not indispensable, but we consider it advisable. Treatment with corticosteroids to prevent edema is not generally indicated because the magnitude of edema is rarely important. After 1 or 2 weeks, a new bronchoscopy should be performed to remove debris that might exist. After cryotherapy, a necrotic crust is formed and falls in around 2 weeks. Sometimes, after a coughing effort, this necrotic tissue can be expelled and can cause bleeding. The patient and his/her family should be adequately informed on the effects and possible complications of cryotherapy.

Other Modalities for Application of Cryotherapy

Cryoablation, Cryoextraction, or Cryorecanalization and Cryobiopsies

In the presence of malignant airway obstruction, cryotherapy can be used to open the airway by mechanical removal of the mass by applying 3–7 s cycles until the probe is completely adhered to the tissue and then remove the probe attached to the material (Fig. 8.3a–c).

The same technique can be used in order to remove foreign bodies from the airway and also to obtain bronchial or transbronchial biopsies (see below).

Cryospray

This new modality obviates the need for contact with the target tissue, using low-pressure sprayed liquid nitrogen, and treating quickly and uniformly larger areas (see below).

Indications/Contraindications/ Complications

Indications for conventional cryotherapy (Table 8.2) are similar to those of laser, except severe acute central airway obstruction, since it is not a fast method to open the airway. In those situations, cryoablation can be applied.

Cryotherapy can be used as a curative method (benign endobronchial tumors) or palliative method (endobronchial malignant tumors). Tumors that are highly vascularized are more sensitive.

Tumors that are highly vascularized are more sensitive: endoluminal and exophytic growing tumors, invasive tumors arising from the esophagus and thyroid or mediastinal metastasis, endobronchial metastasis from renal or colon cancer, or inoperable malignant melanoma can benefit from cryotherapy application. “In situ” carcinoma can be also an indication in selected patients, as well as low-grade tumors such as adenoid cystic carcinoma or carcinoid tumor.

Cryotherapy can be used as a single method or combined with other therapeutic options such as the Nd-YAG laser.

In central airway tumors, some benign tumors are susceptible to treatment with cryotherapy: granulomas are destroyed in 100% of cases. Fibroids, lipomas, post-intubation fibrous stenosis, or amyloidosis are cryoresistant and do not benefit from this technique.

A bleeding tumor is an excellent indication for this treatment for the effective action of cold over vascular tissues.

Some benign stenosis of the tracheobronchial tree (nonfibrous post-intubation stenosis, tuberculosis, Wegener’s granulomatosis, secondary to toxic inhalation, or stenotic complications of lung transplantation) may also respond to this therapy.

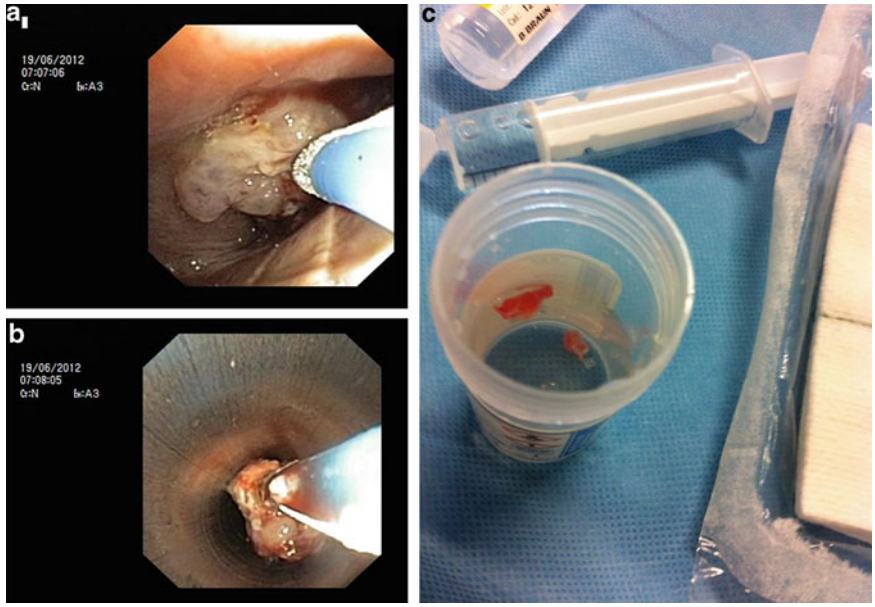

Fig. 8.3 Cryoextraction of endobronchial tumor. (**a**) The cryoprobe is advanced, (**b**) a freezed tumor piece attached to the probe is removed, (**c**) obtained material

Table 8.2 Summary of cryotherapy indications

Malignant tumors: • Surgically unresectable endobronchial tumors in inoperable patients • Recurrent or residual endobronchial tumors following surgery, chemotherapy, endoscopic resection, and/or radiotherapy • Endobronchial tumors in patients that refuse surgery • Malignant tumors from trachea or bronchus, primary or metastatic in inoperable patients
Benign tumors • Cryosensitive benign tumors
Slow-growing tumors • Carcinoid tumor in nonsurgical candidates
"In situ" carcinoma
Benign stenosis • Nonfibrous benign stenosis • Tuberculosis • Wegener's granulomatosis • Secondary to toxic inhalation, anastomotic suture after tracheobronchial surgery
Foreign body removal
Hemoptysis due to a bleeding tumor
Biopsies • Large bleeding tumors • Transbronchial biopsies

Finally, it can be an effective diagnostic method for biopsies of bleeding tumors, given its hemostatic properties. Recently, cryoprobe biopsies have become popular, and they have been used to take bronchial or transbronchial biopsies in the study of interstitial lung conditions.

Conventional cryotherapy is not a treatment for central airway obstruction emergencies since it does not allow immediate reopening of the airway, and in addition, its application generates edema on the treated area that can worsen the obstruction. In case a fast opening of the airway is needed, a different modality such as cryocanalization, also called cryoextraction or cryoablation, has to be applied. Other techniques to be applied are laser resection, electrocautery, or argon plasma coagulation.

Foreign Body Removal

Removal of foreign bodies (FB) can be performed with the aid of different tools, depending on the nature of the foreign body, location, available equipment, and skill of the bronchoscopist. Cryotherapy is a good method to remove some foreign bodies from the airway. Depending upon the water content of the element to remove, some

Fig. 8.4 Cryobiopsy

substances are cryoadherent and others are not. Cryotherapy is effective in porous structures, pills, tablets, and blood clots. It is less effective in bone, metal, and teeth.

Cryobiopsy

As we discussed, cryotherapy has been used to take endobronchial biopsies obtaining samples of acceptable size with a grade B according to the British Thoracic Society Guidelines Recommendations [14]. It has been also applied to take transbronchial biopsies (Fig. 8.4). In a recent multicentric study, the cryobiopsies had a sensitivity of 95% compared to 85% of transbronchial lung biopsies performed with regular forceps [15]. In 41 patients, the specimen diameters with cryobiopsy and forceps were compared: average size was 15.11 mm with the cryoprobe versus 5.82 mm with conventional forceps. Pneumothorax was a complication in two patients. The samples taken with cryoprobe had the additional advantage of showing less crush artifact than the ones taken with biopsy forceps [16].

Another recent report published the results of a prospective study that included 296 patients with endoluminal tumor lesions, evaluating diagnostic yield and safety of cryobiopsy compared to forceps biopsy. Cryobiopsy had a higher yield (89.1% vs. 65.5%). Mild bleeding occurred in 11 cases, moderate bleeding in 3, and severe bleeding in 1 case [17].

A Spanish group presented the results of performing transbronchial lung biopsies using cryoprobes in 10 patients with interstitial lung disease [18]. TBLB was performed in orally intubated patients under deep sedation using the flexible bronchoscope and cryoprobes, with fluoroscopic control. The area of specimen was in average 9.5 mm^2. No pneumothorax was registered, and 6 of 10 patients presented bleeding during the procedure, which was treated by bronchoscopic measures. However, the patient population was carefully selected to avoid complications.

Cryoextraction, Cryocanalization, or Cryoablation

With the development of mechanically stable cryoprobes, direct endoscopic removal of tissue from the bronchial system with cryotherapy is now possible. Tissue is frozen and attaches to the tip of the probe and then removed by pulling the probe together with the fiberscope. In a report on four patients with bronchial obstruction, cryoextraction was performed for rapid recanalization [19]. The procedure had immediate opening effects with few complications. Indications were mucoid impaction, foreign body aspiration, removal of suprastomal granulation tissue prior to decannulation after prolonged mechanical ventilation, and obstruction of the trachea and the main bronchi by a carcinosarcoma.

Cryospray

Cryospray is a new device for the application of cold. Liquid nitrogen is stored in a tank and then propelled through a cryocatheter. The catheter is placed in the appropriate position through visual

observation, and then, the cryogen is applied to the selected area as a spray, freezing the unwanted tissue.

The pilot study on cryospray applied on Barrett's esophagus [20] reported a complete endoscopic and histological reversal of this disease with regeneration of the esophageal tissue on the 11 treated patients and was published in 2005. The FDA approved cryospray application for esophageal cancer in 2007 but is not approved yet for lung cancer treatment.

Another recent study published results on the application of spray cryotherapy and balloon dilation for nonmalignant strictures of the airway [21]. Authors state that this new approach can modulate a healing response leading to less fibrosis and decrease the need or prolong the duration of time to intervention. Krimsky et al. [22] performed cryotherapy in 21 patients using liquid nitrogen cryospray at a temperature of −196°C and 2–3 psi of pressure with the CryoSpray Ablation System (CSA Medical, Inc., Baltimore, MD). In those patients, bronchoscopy and cryotherapy were performed before lung resection. Six patients did not undergo surgical resection due to intraoperative findings. Various levels of cryonecrosis were observed, and they were limited to the mucosal and submucosal layers (approximately 1.5 mm depth) with no damage to the connective tissue. This was the first experience with cryospray applied to human airways. The authors concluded that, based on those preliminary results, spray cryotherapy is a safe and easy method to apply.

Results from a multi-institutional registry on spray cryotherapy showed that its application on 80 patients with malignant airway tumors was associated with airway patency at the end of the procedure in all but one patient. They reported 21 intraoperative events, including hypotension, bradycardia, tachycardia, ST segment changes, desaturation, and an airway tear. Three pneumothoraces and two intraoperative deaths that were associated with bradycardia occurred. Three patients died after been transitioned to comfort care [23]. Prior results on a single institution showed a higher than expected morbidity, with five patients having major intraoperative events including three cardiac arrests (one resulting in death) and two pneumothoraces that required pleural tube placement [24]. More studies are needed in order to make recommendations.

Contraindications

- Those for general anesthesia (many times the procedure will be possible with a flexible bronchoscope)
- Poor clinical status (low index of Karnofsky or ECOG)
- Coagulation disorders (relative)
- Extrinsic compression
- Old atelectasis (nonfunctioning lung parenchyma distal to the lesion)

Complications

The number and type of complications associated with this treatment technique are quite low.

The most feared one is massive bleeding due to the fall of necrotic tissue that occurs after 7–14 days of treatment [26]. Minor bleeding may occur during and after treatment, but it is rare and requires no intervention. A second time bronchoscopy should be performed for a bronchial toilette.

Bronchospasm, cardiopulmonary arrest, and purulent drainage have been reported as complications as well [27].

Transient fever after the procedure has also been observed as respiratory failure due to detachment of the necrotic crust or edema [4].

Death due to respiratory failure secondary to edema was reported in a pneumonectomized patient. In this case, cryotherapy was applied on a carinal tumor recurrence [24]. Deaths following cardiovascular events (bradycardia, acute myocardial infarct) have been reported during and following cryospray ablation [23, 24].

In summary, conventional cryotherapy is a fairly safe method, with low rate of complications and very low risk of tracheobronchial perforation. There is not enough information on the safety profile for the cryoextraction and cryospray modalities.

Conventional Cryotherapy Versus Laser Resection

The overall experience with cryotherapy is good, showing similar results with that of laser resection.

The greatest disadvantages of conventional cryotherapy are the following:

- Lack of immediate action ("slow method")
- Need of several sessions to achieve the desired effect
- Bleeding risk days after the procedure, when necrotic tissue detachment occurs
- Need for a toilet bronchoscopy

Main advantages are the following:

- Cost of the equipment, lower than laser.
- Easier technique.
- Does not produce radiation.
- Safer for the operator (no ocular damage).
- Low risk of wall perforation.
- Inexistent risk of endobronchial fire, no pop corn effect.
- It can be applied with high FiO2.

Some authors, however, disagree with these considerations and state that symptomatic improvement is achieved to a lesser degree when compared to laser, which has also shown a bigger impact on lung function.

Cryotherapy in Tracheobronchial Stenosis

Cryotherapy is not an excellent method for the treatment of tracheal stenosis. However, there are some publications on the use of this technique with good results. Talbert et al. present a series of 17 patients aged between 2 months and 30 years. Conditions treated included: periglottic injuries, two vallecular cysts and a larynx tumor; subglottic injury, post-intubation stenosis, congenital stenosis and smoke inhalation; lesions of the distal trachea (post-intubation injury); and a last subgroup of patients with granulation tissue. Treated patients had heterogeneous tracheal abnormalities, and most of them benefited from treatment [5].

Another study published in the 1980s reported 27 patients treated with cryotherapy for 29 lesions in the airway. Age range was from 3 months to 42 years (most of them were children). All patients had tracheal dilatation as the initial treatment and were referred for failure of this conventional method. All patients except one had tracheostomy. The cryoprobe used was 43 cm long and 3 mm outer diameter, especially designed for use through the pediatric bronchoscope. The tip of the probe was isolated, except in the distal centimeter, to avoid freezing of adjacent tissues. N2O was used as a source of cold, reaching temperatures of −80°C. Temperature of the probe tip was monitored. In all patients, general anesthesia was used. Treatment was applied as follows: the cryoprobe was placed over the area, cooling to −70°C or −80°C for 45 s and then excising the frozen tissue with biopsy forceps. This was repeated over the entire circumference of the stenosis, and the whole procedure was repeated at intervals of 4–6 weeks. When a full dilatation was obtained – defined by endoscopy – patients were extubated.

In the subgroup of subglottic stenosis 16 patients were treated for congenital stenosis and post-intubation stenosis. Cryotherapy was successful in eight patients, who could be extubated. Three patients improved but could not be extubated for other reasons, and two did not benefit from treatment at all (they presented stenosis of a segment of trachea just below the vocal cords). Tracheal lesions did not recur in 4 years, even in patients who could not be extubated.

In the subgroup with tracheal stenosis (ten patients), three had granulation tissue secondary to tracheostomy, one granulation tissue secondary to chronic foreign body, five presented post-intubation stenosis, and in the remaining, etiology could not be determined. Nine patients were successfully extubated without evidence of recurrence in a follow-up period of 2–6 years [1].

Another report on experimental animals compared electrocautery, cryotherapy, and laser treatment in subglottic stenosis, concluding that laser was the treatment associated with more heat damage and secondary stenosis. They found, however, that the three of them were equally safe and effective when used judiciously and with the lowest effective power possible for each particular method [13].

Cryotherapy in Airway Tumors

Results on the application of cryotherapy in the treatment of airway tumors have been published in various medical journals. In general, the following factors have been considered important to alleviate malignant disease with cryotherapy:

1. Temperature of the probe tip from −40°C or less.
2. Large contact surface between the probe tip and the tumor.
3. Two to three repeated applications on the tumor, freezing around −30°C and allowing spontaneous thawing.
4. Local application of epinephrine around the tumor can greatly increase the action of cold by inducing vasoconstriction and ischemia.

The overall effectiveness of cryotherapy in the tracheobronchial cancers is about 75% regardless of cell type [28, 29]. Hemoptysis control is achieved in approximately 80% of cases [4].

In a study published in the early 1980s, a group of 28 patients with malignant disease was presented. Bronchogenic carcinoma was the most frequent pathology, followed by cylindroma, osteochondroplastic tracheopathy, recurrent bronchial carcinoid, and esophageal carcinoma invading trachea. All had been treated with conventional therapy, including surgery and radiotherapy (except for one patient), or were not considered good candidates for surgery. All patients had disease limited to the thorax. After cryotherapy treatment, bronchoscopy repeated every 4–8 weeks was used to evaluate the images and define whether or not they responded, considering a positive response a size reduction of the tumor.

Fifteen patients benefited from treatment, showing tumor size reduction in 8, disappearance or reduction of hemoptysis in 4, and improved airway size in 3. Thirteen patients showed no treatment benefits. Two deaths occurred, probably related to treatment: massive hemoptysis after 5 days of treatment, presumably due to necrotic tissue fall and respiratory failure due to edema probably related to treatment (no autopsies were performed) [26].

Using a cryoprobe with flexible or rigid bronchoscope, cryotherapy was applied to 234 patients treated over a period of 9 years. The pathology included 183 malignant tumors, 44 benign tumors, and tumors of uncertain prognosis [7].

Each treatment was performed under local anesthesia and sedation and involved the application of cold for 1 or 2 min, repeating the cycle two or three times in the same place. The probe tip was placed perpendicularly to the tumor, tangential, or inside the tumor mass. Thawing was obtained spontaneously in all cycles. Six to eight days after surgery, necrotic tissue was removed with an alligator forceps or by using the probe tip applied for 5 s for adhesion to the tumor or by simple suction. In patients with malignant tumors, palliation was obtained in all of them, with improvement of symptoms: pulmonary atelectasis, lobar atelectasis, hemoptysis, dyspnea, hypoxemia, and sepsis. In the group of benign tumors, the results were "almost radical" [12].

The use of a cryotherapy probe through a flexible bronchoscope has brought this technique to the bronchoscopists that have no training in the use of rigid bronchoscope. Through a flexible bronchoscope with a working channel of 2.6 mm, using a flexible cryoprobe and nitrous oxide as a source of cold, treatment was performed in 22 patients with malignant tracheobronchial obstruction (20 patients) and bronchial obstruction after lung transplantation (2 patients).

Posttransplant benign strictures were dilated first with a balloon, and the edges of the stenosis were frozen perpendicular or tangential to the probe tip. Clinical response was evaluated in all patients except one who died early. In a patient with malignant disease, it was impossible to remove the tumor in spite of three sessions. In the remaining 18 patient, the endobronchial component of the tumor was removed. Three patients had extrinsic compression occluding the airway despite treatment. Hemoptysis was controlled in all patients, and dyspnea also improved in all of them. Patients with posttransplant stenosis showed recurrence when treated with dilation alone, but the airway lumen remained open after treatment with cryotherapy [27].

Table 8.3 Conventional cryotherapy compared to other methods in symptom control

Method	Cryotherapy	Nd-YAG	EC	PDT	Prosthesis	
Parameter	%	%	%	%	%	Brachytherapy
Control of hemoptysis	65–86	60	90	ND	Possible	80
Cough and dyspnea	66	80–90	50–60	70	90	85
Pulmonary function test	50	85	73	ND	71	80
Drainage of the airway	75 (delayed)	90 (immediate)	84 (immediate)	50–60 (delayed)	90 (immediate)	80 (delayed)
Duration (months)	3–4	2–3	ND	ND	4	6.5
Possibility to repeat the treatment	Yes	Yes	Yes	Yes	Yes	No
Curative intention (early stage cancer)	Yes	Yes	Yes	Yes	No	Yes

Adapted from Vergnon et al. [25]
ND not defined, *EC* electrocautery, *PDT* photodynamic therapy

Application of cryotherapy to superficial malignant lesions has been described as satisfactory. Ozenne et al. have reported outcomes for 18 lesions in 14 patients with "in situ" and microinvasive carcinoma. Fourteen lesions showed apparent cure [30].

The French experience published by the Study Group on Cryosurgery describes 36 patients with "in situ" and microinvasive carcinoma. 42% of them had been previously treated for invasive ENT cancer or bronchial tumors. At 1 year, the clinical and histological improvement was achieved in 89% of cases. Follow-up at 32 months showed persistent effects in 70% of cases. Median survival was 30 months. Treatment failure was associated with undefined tumor edges or tumors located distally in the upper lobes, with a difficult access [31].

A protocol published by Vergnon et al. explored the outcomes of patients with inoperable "non-small-cell" lung carcinoma, who were treated with cryotherapy followed by radiation therapy, demonstrating that the combination of both treatments is safe and presented an efficacy of 68% in opening the airway. They concluded that survival was improved with this combination therapy when compared with other series using radiotherapy alone, laser alone, or a combination of laser and radiotherapy [10]. This work has no control group, and other publications were used to compare results. However, it appears that the response rate is good and can be considered as a valid treatment modality. Synergy effect of these two methods requires further studies to really make valid conclusions.

It has also been published that chemotherapy accumulates selectively inside the tumor after cryotherapy. It seems to exist as a synergistic effect between chemotherapy and cryotherapy as well [11].

Table 8.3 (adapted from Vergnon et al. [25]) compares the results of different palliative methods.

Conclusions

Several different techniques are available today for the bronchoscopic treatment of tracheobronchial benign and malignant lesions. The most commonly used are laser, electrocautery, cryotherapy, photodynamic therapy, and brachytherapy. The objectives are radical treatment of nonmalignant diseases and palliative treatment for the malignant tumors. The advantages of conventional cryotherapy are safety, easy application, low risk for tracheobronchial wall injury, low risk of airway fire or "pop corn" effect, and the ability to treat infiltrative tumors and longitudinally extended wall tumors where the laser is dangerous to use. There are no ocular risks to the operator, no emission of radiation, the possibility of

using high FiO2, and no need for a cooling system. Aditionally, it is a low cost therapy: equipment, ancillary tools and maintenance can be obtained at a fraction of the cost of laser [12].

For malignant tumor treatment, external radiation is widely used to control local growth in patients with unresectable tumors. However, many patients have poor lung function and cannot tolerate further destruction of lung tissue produced by external radiation. In addition, radiotherapy does not relieve symptoms quickly, and recanalization of the bronchial lumen occurs in only 21% of cases [27]. In fact, the local control is obtained in only 35% of cases.

Conventional cryotherapy is a treatment modality that should be considered as an option in obstructive lesions of the airway of some etiologies (considering that some tissues are cryoresistant) [27]. It can be complementary to other therapeutic methods such as laser, electrocautery, external radiation, and chemotherapy. It has not proved superiority to any other available technique. The recently described cryoextraction and cryospray modalities are still under investigation, and available information does not allow to make further recommendations at this time.

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Endobronchial Brachytherapy: Concept, Indications, Technique, and Outcomes

9

Aruna Turaka and Michael Unger

The term brachytherapy derives from the Greek brachos (short), signifying a technique based on a short distance of delivery. In this case, it also relates to delivery of radiation therapy.

This chapter will review the concept, history, indications, technique, results, and complications, as well as the benefit/risk ratio as they apply to the treatment of lung processes which can be reached endoscopically, with the help and guidance of a bronchoscope.

The Concept

The objective of brachytherapy is to provide and deliver an optimal therapeutic dose of radiation to the target tissue, which is in proximity to the radiation source, while at the same time to reduce as much as possible the amount of radiation to the surrounding unaffected tissues, thus minimizing damages and risks.

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The effectiveness and safety of this procedure are optimized by a multidisciplinary approach, including a trained bronchoscopist, radiation oncologist, and medical radiation physicist.

Historical Progress of Endoscopic Brachytherapy

The idea of brachytherapy was first considered shortly after the discovery and development of the clinical application of radioisotopes. Pierre Curie suggested, already in 1901, the insertion of radium in a tube and its placement in the tumor. Subsequently, publications appeared in German literature suggesting the use of various combinations of radioactive devices for tamponading potential bleeding (Fig. 9.1). In 1914, Stevenson and Joly discovered a way to incorporate radium sulfite in needles of steel or platinum. The first use of radon seeds was reported from Memorial Hospital in New York in 1917. Yankaver provided first reports of bronchoscopic treatment of lung cancer with radium, followed by Kernan and Cracovaner, who described insertion of radium needles through a rigid bronchoscope in 1929. Then Kernan reported in 1933 the results of treatment in seven patients, with four out of seven remaining without evidence of disease after 2 years of follow-up. Larger series (42 patients) of patients treated with radon seeds were reported by Pool in 1961, where about ten stump recurrences survived up to 29 months after treatment. The technology progressed, and in 1979, Hilaris from

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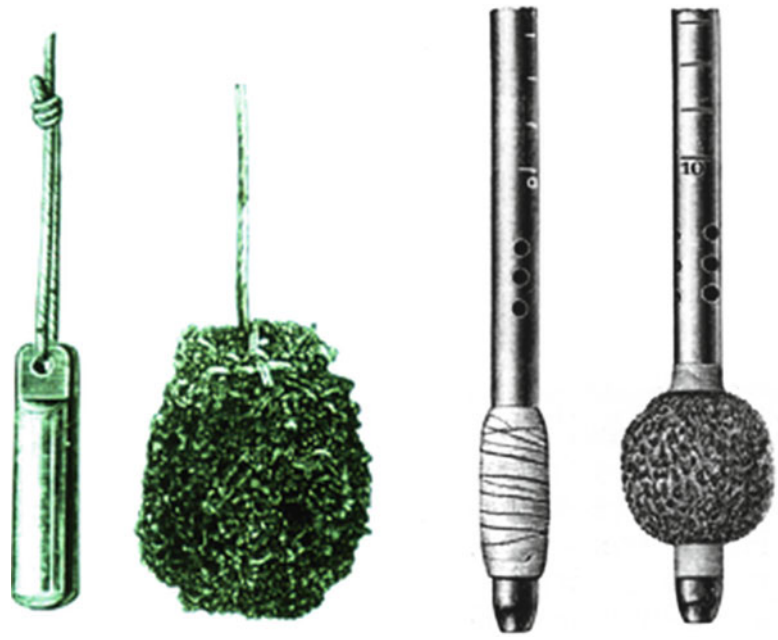

Fig. 9.1 Bronchial tamponade courtesy Prof. Becker

Table 9.1 Brachytherapy classification (ICRU report 38)

Brachytherapy classification	Dose rate (Gy/h)
High dose rate (HDR)	>12
Medium dose rate	2–12
Low dose rate (LDR)	0.4–2

ICRU International Commission on Radiation units and Measurements, *Gy* Gray, *h* hour

New York reported on treatment of 61 patients using again radon or iodine-125 isotope seeds with good results. The first reported use of iridium-92—in tracheostomized patient with adenocystic carcinoma—was reported by Percarpio in 1978. Additional progress was reported by Boedker with placement of a catheter through an indwelling endotracheal tube. However it was not until the publication of utilization of a transnasal catheter for endobronchial brachytherapy by Mendiondo in 1983 that this technique developed more rapidly with considerable improvements and new applications.

Many groups experimented with various isotopes (^{226}radium, ^{222}radon, ^{125}iodine, ^{137}cesium, ^{60}cobalt, ^{198}gold, ^{122}palladium). The isotope that is most commonly utilized and has the most applications at the present time is ^{192}iridium.

The dose of delivery of this isotope can be modulated, and we now distinguish three separate techniques of treatment (Table 9.1).

The low dose rate delivering 0.4–2 Gy/h. has an advantage of relative ease of production and lower cost. It does not require any special equipment. However, to achieve the therapeutic level (2–2.5 Gy) at the target level, the source of radiation has to dwell and remain in place for about 48 h for treatment, thus requiring hospitalization with appropriate radiation exposure precautions. Because of its long duration, albeit single session of treatment, there is obviously an increased risk of migration of the catheter or its dislodgment with the inherent risk of inappropriate radiation.

The medium dose rate (2–12 Gy/h) presents different challenges. The production of the predetermined length strip, containing a specified number of radioactive seeds, is more costly. Considering that the loading of this device must be done manually, it potentially increases the radiation exposure to staff. The total intended treatment dose is generally delivered also during a single session of treatment of short duration of 2–4 h; treatment by this modality can be done as an outpatient procedure without need for hospitalization and with reduced risk of radiation source displacement. This technique is markedly less expensive than the next described high dose rate—HDR (>12 Gy/h).

Because of high intensity of radiation of this source, high-dose-rate loading has to be done,

without undue risk to the staff, thus entirely remotely by robotic computer-controlled device in a special high radiation protection room which raises the cost exponentially. With this technique, however, each session of treatment is short (few minutes). The treatment is done on an outpatient basis, with no need for hospitalization, although to achieve positive results, multiple (on average two to three) procedures are needed, thus further increasing the operational cost of total therapy. Considering the very high dose rate of radiation delivered by this technique, there is potentially more risk for local necrosis.

Indications

The aim of endobronchial brachytherapy (EBB) is to deliver a maximum therapeutic radiation dose to the targeted tissue. Thus, the type, location, size of the lesion, and proximity of other adjacent organs or structures are of utmost importance in success of the brachytherapy.

Dosimetry is obviously distance-dependant from the source and requires meticulous calculations. The dose rate measured at a distance from the source of radiation decreases as a function of inverse square of the distance from this source. So, for example, in our case (Fig. 9.2), the source delivery is 1,500 cGy, the tissue target delivery dose at 10 mm from the source is 750 cGy (reduction by factor of 2), and 375 cGy at 20 mm (one-fourth of that measured at the source).

Unfortunately there is no standardization of measurements in various studies, and the calculations are variably reported as the dose to 5 mm or 10 mm distance from the source.

Considering the potential effects of radiation on neoplastic tissue, it can be used to treat endobronchial or endotracheal tumors and reduce bleeding by abrogation or suppression of vascular supply to the area of treatment. Reduction of vascular supply and necrosis of the tumor might permit recanalization of the lumen of the treated airway. In cases of obstruction of the lumen by extrinsic compression, however, the effectiveness of brachytherapy is probably negligible. This applies predominantly to large tumors in which achieving a uniform therapeutic dose of radiation to the whole mass is not safely possible. Brachytherapy is much more effective in smaller lesions and above all in early lesions with reduced depth of penetration beyond the bronchial or tracheal wall.

In these very selective cases, complete local control of disease can be achieved. Otherwise, brachytherapy is more of palliative modality. For this reason in general, patients are first considered and treated with external beam radiation or stereotactic radiation. As a palliative modality, endobronchial brachytherapy is then reserved for patients who already failed other modalities, with the aim of not exceeding tolerable doses and minimizing risks of toxic doses to surrounding structures. In this way the tumor itself can receive a much higher total dose of radiation, while vascular or neurologic structures receive reduced exposure. In a case of massive endobronchial obstruction, it is advisable to treat this area first with endoscopic debulking of the mass (Nd: YAG laser, electrocautery, cryotherapy, etc.) providing improved aeration to peripheral structures.

Technique

Regardless of the dose-rate delivery system, the basic principle of localization and introduction of the catheter, which eventually will contain the radioactive source, is similar [1].

In general, the reason and planning for using endobronchial brachytherapy is discussed by the multidisciplinary team after initial bronchoscopy, which provides crucial information on the type of the tumor, its location, and size of the treatment area. In cases of obvious endobronchial obstruction, laser or other debulking therapies are advisable to restore at least partially the lumen and possibly penetrate beyond the distal part of the tumor.

On the day of treatment, patients are prepared as usual for flexible bronchoscopic procedure, and the bronchoscope is preferentially introduced through the nose. This permits later fixation and stabilization

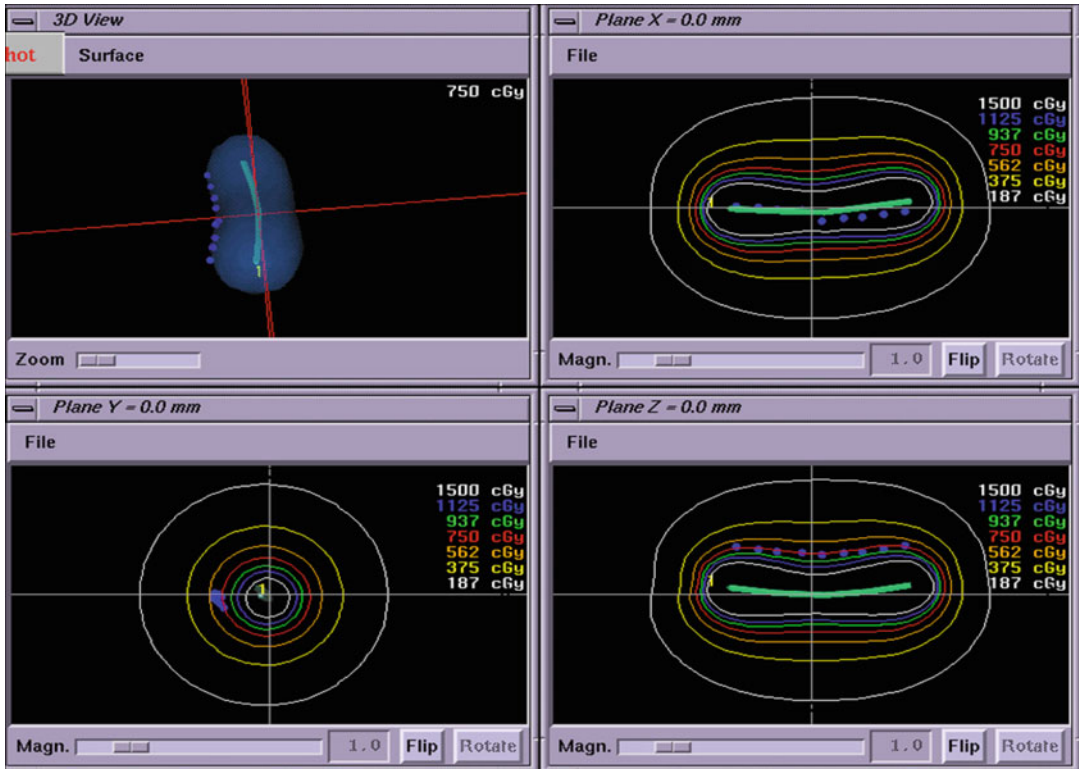

Fig. 9.2 Simulation and calculation of gradual dose delivery in relation to the proximity to the source of radiation

of the catheter in place at the nostril level, thus minimizing the chance of displacement.

The length of the treatment area is remeasured during the bronchoscopic evaluation, and then a temporary guide wire is passed through the working channel of the scope beyond the treatment area, while the scope is removed. The patient is then again re-bronchoscoped, and when the target is localized, a catheter is introduced over the guide wire and anchored properly beyond the planned treatment area, providing adequate margin of at least 10–20 mm. The guide wire is removed and replaced by a simulator ("dummy") until it reaches the sealed end of the catheter wire. This wire contains radiopaque markers (spaced at 10 mm distance), adding in simulation and dose measurement.

At this point fluoroscopic guidance is necessary to ascertain, by placement of the scope at the distant and proximal end of the lesion, the precise length of treatment for seed placement (Fig. 9.3).

Bronchoscopic expertise is useful in proper anchoring of the catheter in the bronchial tree, taking into account catheter stiffness and torque with the aim to have the catheter at proximity of the area to be treated, thus optimizing also calculation and dose delivery.

Once the location of the catheter is secured, the patient can be moved to the treatment room (Fig. 9.4).

Three-dimensional computer simulation and calculation of the planned dose to be delivered are done by a radiation physicist, after which the radiation seed or seeds are inserted either by a remotely controlled robotic delivery system or by a manual after-loading technique. Once the treatment dose is delivered, the catheter is removed.

On some occasions, more than one catheter might have to be inserted for multiple locations or different approaches to the tumor (Figs. 9.5 and 9.6).

There have also been attempts and trials to develop special catheters with a radial anchoring

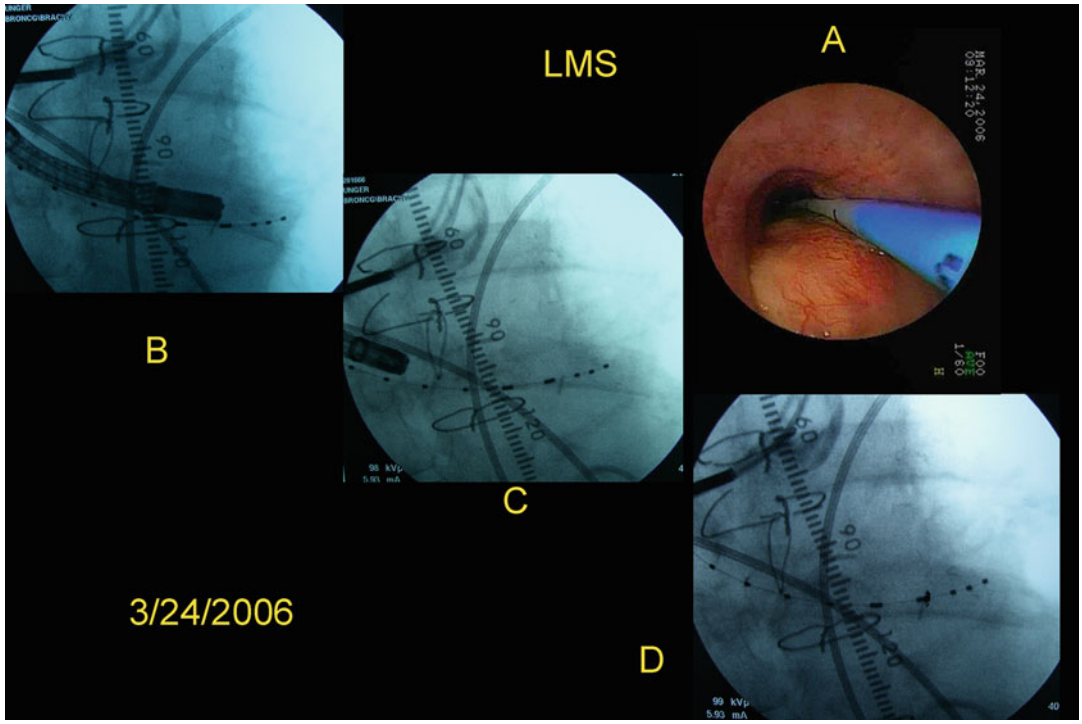

Fig. 9.3 Technique of measurement of length of deployment of the source of radiation. (**a**) An endobronchial image of the catheter in place. Fluoroscopic images: (**b**) Location of the distal end of treatment area, (**c**) proximal end. (**d**) Control with simulator wire and graded markers

Fig. 9.4 HDR procedure room

system, with the goal to keep the catheter centrally in the lumen of the airway (in particular, in cases of tracheal therapy) to minimize potential movement during respiration (Fig. 9.7).

Results

Chella et al. compared the Nd: YAG laser with and without brachytherapy (a prospective, randomized study) in 29 patients with central airway

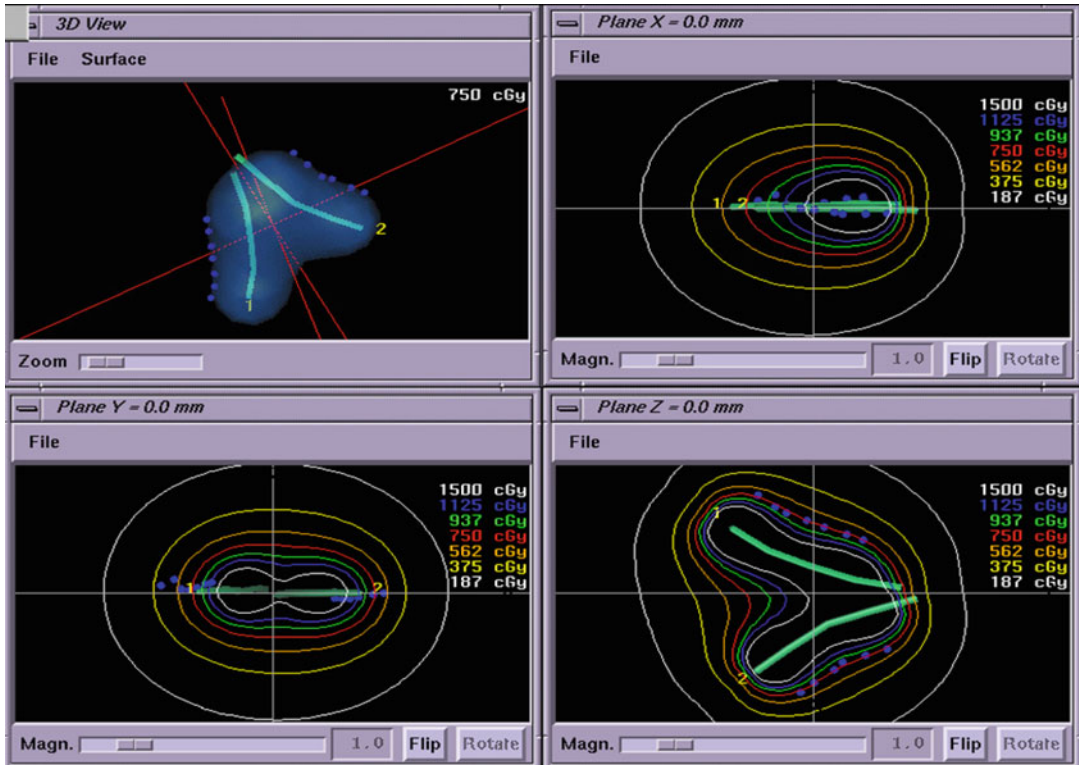

Fig. 9.5 Three-dimensional reconstruction of simulated dose delivery with two catheters in place

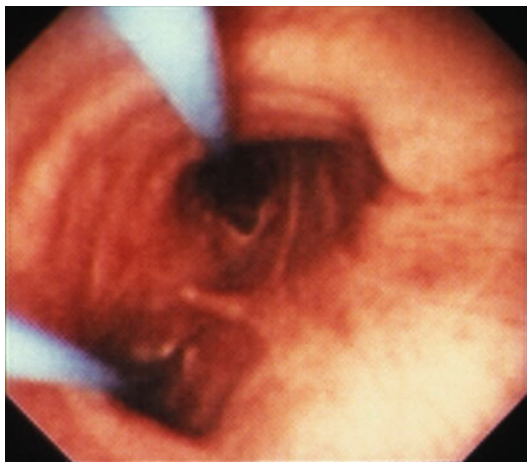

Fig. 9.6 Main Carina after bilateral previous YAG laser therapy and insertion of two catheters to optimize radiation dose to the subcarinal area

involvement. There was improvement in both the symptom-free interval (2.8 vs. 8.5 months, $p<0.05$) and the disease-free interval (2.2 vs. 7.5 months, $p<0.05$). Additionally, the number of endoscopic treatments reduced from 15 to 3 with the use of HDR, thus reducing the cost of treatment [2].

In different series, HDR brachytherapy helps in palliative control of symptoms in 60–90% of cases, and the endoscopic responses were 30–100% depending on the extent of bronchial narrowing, histology, and combination of different treatment modalities.

The efficacy and tolerance of HDR brachytherapy was assessed in 226 inoperable patients of NSCLC by Guilcher et al. from France [3]. The dose was prescribed at 10 mm from the source and treated to mean total dose of 28.7 Gy (24–35 Gy) in 5–6 fractions, once weekly. The 3-month local control was 93.6% with 2- and 5-year overall survival rates of 57% and 29%, and the cancer-specific survival rates were 81% and 56%, respectively. A single catheter was used for most of the patients with proximal tumor location, and two catheters were used for distal tumors. Disease-free survival was longer for

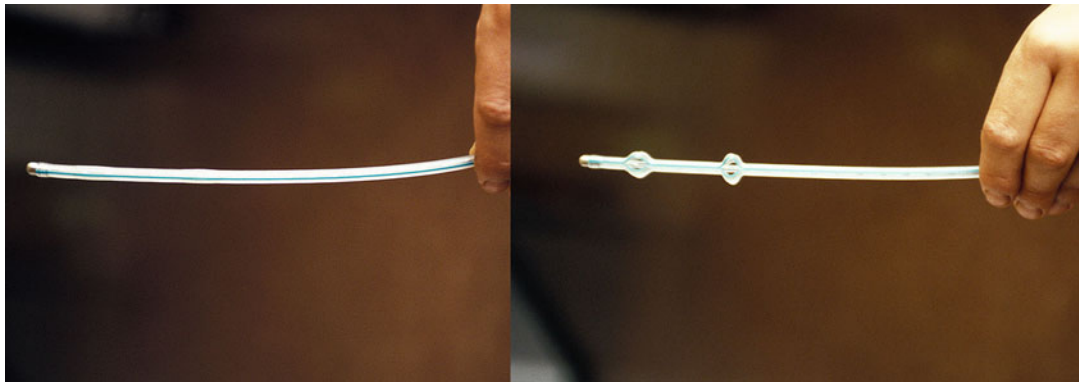

Fig. 9.7 Endobronchial catheter which will contain the HDR source before and after deployment of centro-luminal stabilizers to optimize distribution of radiation (courtesy of Prof. Heiner Becker)

distal tumor location and in patients treated with more than one catheter both on univariate and multivariate analyses.

In another contrast study by Marsiglia, multiple catheters were used in proximal tumors in order to obtain the contact between the catheter and the tumor, but there was no difference in local control based on location of the tumor [4].

Hennequin et al. reported outcomes of HDR brachytherapy in 106 NSCLC inoperable cases treated with six fractions of 5–7 Gy at 10 mm from the source. The 5-year local control was 51.6% and cause-specific survival was 48.5% [5].

Huber et al. compared different HDR fractionation regimens in a prospective randomized study of 73 patients with advanced NSCLC (four fractions of 3.8 Gy, weekly vs. two fractions of 7.2 Gy, 3 weekly, with 10 mm depth prescription). The overall response rate was 58.9% at 3 months, and the 1-year survival was 11.4% and 20.4% for groups 1 and 2, respectively, and the median survival was similar (19 and 18 weeks). The median survival was better for squamous histology compared with others (19 vs. 9 months) [6].

Thus, shorter treatment courses provided similar results compared with protracted regimens with similar rates of toxicity (fatal hemoptysis 22.2% vs. 21.1%). A summary of the randomized studies using HDR brachytherapy and its benefits in combination with EBRT are shown in Tables 9.2 and 9.3 below.

High-dose-rate brachytherapy is a relatively recently introduced technique, and prior to this, low dose and medium dose of Ir-192 wire were used generally as a boost after external beam radiation therapy. Schray et al. [13] from Mayo Clinic reported use of LDR brachytherapy in combination with laser therapy among 65 patients with airway compromise. All patients were treated with prior EBRT and Nd: YAG laser and found to have inoperable disease with obstructing bronchial tumor. A dose of 3,000 cGy was prescribed to 5 mm and 10 mm radii over 20–40 h in the bronchus and trachea, respectively, with a dose rate of 50–75 cGy/h. Forty of fifty-nine patients treated with palliative intent had bronchoscopic follow-up with 60% positive response rate. For patients with prior EBRT, the response rates at successive periods of >12 months, 6–12, and <6 months were 83%, 50%, and 31%, respectively. Eleven patients experienced fistula and/or hemorrhage, of which seven (11%) were treatment-induced.

A retrospective comparison of LDR brachytherapy (110 patients) to prospectively treated patients with HDR brachytherapy (59 patients) was done by Lo Theodore et al. at Lahey Clinic [14]. LDR brachytherapy was done with manual loading of Ir-192 seeds in one to two sessions to deliver a dose of 30–60 Gy, calculated at 10 mm from the source, and HDR brachytherapy was given in 3 weekly sessions of 7 Gy each, calculated at 10 mm radius. Prior EBRT was given to 88% and 85% of patients in each group and laser in 36% and 24%, respectively. Clinical and bronchoscopic improvement was better for the

Table 9.2 Randomized studies of HDR brachytherapy with/without EBRT, Nd: YAG laser

Study	No. of patients	Local control at 3 months (%)	2-year overall survival (%)	Median survival, months
Gulcher et al. [3]	226	93.6	57.0	28.6
Hennequin et al. [5]	106	81.2	47.4	21.4
Marsiglia et al. [4]	34	85.0	51.0 (3 years)	14.4
Peiffert et al. [7]	35	94.3	53.8	23.0
Taulelle et al. [8]	22	95.5	46.0	17.6
Perol et al. [9]	19	83.0	58.0	28.0

Table 9.3 Endobronchial HDR brachytherapy with or without EBRT for occult lung carcinoma

Authors	No. of patients	EBRT dose (Gy)	HDR, total dose (Gy)	Mean follow-up (months)	Cause-specific survival (%)
Sutedja et al. [10]	2	No	30	40	100
Perol et al. [9]	19	No	35	28	78
Furuta et al. [11]	5	40	18	30	100
Tredaniel et al. [12]	29	Yes	42	23	NA

HDR group (85%) than for the LDR patients 72%, $p > 0.05$. The complication rates were comparable (3.6% vs. 2.7%) with equal survival rates (median <6 months).

A phase II study from Japan included 41 patients with occult inoperable endobronchial tumor and treated with LDR brachytherapy after EBRT (40 Gy in 20 fractions over 4 weeks) [15]. A dose of 25 Gy was delivered in five fractions over 2.5–5 weeks, with a reference point of 3–9 mm radius according to the diameter of the bronchus. A complete bronchoscopic response was noted in 39 evaluable patients. At a median follow-up of 24.5 months, recurrence was noted in two patients. In their updated results among 79 patients in 2000, 19 cases of bronchial stenosis and 23 cases of bronchial obstruction were observed [16]. The 5-year disease-free survival and overall survival rates were 87.3% and 72.3%, respectively.

Complications

The risks of complications of endobronchial brachytherapy depend on the tumor location, number of catheters used, dose, frequency of application, and prior therapy. However, no clear prognostic factors are identified. A fatal hemoptysis [6–9, 11, 12] rate of 0–32% is reported in the published data [3, 4, 6, 17–19]. It appears that these events occur more frequently when treatment is aimed at the entrances to the right and left upper lobes and related to the potential invasion of the large pulmonary artery by the tumor. It is important, however, to remember that massive hemoptysis is also part of natural history of even untreated malignancies in this area.

High radiation doses to the bronchial mucosa can cause bronchitis and bronchial stenosis [6, 17, 18]. Different degrees of reaction may justify various additional interventions as summarized by Table 9.4.

Bronchial wall necrosis and tracheobronchial fistula are also reported in a few series [6, 19]. Zaric et al. reported a 5.4% complication rate in 761 patients treated with advanced cancer in a multimodality setting [20].

Independent risk factors can contribute to the high rate of complications. These factors include acute myocardial infarction 6 months previously, hypertension, arrhythmia, chronic obstructive pulmonary disease (COPD), stabilized cardiomyopathy, previous external beam radiation therapy, chemotherapy, and interventional pulmonology treatment, apart from age, sex, tumor histology, and tumor localization.

Table 9.4 Classification of post-EBBT bronchitis and stenosis by order or severity in need for potential additional intervention

1. Whitish fibrinoid circumferential membrane, no significant luminal effect, minimal symptoms, might respond to steroids
2. Fibrinous exudates, mild obstruction, debridement needed, steroids helpful
3. Severe inflammation with fibrinous exudates and fibrosis needs multiple debridements
4. Fibrosis with severe stenosis and lumen reduction, need for photoresection/dilatation and/or stent

In summary, endobronchial brachytherapy is a technique of high utility with a very good safety profile in appropriately selected cases. Its palliative effects, especially in advanced cases of lung carcinoma with airway invasion and recurrent obstruction are particularly salutary. Additional studies are required to determine long-term benefits and cost-effectiveness in cases of minimally invasive neoplastic processes and possible other, more benign pathology.

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Photodynamic Therapy for Early and Advanced Lung Cancer

10

Jose Pablo Díaz-Jimenez and Rachid Tazi Mezalek

Introduction

Lung cancer is the leading cause of cancer deaths in the world [1]. In spite of important efforts developing research lines oriented to increase curability and improve survival, prognosis of lung cancer remains poor.

Photodynamic therapy (PDT) has been studied from decades, and it has been recognized as a useful treatment for a large variety of malignant tumors. In the last years, indications of lung cancer treatment have expanded, and PDT can now be indicated in selected patients as a unique treatment or as neoadjuvant or palliative therapy in the context of a multimodality approach. PDT has many advantages:

- It is minimally invasive; it can be applied as outpatient.
- It is selective, damaging tumor tissue and sparing normal cells.
- It does not compromise additional of future treatments.
- It does not produce long-term side effects.
- It can be repeated many times.
- Low systemic toxicity.
- It is not mutagenic.

The photodynamic reaction is obtained by the association of light and a sensitizer in the presence of oxygen. This combination results in reactive singlet oxygen, killing selectively tumor cells. Cellular death is obtained by more than one mechanism and mainly involves apoptosis or necrosis, vascular damage, inflammatory reaction, and immune response. The surrounding normal tissue is basically respected, but it can be minimally damaged regenerating afterwards [2, 3].

The photosensitivity phenomenon was already known in the early twentieth century. Photodynamic therapy has evolved with the use of new photosensitizing agents. Several sensitizers (known as photosensitizers, PS) are available with different chemical properties and different therapeutic indications. Porfimer sodium (Photofrin) is the most commonly applied to treat patients with thoracic malignancies.

In 1995, the FDA (Food and Drug Administration) approved the use of porfimer sodium for esophageal cancer, and in 1998, it was approved for both early and advanced lung cancer treatment.

Research on PDT is very active. As of today, there are 273 active studies on PDT published on http://www.clinicaltrials.gov. They involve the following lesions: cholangiocarcinoma, skin cancer (melanoma and non-melanoma), prostate cancer, primary and metastatic intracranial tumors, macular degeneration, hepatocellular carcinoma, liver metastasis from colorectal tumors, neurofibroma, head and neck cancers, metastatic NSCLC (spread

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to the pleura), lung cancer, bladder cancer, renal cancer, cervical dysplasia and cancer, breast cancer, esophageal cancer, Kaposi's sarcoma, malignant mesothelioma, lymphoma, chronic leukocytic leukemia, graft versus host disease, transplant rejection, etc.

PDT indications in early and advanced lung cancer will be reviewed in this chapter, discussing the available evidence supporting its application.

Principles

The mechanism of PDT action is based upon the photosensitive molecule activation by a specific wavelength light with the consequent creation of oxygen active forms, being oxygen singlet the most important one. This reaction is known as the photodynamic reaction.

Singlet oxygen produces peroxydatives reactions in cell membranes, cytoplasm, and organelles leading to damage and cell death.

Once the photosensitizer agent has reached the blood stream, it is absorbed by all cells in the body. Normal cells eliminate the photosensitizer soon (in about 48 h), but abnormal or proliferating cells, such as cancer cells or tumor tissues, retain it for a longer period of time (more than 48 h). Its photo activation with appropriate wavelength light from a laser or other source produces a specific tumor tissue ablation [4].

The destruction process is quite complex and not fully understood. Basically, the damage of specific subcellular targets depends upon the location of the photosensitizer, since migration capacity of oxygen from the site of activation is reduced. Porfimer sodium, for example, is accumulated within the mitochondria, and once activated, it causes apoptosis. Other photosensitizing substances have empathy for different organelles, for example, lysyl chlorine p6 accumulates in lysosomes and monocationic porphyrin within cell membranes. PDT produces lethal damage in cells membranes that can be observed within few minutes of light exposure: edema, blistering, ruptured vesicles containing enzymes, reduction of active cell transport, membrane depolarization which produces more photosensitizer intake, increased membrane permeability, and ATPase inhibition [2].

Photodynamic Reaction

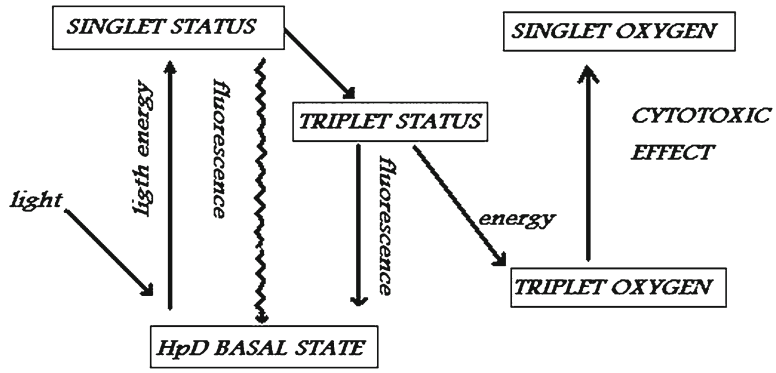
Once the photosensitizer (PS) has been administered, it needs to be illuminated in order to activate. Light used is typically a laser light between 600 and 800 nm within the optical window. Light is then absorbed, producing energy transfer within the PS, thus generating an unstable excited PS (singlet PS*). Singlet PS* can return to its ground state emitting the excess energy as a photon and producing the fluorescence phenomenon and/or heat, or it can go to a higher, more stable energy level, known as "Triplet PS." To return to its ground state, Triplet PS can take two ways; in the presence of oxygen, it can generate a type II reaction (most common) whose end result is singlet oxygen, responsible of cell damage. In anaerobic conditions, it will produce a type I reaction generating free radical formation. Both types of reactions ultimately result in cellular death (Fig. 10.1).

This cascade of reactions is known as photodynamic reaction; it starts with the absorption of a photon and ends up with the formation of free radicals and singlet oxygen whose effects are cytotoxic.

Tumor Destruction

PDT targets are tumor cells, microvasculature, and the inflammatory and immune system. Tumor destruction is based upon three facts:

1. After intravenous injection, the photosensitizer is distributed in all cells.
2. Due to differences in the vasculature and lymphatic drainage, and the uptake of photosensitizer, the latter is selectively retained in tumor cells and interstitial tissue, so that after two days, the concentration is higher within the tumor than in the surrounding tissues.
3. The photosensitizing substance absorbs the light energy and produces derivatives of oxygen (singlet oxygen), with the consequent destruction of tumor [5].



Laser light of 600 to 800 nm wavelength is absorbed by the photosensitizer (PS). Ligth stimulation produces changes in the PS, that passes from a basal energy level to a higher level known as Singlet State. The "Singlet PS" can return to its ground state emitting a photon and producing the fluorescence phenomenon and/or heat; or it can go to an even higher level of energy, more stable, called "Triplet PS."

To return to its ground state, Triplet PS can take two ways: in the presence of oxygen, a Type II reaction originates resulting in singlet oxygen responsible for cell damage; or through a type I reaction (that presents in anaerobic conditions) producing free radical formation. Both types of reactions ultimately result in cell death.

PHOTODYNAMIC REACTION

Fig. 10.1 Photodynamic reaction

Antitumor activity of inflammatory cells and immune reactions are triggered by the sensitized tumor. These two reactions contribute to more complete tumor destruction. But there are some factors that limit it, such as the uneven distribution of the PS agent inside the tumor or oxygen availability. Likewise, some drugs affect the final result of photodynamic therapy, such as adriamycine [6] and corticosteroids [7, 8], both enhancing the effects of PDT.

Animal studies by Diaz-Jimenez et al. have shown that the photodynamic reaction, even when it starts almost immediately after exposure to light, continues to act slowly over a rather long time. "In vivo" model showed that tumor cells transplanted immediately after treatment were able to be implanted and to reproduce, while those transplanted 24 h after treatment were not [9].

Photosensitizers: Past and Present

Most of the photosensitizers were first derived from a cyclic molecule called hematoporphyrin. Hematoporphyrins are tetrapyrrolic pigments, whose base is the porphyrin molecule, formed by four pyrrolic units linked by four methylic bridges.

Hematoporphyrin is obtained from the blood by two consecutive steps. In a first step, hemin is obtained by treating blood with sulfuric acid, hydrochloric acid, and alcohol. In a second step, the extracted iron is used to obtain crystallized hematoporphyrin. This crystallized form of hematoporphyrin is quite impure. In 1961 Lipson, Baldes, and Olsen from the Mayo Clinic treated hematoporphyrin with sulfuric acid and glacial acetic acid, followed by several recrystallization processes, finally obtaining a new and pure

compound suitable for human use. This was called hematoporphyrin derivative (HpD) [10, 11].

Following the same line of research, many others PS were found: the end products of the acetylation of hematoporphyrin, when dissolved in sodium hydroxide, rapidly hydrolyze to a mixture or porhyin, which is active in the location and sensitization of tumors [12].

In 1983, Dougherty described a new component in the HpD: bis-1, 3 (R hydroxylethyl) deuteroporphyn dihematoporphyrin ether or ethyl 8 (DHE), which seemed to be responsible, beside the components mixture of HpD, of the ability to sensitize tumors [13].

Another known sensitizer is tetraphenyl porphyrin sulfonate (TPPS), which is able to be as active as HpD, but it produces neurotoxicity and has a slow serum elimination, and thus, it has no clinical application [14].

The first successful photodynamic treatment was performed at Roswell Memorial Park Institute in the 1970s. It was applied to an animal model using a xenon lamp as light source. The subsequent development of laser technology represented a huge progress for PDT application. After 10 years of research, during 1980, it was already indicated to treat early stage squamous cell lung cancer [15].

Porfimer Sodium

It is the most extensively studied photosensitizer. Porfimer sodium (Photofrin®) and its predecessor, hematoporphyrin derivative, are obtained from hematoporphyrin and complex mixtures of esters and oligomeric hematoporphyrin ethers. At the beginning, initial investigations showed that these substances accumulate selectively and are retained for a longer time in tumor tissue compared with non-tumor tissue. Cytotoxic capacity of PDT with porfimer sodium is limited by the maximum penetration capacity of the 630 nm wavelength light. This wavelength has the highest power to penetrate tissue from 3 to 5 mm. Following the treatment, there is a systemic photosensitivity period that can last up to 6 weeks. Patients should avoid exposure to sunlight or other strong light sources, artificial light, and heat sources (e.g., hair dryers) during the treatment and the posttreatment period [4].

In January 1998, the Food and Drug Administration approved the use of porfimer sodium for PDT in patients with microinvasive lung cancer who are ineligible for surgery or radiotherapy, and later the same year, it was approved to treat advanced lung cancers [16]. Until now, approved indications of porfimer sodium in the USA are advanced esophageal cancer, Barrett's esophagus, prophylactic treatment of papillary bladder tumors, some tumors of the vagina, vulva, and cervix that can be reached by the activating light, low stage lung tumors "in situ" carcinoma, and advanced non-small cell lung tumors.

Benzoporphyrin Derivate:

Benzoporphyrin derivate (BPD) is a second generation photosensitizer. It is a hydrophobic molecule with a maximum absorbing peak at 690 nm. This wavelength is higher than the hemoglobin absorbing peak, so that the light is not significantly attenuated by the blood or red blood cells and its tissue penetration is maximum. Another advantage is that it quickly accumulates in tumor tissue, allowing treating from 30 to 150 min after intravenous injection. Also, it is rapidly cleared from the body. Skin hyperphotosensitivity does not extend more than a few days [4].

5-Aminolevulinic Acid

Endogenous photosensitization induced by 5-aminolevulinic acid (ALA) (Levulan®) is a new approach for photodynamic therapy and tumor detection. It uses a biosynthetic reaction to produce endogenous porphyrins Heme, particularly photoporphyrin IX, which is a very effective photosensitizer that accumulates in mucosal surfaces, such as skin, conjunctiva, oral, rectal, vaginal, endometrial, and ureteral mucosa [2]. It has been used with acceptable results to treat superficial

tumors of the skin, such as the basal cell carcinoma, squamous cell carcinoma, and adenocarcinoma. Residual photosensitivity after treatment lasts about 48 h.

ALA has been also applied orally and by aerosol inhalation via jet nebulizer, showing that both modalities were well tolerated, allowing tumor visualization, and after oral administration, it was possible to perform photodynamic therapy. At 5 and 12 weeks after PDT, marked reduction in tumor volume and recanalization of the bronchus was observed bronchoscopically, with no associated adverse effects [17].

ALA fluorescence can be used in the detection of bladder lesions, early stage "in situ" lung carcinoma, and malignant glioma.

N-Aspartyl Chlorin E6

It belongs to the second generation PS, standing out for its excellent antitumor effects and rapid skin clearance in laboratory animals [18]. The *N*-aspartyl chlorin E6 (Npe6) has a longer absorption band (664 nm), and for that reason, it has a slight advantage in deep tumors treatment. The administered dose is 40 mg/m^2, and the laser power density applied is 100 J/cm^2. Adverse effects are minimal, and cutaneous photosensitivity disappears within two weeks after administration.

In 2004 it was approved by the Japanese authorities (Japan Commonwealth of Health, Labor and Welfare) for early lung cancer treatment and in 2010 for advanced lung cancer treatment.

Other Photosensitizers

As we mentioned above, many PS are now available for different indications. So far the PS approved for treatment of lung cancer are porfimer sodium (USA, Europe, Asia), temoporfin (*m*-tetrahydroxyphenylchlorin, Foscan, in Europe), taloporfin (mono-L-aspartylchlorin-e6, LSII, in Asia), and 2-(1-hexyloxyethyl)-2-devinyl pyropheophorbide-a HPPH, under research.

A summary of the main PS is depicted in Table 10.1.

Technique

Photodynamic therapy is a minimally invasive technique that involves administering a PS agent, which is selectively retained by tumor cells and activated with light of a specific wavelength producing the photodynamic reaction as discussed above.

Administration of a sensitizer can be done by slow intravenous injection (over 3–5 min), orally, by aerosol inhalation via jet nebulization, or topically. Porfimer sodium, the most used agent in lung cancer is administered intravenously.

Doses and window period until bronchoscopic illumination are variable depending upon the selected product. Porfimer sodium is given 48 h before bronchoscopy at a dose of 2 mg/kg while Npe6 injection is administered 4 h before illumination at doses of 40 mg/m^2.

After the appropriate drug-to-light interval, bronchoscopy is performed under topical anesthesia or conscious sedation. The tumor area is illuminated with a 630 nm wavelength laser light without thermal effects, being the Argon-Dye laser or diodes laser the most commonly used (Fig. 10.2). Hematoporphyrin is activated and made cytotoxic and hardly affects healthy tissue. Two types of quartz fiber of 100–200 J/cm^2 are available: front light microlens fiber (Fig. 10.3) or 360º diffusing light cylindrical fiber (Fig. 10.4). The microlenses are used for small and superficial tumors such as "in situ" carcinoma. The cylindrical fiber is appropriate for parallel bronchial lumen tumors, those that involve small branches of the bronchial tree and in exophytic tumors. It is also useful for large tumors in which the fiber is inserted directly inside the tumor.

Two days after treatment, a clean-up bronchoscopy should be performed to remove viscous mucus and debris that cannot be expelled spontaneously by the patient. Sometimes, it takes more than one cleaning session to avoid complications such as infection, respiratory distress, or respiratory failure [20].

Table 10.1 Photosensitizers[a]

Photosensitizer/generic name	Commercial name	Administration formulation	Approved indications/clinical trials	Skin photosensitivity
Hematoporphyrin derivates (HpD)/porfimer sodium	Photofrin®	IV/topic/powder for solution Wavelength: 630 nm	Esophageal cancer, Barrett's esophagus, gastric, cervical dysplasia, bronchial, bladder, and lung cancer	1–3 months
Benzoporphyrin derivate monoacid ring A (BPD–MA)/verteporfin	Visudyne®	IV/liposomes	Age-related macular degeneration	3–5 days
Mesotetrahydroxyphenylchlorin (m THPC)/temoporfin	Foscan®	IV/Solution in ethanol and propylene glycol Wavelength: 652 nm	Palliative advanced head and neck cancer/squamous cell carcinoma	Up to 6 weeks
Tinethyletiopurpurin (SnET2)/rostaporfin	Purlytin®	IV/lipid emulsion	*Clinical trials*: skin, prostate, and metastatic breast cancer, Kaposi's sarcoma, and aged-related macular degeneration	2–3 weeks
Lutetium texaphyrin/motexafin lutetium	Lutrin®	IV/powder for solution	*Clinical trials*: skin and breast cancer	1–2 days
5-Aminolevulinic acid (5 ALA)	Levulan®	Topical/oral/IV/powder for solution/cream	Active keratosis. *Clinical trials*: Basal cell carcinoma, esophageal, gastrointestinal, lung, and non-melanoma skin cancer	1–2 days
Methylamino levulinate	Metvix®	Topical/cream	Active keratosis, basal cell carcinoma, Bowen's disease. *Clinical trials*: acne	Uncommon
Hexylaminolevulinate (HAL)	Hexvix®	Topical powder for solution/gel	Bladder cancer diagnosis. Clinical trials: rectal adenoma and cancer diagnosis, cervical dysplasia	Uncommon

[a]Adapted from Wachovska et al. [19]

Current protocols use a power of 200–400 mW/cm^2 to apply a total light dose of 100–200 J/cm^2 in a treatment time of 500 s [20].

In addition to Argon-Dye and diodes lasers, other sources of light have been applied, such as the gold vapor laser, copper-dye laser, ecximer-dye laser, YAG laser (yttrium, aluminum, and garnet), and KTP laser (potassium titanyl phosphate), or an optical parametric oscillator [21].

Indications

Selected patients with early and advanced lung cancer (Table 10.2).

Contraindications

- Porphyria or porphyrin allergy
- Those of flexible bronchoscopy

Adverse Effects

- Skin and eye photosensitivity: It lasts from 4 to 6 weeks when porfimer sodium is administered and less with other PS such as the new generation PS (see text and Table 10.1). Patient should avoid direct exposure to sun or any other source of intense light or heat such as halogen lights and hair dryers.

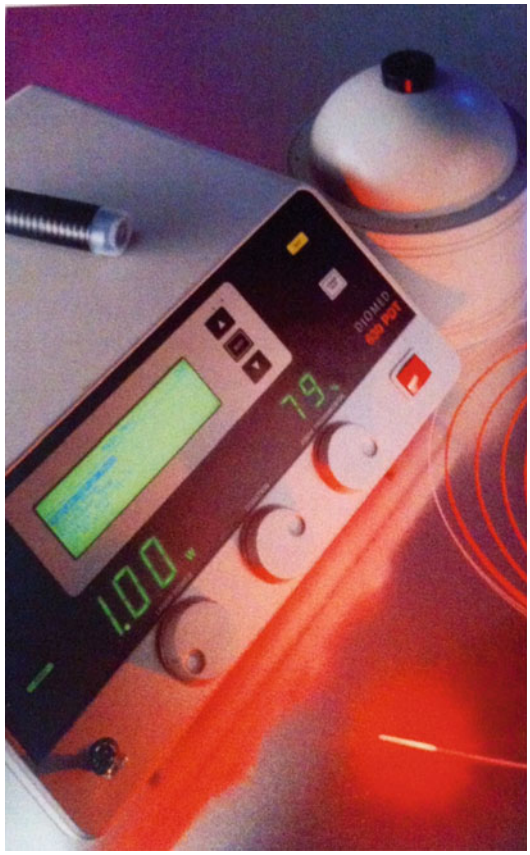


Fig. 10.2 Diodes laser of 630 nm

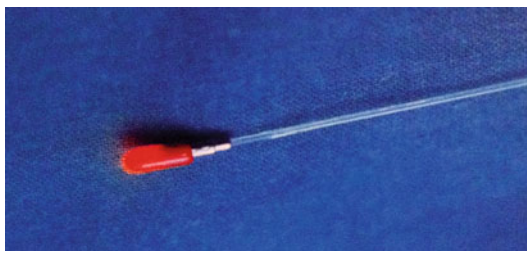


Fig. 10.3 Microlens fiber

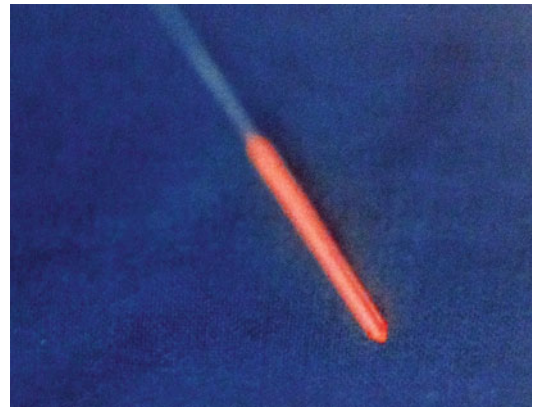


Fig. 10.4 Cylindrical fiber

Table 10.2 PDT summary indications

Definitive therapy for early stage central endobronchial tumors
Definitive therapy for early stage locally recurrent central tumors following surgery or radiation therapy
Definitive therapy for roentgenographically occult central tumors
Definitive therapy for synchronous primary carcinomas
Palliation to reduce endobronchial luminal obstruction and tumor stenosis, improve performance status and respiratory function, and resolve acute hemoptysis and poststenotic pneumonia
Neoadjuvant therapy to reduce the extent of surgical resection (pneumonectomy → lobectomy)
Neoadjuvant therapy to convert originally inoperable patients to surgical candidates
Treatment of locally advanced disease as part of multimodality therapy
Treatment of disease with pleural spread as part of multimodality therapy

- Adverse reactions to photosensitizing substance.
- Fever (approximately 20%).
- Dyspnea due to airway edema and accumulated secretions. A clean-up bronchoscopy may be indicated.
- Atelectasis or respiratory failure due to retained secretions.
- Infections: bronchitis, post-obstructive pneumonia.
- Massive hemoptysis.

Patient Selection for Curative Treatment

Patient should be carefully selected when planning this treatment. The limits of the tumor and its penetration in the bronchial wall are crucial for successful results.

The Japanese Society of lung cancer defines the criteria of early central lung tumor selection [22]:

Table 10.3 PDT contraindications (advanced lung cancer)

• Extrinsic compression or submucosal infiltration
• Erosion or invasion of vascular structures (high risk of bleeding)
• Tracheoesophageal or bronchopleural fistula
• Tracheobronchial obstruction lesions that involve more than 50% of the airway lumen of trachea, main bronchi, carina, or patients with pneumonectomy
• Acute obstruction of the airway
• Porphyria, allergy, or hypersensitivity to porphyrin
• Leukocyte count less than 2,000/mm^3, or platelet count less than 100,000/mm^3, or prothrombin time upper than1.5 of normal limit

Table 10.4 PDT in early stage lung cancer

References	Pathology (*n*)	Response	Surviving (months)
Edell et al. [30]	14	CR 14/17 (71%)	7–49 (10 pat.)
Furuse et al. [31]	59	CR 45/59 (83%)	14–32
Imamura et al. [32]	39	CR 25/39 (64%)	4–169 (17 pat.)
Okunaka et al. [33]	10 (sync)	CR 10/10 (100%)	38 (media)
	17 (met)	CR16/17 (94%)	
Sutedja et al. [34]	39	CR 28/39 (72%)	2–95

CR complete response, *Sync* synchronic, *Met*. metachronic, *Pat.* patients

1. The tumor must be located at a subsegment level or more proximal (more distally located tumors are difficult to illuminate).
2. Tumor margins must be visible bronchoscopically.
3. Major axis of the tumor <2 cm.
4. Histological type by pathology sampling: squamous cell carcinoma.

It also defines three types of lesions by endoscopic appearance: flat lesions, nodular lesions, and early polypoid lesions. It has been shown that lesions protruding (nodular or polypoid) tend to invade the bronchial wall in more depth than the flat-type lesions. Flat lesions less than 10 mm in diameter and visible distal margins are "in situ" carcinoma in 90% of cases, suggesting to be the ideal indication for curative PDT [23, 24].

PDT in Early Stage Non-Small Cell Lung Cancer

PDT application can be indicated in the following situations:

- Early stage intraluminal and central tumors: size <1 cm length, no extracartilaginous wall invasion, and no lymph node compromise
- Roentgenographically occult central tumors: visible under bronchoscopy, size <1 cm, no extracartilaginous wall invasion, no lymph node compromise, and no lesions appearing in high-resolution computerized tomography

Important: If there is lymph node involvement, PDT is formally contraindicated as the only and definitive treatment.

Early stage lung cancer can be successfully treated with PDT. Cortese et al. [25, 26] set the basis for this important line of research at the early 1980s, when they reported complete response in patients treated with PDT for microinvasive tumors with <5 mm depth of invasion. In Japan, Hayata et al. have studied extensively PDT in early stage lung cancer, showing that approximately 90% of superficial tumors <1 cm of diameter can be completely eradicated with PDT. Patients with nodular tumors <0.5 cm of diameter showed the same results [27]. Of 81 patients who had complete response to treatment, only two died of primary disease in the follow-up. Fifteen patients were alive and free from disease at 5 years, three showing similar results at 10 years follow-up. The complete response rate was 71%.

In 55 patients with early lung tumors and treated with PDT, 89% had a complete response, with the best results obtained in those patients with lesions smaller than 1 cm diameter whose distal margins were visible under flexible bronchoscopy [20]. Larger tumors tend to penetrate deeper into the bronchial wall with more risk of nodal involvement. In the group of patients treated by Cortese et al. [25], ten patients treated with PDT ultimately required surgery and 30% of them presented N1 nodal staging during surgery.

Nodal involvement represents a direct tumor invasion, and the unanswered question after analysis was if this nodal compromise was a result of a delay in surgical treatment caused by PDT application. PDT is not curative when there is nodal involvement, so it is very important to be aggressive in the search of nodal compromise before indicating treatment. Endobronchial ultrasound has been presented as a useful method to determine the depth of invasion of small tumors and to detect nodular involvement.

In the Surgery Department of Tokyo Medical College, 251 patients with 297 lung cancers received PDT from the year 1980 and afterwards [15]. At follow-up, 81% of 95 patients that presented with 116 early stage lesions had complete remission. Of the 77 patients with complete remission, 12 had recurrence. A follow-up during 1997 showed that 72 patients were disease-free after 2–195 months. Patients who had superficial lesions had complete remission [28].

Cortese et al. presented a group of 21 patients with early stage lung cancer treated with PDT [25]. Fifty-two percent of them had a complete remission over 1 year. A total of nine patients, who were followed for an average of 68 months, did not need a surgical procedure. The authors concluded that 43% of patients (range 22–66.6%) who are candidates for treatment with PDT can avoid surgery. The cost-effectiveness analysis favors the use of PDT in those patients. PDT offers a better quality of life particularly in patients with multiple tumors or elderly patients [15].

A lung tumor is considered roentgenographically occult (RO) when it is detected by bronchoscopy but cannot be seen by the available image methods. Another scenario is a patient with positive sputum cytology that undergoes bronchoscopy, detecting a cancer lesion not visible in radiological images. The majority of patients with roentgenographically occult carcinoma ultimately will have a centrally located early stage squamous cell carcinoma. Surgical resection has been the historical therapeutic choice for RO lung carcinoma, but PDT is gaining more and more literature support, showing good results.

Endo et al. [29] in Tohoku University Hospital treated 48 patients with a follow-up of 12 years. All of them were surgical candidates and presented with radiologically occult bronchogenic squamous cell tumor with <10 mm length. After treatment with PDT, 94% of them had a complete response with a survival rate of 81% at 5 years and 71% at 10 years.

Fujimura et al. consider PDT as a first line treatment modality for patients with roentgenographically occult carcinoma of the lung, bronchoscopically visible and less than 1 cm length, without extracartilaginous invasion or lymphatic node involvement [30].

PDT-treated patients can be at higher risk for recurrences, and they require close follow-up. Recurrences following PDT can be treated again with PDT, surgery, or radiation therapy.

Synchronous bronchogenic tumors can appear in 1–15% of patients with lung malignancies. They typically present in a central localization and most often are squamous cell tumors [31]. PDT has been typically considered in patients with poor medical condition or low lung reserve, which cannot receive aggressive radiation and/or are not curable with surgery. PDT could be considered as well in properly selected patients who could be surgical candidates. Sokolov et al. reported that there is a correlation between tumor size and the chance of regression. In a group of 104 patients presenting with synchronous lung primary tumor treated with PDT, a complete regression was observed in tumors less than 1 cm in diameter [32].

Indications under research are peripheral lung cancer of less than 1 cm in nonsurgical candidates. Illumination of these lesions is performed via transthoracic, inserting the catheter within the tumor [33].

In Summary

The average survival of patients with lung cancer is about 13% [32]. A third of these tumors are non-small cell carcinomas. At the moment of diagnosis, approximately one-third of the patients are in stage I or II. Surgery is the standard of

therapy for patients in stage I, II, or IIIA, and regardless the size of the lesions, approximately 70% of patients will require lobectomy. The remaining 30% will require bi-lobectomy or pneumonectomy [34]. The survival for stage I patients has been established from 55 to 75%. For the subgroup of patients with T1N0 disease, survival at 5 years ranges from 60 to 82% [35, 36].

However, even in early stages, recurrences can occur. According to a report, the recurrence rate is about 27%, with 60% of patients recurring during the first 2 years after resection. Recurrence in the same lung or in the stump area was more common in squamous cell carcinoma histological type. The incidence of a second primary tumor was 34% (synchronous in 12% and metachronous in 88%). Therefore, in spite of surgery, patients with early stages lung cancer have a high rate of tumor recurrence and a high probability of developing a second tumor [37].

Since the majority of lung cancer patients have underlying COPD with diminished pulmonary reserve, it is desirable to offer a therapy with minimal impact on lung function. As discussed, the incidence of second primary tumors is increased in lung cancer patients, and when treating an early lung tumor, we have to take into account that the patient may need additional surgery or other therapies in the future that may further decrease the lung capacity.

Radiation therapy is the standard second-line treatment for patients who are inoperable, with a range of complete responses from 50 to 70% and median survival of 22–48 months for stage I disease. The 5-year survival for patients with T1 tumors who are treated with external radiation varies from 10 to 40% [38]. The best results observed in surgical patients may be due in part to the fact that they are more carefully staged.

Patients who are inoperable due to a poor pulmonary reserve will suffer further deterioration in lung function after radiation, secondary to radiation pneumonitis and fibrosis. Also, those patients receiving surgery or maximum radiation doses cannot be retreated in most cases, which is a great disadvantage in a disease with a high recurrence rate.

It is evident that, in patients with poor lung reserve, there is a need for therapeutic modalities that can be repeated if necessary and that do not exclude the use of other methods, if more tumors develop.

In the attempt to spare lung function, treatment modalities that produce local damage to the tumor including brachytherapy, cryotherapy, electrocoagulation, laser, and photodynamic therapy have been applied. With the exception of brachytherapy, their application is limited to centrally located tumors within the endoscopic view, and they all have a penetration power of few millimeters. While most of these treatments produce nonspecific tumor damage, PDT causes selective death of tumor cells with subsequent necrosis of the tumor, respecting the adjacent healthy tissue.

The curative effect of PDT in early stage and superficial tumors has been studied extensively and has been documented in several studies in phases II and III. Curative results range from 80 to 100% in the short-term follow-up and from 50 to 60% in long-term follow-up. The main influencing factors for survival are tumor size and penetration depth. Success also depends on the ability to visualize the full extent of the tumor during bronchoscopy, allowing complete illumination of the lesion. Evaluation of location and tumor size is therefore very important. The use of bronchoscopy and high-resolution computed tomography may improve staging and response assessment. Ultrasound has also been used to estimate the depth of the tumor in patients with roentgenographically occult cancer.

One of the reasons for long-term therapy failure is the high incidence of a second primary. Therefore, patients must be followed with regular bronchoscopies, to control local recurrence and to exclude the presence of metachronous lesions, which can be treated with PDT if present.

Complete and prolonged remissions that have been published are promising, but they do not reach the success of surgery (more than 80%). However, it is essential to consider that the term "early cancer" is generic and includes different histological types, with different biological properties and prognosis.

PDT is a first line therapy for "in situ" carcinoma. Microinvasive carcinoma, however, is an optional indication to be only used in patients with high risk of surgery or inoperable. Invasive carcinoma is an indication only in a highly selected group of inoperable patients. Severe dysplasia is not a formal indication for this treatment so far.

PDT in Advanced Non-small Cell Lung Cancer

PDT can be applied in advanced lung cancer in the following situations:

- To relieve endobronchial obstruction from primary or metastatic tumors.
- To relieve symptoms such as hemoptysis or post-obstructive pneumonia.
- To downstage inoperable patients making them candidates for surgical treatment or to limit the extent of surgery by reducing tumor extension.
- As a part of a multimodality treatment in locally advanced disease, slowing disease progression and prolonging survival. Same results can be obtained in pleural spread of the tumor.
- To treat surgical stump recurrence.

A review of lung cancer death showed that 57% of patients with nonsurgical disease will die of local complications such as asphyxia, hemoptysis, pneumonia, and empyema [39–41]. Other publications show that 36% die from the same causes, whether or not they had surgery. Similar causes of death were found in 58% of patients with surgery versus 83% without surgery in another report [42]. Considering that at most, 20–30% of patients with bronchogenic carcinoma are surgical candidates at the time of diagnosis, it can be assumed that most inoperable patients will require palliative treatment at some point during the course of their disease.

However, the use of PDT as palliation in inoperable obstructive cancer patients should be evaluated in the context of what can be obtained with conventional treatment. Laser therapy coagulates and vaporizes tumor tissue, being highly effective in debulking the airway, particularly in centrally located tumors. It requires general anesthesia but is fast and safe. Massive hemorrhage, respiratory failure, or cardiac arrest are possible as severe complications of laser photoresection, but its incidence is quite low (1.5%). Laser treatment can be associated to minor complications as well, in the order or 0.5% of cases [20].

Based on the available literature, photoresection using Nd-YAG laser is considered, by many experts, as the "gold standard" to treat central airway partial or complete obstruction which is due to nonsurgical and malignant primary or metastatic disease [43, 44]. However, PDT is a useful palliative method with some advantages over laser therapy, particularly in peripheral tumor localization. In fact, PDT produces more complete tumor destruction, and a better survival rate has been found in many studies comparing laser versus photodynamic therapy.

In 1998 a multicenter prospective randomized study comparing PDT versus Nd-YAG laser in partially obstructive lung cancer was published. Results from 15 centers in Europe and 20 in the USA and Canada were analyzed. In the European group, only 40% of patients had prior treatment, while in the American group, all patients had some type of treatment prior to PDT. The study showed that tumor response was similar for the two therapies at the end of the first week, but within a month, 61% and 42% of patients treated with PDT in Europe and the USA/Canada, respectively, had further response, while patients treated with Nd-YAG, 36% and 19%, respectively, were responding in the two workgroups (Europe and USA/Canada). Twelve and 6% of patients treated with PDT versus 3% and 5% of patients treated with Nd-YAG experienced biopsy-proven complete response, respectively. The improvement in dyspnea and cough was higher in patients treated with PDT in Europe and was similar in both treatments in the USA/Canada group. The study conclusion was that PDT was superior to Nd-YAG laser to improve dyspnea, cough, and hemoptysis. The incidence of adverse

events was similar in both groups, and 20% of patients treated with PDT showed photosensitivity reactions. Those events were due to failure to comply with the precautions suggested [2].

Another 14-year prospective experience in 175 patients treated with PDT for squamous cell tumor or endobronchial adenocarcinoma and tracheal adenocarcinoma was published [5], including patients that had failed or refused treatment or were ineligible for conventional treatments. Results showed that survival was affected mainly by the stage of the cancer.

Analysis of time to re-obstruction in patients treated with Nd-YAG laser versus PDT showed that even when immediate results were better in patients treated with laser resection, affected areas were re-obstructed faster in the laser resection group of patients (2 weeks in the laser-treated group versus 4 weeks in the PDT group).

A randomized study conducted in the USA, comparing efficacy and safety of PDT versus Nd-YAG laser in obstructive lung cancer, showed that both treatments were equally effective in relieving endobronchial obstruction. Time to treatment failure was slightly longer in the PDT group while the risk of local recurrence after PDT was lower than after Nd-YAG laser treatment [45].

Another prospective study of 41 patients compared the combination of PDT and radiotherapy versus radiotherapy alone. Results showed that the airway opened completely in 10% of the patients treated with radiation therapy versus 70% of patients treated with the combination of PDT and radiotherapy. Twenty percent of patients did not respond to any of the two treatments [46].

A group of ten patients with inoperable non-small cell carcinoma with different degrees of tracheobronchial obstruction (86% ± 2) showed an improvement in the obstruction of 50% or more in four patients and 50% or less in six patients. However, all patients improved their symptoms, especially cough. Adverse effects included burns in two patients and one moderate anasarca [47].

We found similar results in a group of 31 inoperable NSCLC patients with airway obstruction [48]. These patients were prospectively randomized to PDT or Nd-YAG laser. The immediate initial response was better in the group treated with Nd-YAG laser, but the duration of response was longer in the PDT group, with a better survival rate. The number of complete, biopsy-proven responses was very low and of short duration. Palliation of symptoms by Karnofsky index was similar in both groups. The PDT group had higher incidence of adverse effects, and these were more severe than in the group treated with Nd-YAG laser. Photosensitivity was the most important one.

In surgical stump recurrence, PDT has proved benefits also. Historically, the survival of these patients is around 9 months. McCaughan and Williams have observed 5-year survival of similar cases treated repeatedly with PDT [5]. Some authors [20] disagree with this view and discourage the use of PDT for the treatment of recurrence in the surgical stump, based mainly on the difficulty on applying laser light in the areas located distally to the surgical suture. However, a complete response has been reported following PDT application in those patients, although they presented 33% recurrence rate with the need of repeated applications within 15 months of the initial therapy [49].

PDT can be of help in treating hemoptysis, since it produces thrombosis of small vessels. In a publication, the amount of bleeding was recorded before, during, and after treatment with PDT, and there was a statistically significant reduction of bleeding during and after treatment [5]. PDT has been also described as effective in the palliative treatment of patients with uncontrollable life-threatening hemoptysis [50].

In cases of non-small cell lung cancer with pleural dissemination, patients can be treated by PDT following a complete surgical resection.

Historically, advanced lung cancer has been treated with the combination of chemotherapy and radiotherapy. However, new combinations are accepted as a valid therapy in the palliative management of non-small cell carcinoma. Application of PDT as a part of a multimodality treatment has proved benefits, particularly in

pleural spread. Friedberg et al. presented a group of patients treated by complete or partial surgical resection, followed by pleural PDT. Results showed that at 6 months, 73% of patients had local control, with a median survival of 22 months, compared to a survival of 9 months in similar historical control patients [51].

PDT treatment associated with external radiotherapy seems less harmful than the combination of radiotherapy and brachytherapy. It is reasonable to assume that PDT produces less toxicity and it can be a valid option in the multidisciplinary palliative treatment. Studies have shown better symptom control and clinical signs in patients treated with a combination of PDT and external radiation compared to those treated only with external radiation [52].

Similar results have been found with the combination of brachytherapy and PDT, obtaining good local control, distal metastasis-free survival, and overall survival rate [53].

A synergistic effect has been also proposed for the combination or PDT and chemotherapy [54].

In Summary

Based on available literature, PDT is a valid palliative option for advanced non-small cell lung cancer. PDT can be a palliative option for patients with locally advanced or metastatic non-small cell lung cancer, decreasing symptoms, and improving quality of life and survival.

Since Nd-YAG laser has been applied as a palliative method from the early 1970s and according to some it is the treatment of choice in tumor debulking of the airway, most of the studies compare PDT to laser resection. Available results on laser resection versus PDT in the treatment of tumor obstructive lesions showed that both methods are similar in obtaining palliation and alleviating symptoms. PDT may be easier to apply and does not require general anesthesia, but it can produce photosensitivity following the application. The choice of one method or the other depends upon several conditions, such as patient clinical status, availability, costs, and operator experience.

Resection with Nd-YAG laser seems to be the best choice in centrally located tumors, which are easily reached with the rigid bronchoscope, coagulated, and then resected. PDT, in turn, can be applied with fiber-optic bronchoscope and can treat more peripheral lesion and does not require mechanical removal immediately after irradiation. However, a cleaning bronchoscopy after PDT is needed to remove debris.

PDT is discouraged in patients with tracheal lesions that extend to both main bronchi, extensive carina involvement, or in patients with pneumonectomy. The inflammatory reaction that follows PDT generates significant edema, and when tumors are located in these critical areas, it can severely compromise respiratory status and produce respiratory failure.

PDT is not a fast airway opening treatment. Patients who present acute obstructive symptoms are not candidates for this treatment and should be treated with another fast-opening modality.

PDT is not recommended when the tumor has infiltrated the tracheobronchial wall or vascular structures, since it may cause perforation, fistulas, and/or fatal bleeding.

Adverse events are similar in both laser and PDT treatments. However, some studies show a relationship between the use of PDT and fatal bleeding events posttreatment. Four of the 178 patients in the work of McCaughan and William [5] died of pulmonary hemorrhage within thirty days after treatment. All of them had hemoptysis before treatment. The percentage of deaths due to hemorrhage does not seem higher than after laser treatment.

Palliation length is better in PDT-treated patients. The rate of complete response is low for both methods.

Photoresection with Nd-YAG laser and PDT are both ineffective when there is submucosal infiltration or extrinsic compression. In this case, patients can benefit from radiation therapy and, if necessary, placement of an airway prosthesis [20].

PDT has been applied successfully as preoperative therapy, obtaining a reduction in the extension of the disease and/or converting patients in operable candidates. In selected patients, it can

be able to limit the extent of the resection (i.e., lobectomy instead of pneumonectomy).

Since most patients have a combination of intraluminal, submucosal, and peribronchial disease, it seems reasonable to use multimodality therapy to treat advanced cancer. The information available shows that the combination of PDT and external or internal radiation and chemotherapy can have synergistic effects. Some issues remain to be clarified, such as the appropriate sequence of this different therapies application.

Strict monitoring of patients treated with PDT as single or multidisciplinary treatment is guaranteed, since recurrences are frequent. Available techniques that can help diagnosing them and evaluating its extent are autofluorescence bronchoscopy and endobronchial ultrasound.

Endobronchial Ultrasound: A Complementary Method for PDT Application

The endoscopist view is limited to the surface of the airway. Ultrasound can evaluate structures in depth. Processes located on the wall or outside the lumen can only be suspected by indirect signs such as discoloration, edema of the wall, changes in the vasculature, elevation of the mucosa, and distortion of the bronchial wall.

Many abnormalities involving the peribronchial structures have not visible signs. Advanced imaging techniques such as computerized axial tomography or magnetic resonance imaging are useful, but they are limited in detecting carcinomatous spread in peribronchial areas. While evaluating a patient with early stage lung cancer, endobronchial ultrasound (EBUS) can help assessing depth of wall invasion. In many cases, the mucosa appears macroscopically intact or has only minimal changes. In a study, EBUS could detect submucosa invasion and peribronchial extension [55]. The absence of invasion confirmed by the EBUS suggests localized tumor and can be treated endoscopically with curative intent. Other authors suggest that the absence of tracheobronchial wall invasion assessed by EBUS is enough to define the lesion as "early disease" and therefore should be considered an indication for the successful application of PDT [56].

Kurimoto et al. demonstrated the usefulness of EBUS, using 20 MHz probes, in studying the depth of invasion of the bronchial wall and its correlation with histopathological findings. In a 95.8%, there was agreement between both methods. Five layers of the bronchial wall can be defined in ultrasound images; from the third to the fifth, they correspond to the cartilage. Photodynamic treatment response is complete in lesions whose third (sonographically defined) layer is intact [57].

EBUS can complement diagnosis of localized bronchial lesions and improve the selection of patients that can benefit from PDT.

Summary and Recommendations

PDT is available from the 1980s, and since then, the number of patients who have benefited from it is increasing every day. The best results are obtained when the tumor is in early stage, where PDT is a first line option for both inoperable and operable selected patients. PDT has also proven to be an effective palliative treatment.

PDT can be used alone or in combination with other treatment options in a multimodality fashion.

PDT is minimally invasive and well tolerated, being photosensitivity its main adverse effect. The photosensitizing agent used in most clinical trials is still porfimer sodium whose photosensitivity lasts around 6 weeks. Newer agents have a very short period of photosensitivity after application. Skin protection is essential, and patients must be advised to avoid sunlight and other sources of light and heat as discussed; otherwise, severe retinal and skin damage can occur [58, 59].

In summary, PDT is a valuable therapeutic option for early and advanced disease that should be considered when dealing with lung cancer patients. Decision on administering this treatment should be discussed in a multidisciplinary team, on a case by case basis.

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Benign Tracheal and Bronchial Stenosis

11

Jose Pablo Díaz-Jimenez and Rosa M. López Lisbona

Introduction and Definition

Benign airway stenosis is characterized by the progressive reduction of the airway diameter. Following an injury of the tracheal or bronchial mucosa that produces an abnormal re-epithelization, a replacement of normal wall tissue by fibrous tissue takes place.

The most common cause is iatrogenic, as a complication of prolonged endotracheal intubation or tracheostomy [1, 2]. Other causes are idiopathic, infectious, chemical damage (such as gastroesophageal reflux or toxic inhalation), radiotherapy, and associated to systemic diseases (e.g., Wegener's granulomatosis, amyloidosis)

Patients can present with variable symptoms, depending upon to the severity of the stenosis and to his/her cardiorespiratory reserve, from no symptoms at all to dyspnea on exertion, progressive dyspnea, dyspnea at rest, wheezing, stridor, and a life-threatening situation such as respiratory failure or respiratory arrest.

Management of this condition is still not standardized or unified around the world, but it is well established that treatment of benign tracheal stenosis requires a multidisciplinary approach by a team of dedicated and experienced physicians.

The initial intervention and the type of treatment depend upon location of the stenosis, wall integrity, length, and severity, as well as to the presence of comorbidities and overall health status of the patient.

Traditionally, surgery has been the mainstay of treatment, with excellent results in 90% of cases [2–4]. However, surgery is not always definitive and there is a percentage of recurrence that can reach 10% in some series [5]. Surgery involves some risks, and associated complications have been reported to be greater than 8–12% with a mortality rate of 5% [2, 6, 7]. Moreover, many patients are unable to undergo a surgical procedure because of underlying cardiopulmonary limitations.

Endoscopic management of tracheal stenosis provides a safe and efficient therapeutic option and is often the first-line therapy in patients who are not appropriate surgical candidates or who have failure after airway resection. Several modalities have been used to relieve endoluminal obstructions, including mechanical approaches such as dilatation with a rigid bronchoscope or with balloon; heat-related modalities such as laser, electrocautery, and argon plasma coagulation; contact probe cryotherapy; and a variety of airway stents [1, 8].

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Drug therapy combined with endoscopic treatment (intralesional injection of corticosteroids or more recently topical application of mitomycin-C) is another option in the treatment of this pathology, but experience is very limited and results are variable [9, 10]. So far none of these treatments is curative.

Causes of Benign Airway Stenosis

Congenital Tracheal Stenosis

Congenital anomalies are the most common cause of airway narrowing in the pediatric population. They are rare malformations produced by the absence of most of the membranous portion of the trachea in the affected segment, and the cartilaginous rings extend along the entire circumference of the tracheal wall. There have been three anatomical types described: (a) generalized stenosis, from the cricoid to the carina with possible bronchial involvement; (b) infundibular stenosis, where part of the trachea, proximal or distal, has a normal caliber; and (c) segmental stenosis, with involvement of a short portion of the trachea.

These malformations can appear alone or, very often, associated with other abnormalities of the bronchovascular tree and other organ malformations, of which the most frequently seen is esophageal atresia [11, 12].

Management of congenital stenosis is very challenging. Children can present stridor, recurrent pneumonia, cyanosis, wheezing, and sometimes respiratory failure.

Corrective surgery is the treatment of choice; in short stenosis, resection of the compromised segment and anastomosis is the best option. When the stenosis affects long segments of the trachea, anastomosis becomes difficult for excessive pressure on the suture line, and the endoscopic approach can be an effective alternative to help these patients.

Postintubation and Post-tracheostomy Tracheal Stenosis

Postintubation tracheal stenosis was recognized for the first time as an entity in 1880, after MacEwen instituted prolonged endotracheal intubation as a therapy in four patients with main airway obstruction [13].

Since then, many reports have been published on serious complications resulting from post-intubation stenosis (PIS) or post-tracheostomy stenosis (PTS). The rate of presentation varies: among all intubated patients, 0.6–21% will develop tracheal stenosis. PTS in turn can present from 6 to 21% of all patients that have undergone tracheostomy [7, 14]. Only a minority of them (1–2%) will present with symptoms or severe stenosis [15].

Currently, the calculated incidence of moderate or severe stenosis resulting from endotracheal intubation or tracheostomy is estimated on 4.9 cases per million per year in the general population [16].

Prolonged tracheal intubation can produce tracheal stenosis at many tracheal levels [17], from the tip of the endotracheal tube to the glottic and subglottic area, but the most affected places are the level of the endotracheal tube (ETT) cuff and around the stoma in tracheostomized patients.

The development of the stenosis has many stages; at the beginning there is mucosal ulceration due to decreased blood flow at the level of contact with the ETT cuff. Then, cartilages exposure and perichondritis develop, followed by granulation tissue formation, which over time becomes an established fibrous stenosis, that can be more or less fixed. In the worst cases, cartilage destruction occurs and the airway wall loses its support.

PTS usually affects the area of the stoma, where the tracheostomy tube curves down, following the same sequence mentioned above. Sometimes granulation tissue is formed above the bend of the tube and progresses toward fibrosis [18, 19]. The presence of infection, very common in ventilated patients (tracheitis, mucositis), is a contributing factor for the development of airway stenosis [20]. A common finding in post-tracheostomy patients is retraction of the tracheal cartilage at the area of the ostomy, producing different degrees of stenosis (Fig. 11.1). Surgery is the treatment of choice in these situations. When the patient is not a

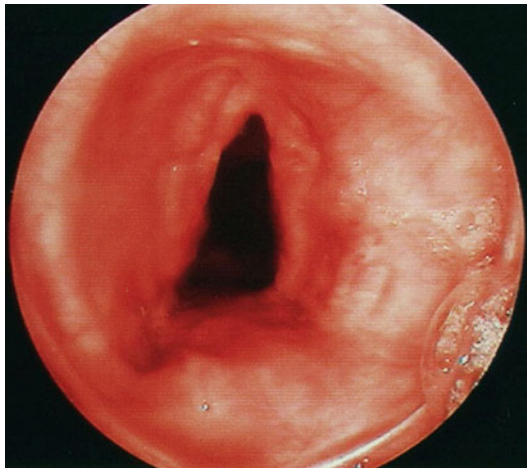


Fig. 11.1 Post-tracheostomy tracheal stenosis

surgical candidate, an airway stent may be beneficial.

Percutaneous tracheostomy is a procedure that is increasingly indicated in the critically ill patient, and it is associated to the development of tracheal stenosis as well.

A publication on 100 patients that underwent percutaneous tracheostomy revealed that major postoperative complications were presented in 2.4% of cases, and these included death, cardiac arrest, loss of the airway, pneumothorax, tracheoesophageal fistula, and injury to the posterior wall of the trachea (mucosal tear). The rate of minor complications such as bleeding or cellulitis were present in 1.8% of cases. Tracheal stenosis was reported in 31% of patients, 20% of which were symptomatic [21].

Long-term complications of percutaneous tracheostomy are infrequently mentioned in the literature; however, some published data suggests that the rate of tracheal stenosis is significantly higher than reported [22].

VanHearn et al. showed that of 80 patients decannulated after percutaneous tracheostomy, an index of stenosis >10% was found in 26% of them, being moderate in 4% of the cases and severe in 2% [23].

Another study evaluating 214 of 356 patients with percutaneous tracheostomies revealed that 8 of them (3.7%) developed symptomatic tracheal stenosis [24].

Infectious

Many airway infections can cause damage to the tracheal mucosa, resulting in stenosis. Tuberculosis (TB), fungal infections, bacterial tracheitis, histoplasmosis, and diphtheria are some of them, TB being the most frequently seen.

Tuberculosis is the most common infectious cause of airway stenosis. It usually produces distal stenosis (at the level of the bronchi), but central airway stenosis can also occur. This complication can present at the time of the active infection or long after that, up to 30 years [25]. The most important risk factor for developing airway stenosis is the presence of tuberculous bronchitis, which is found in 10–37% of patients with pulmonary tuberculosis when bronchoscopy is performed [25, 26]. In those cases, over 90% of patients will develop tracheobronchial stenosis in spite of correct TB treatment [27].

Infectious stenosis is more prevalent in underdeveloped countries, particularly in Asia and Africa. Active infection produces necrosis and ulceration of the bronchial mucosa, giving rise to granulation tissue and subsequent fibrous stenosis.

During fibrous, established stenosis, dilatation of the lesion is an option. When the stenosis occurs at bronchial level, balloon dilatation can be offered. At tracheal level, rigid bronchoscope dilatation is useful as well. Repeated dilatations or stent placement is often required, since recurrence rate is very high.

Idiopathic Tracheal Stenosis

The term idiopathic stenosis (ITS) is used to include patients with tracheal stenosis when all other etiologies have been investigated and ruled out. It is thought to be a result of an inflammatory process of unknown etiology. Since location and general characteristics are similar to inflammatory and post intubation stenosis, the investigation of potential causes has to be exhaustive before this term is applied.

ITS is a rare condition, characterized by circumferential fibrous stenosis beginning at the

subglottic area and compromising the proximal segment of the trachea. It typically affects women on their third to fifth decade and presents with months to years of symptoms such as progressive dyspnea, wheezing, stridor, or a combination of all of them. In many cases patients are misdiagnosed as difficult-to-treat asthmatics [28].

Grillo et al. [28] presented 49 patients with tracheal stenosis where no etiology was found after extensive evaluation. A retrospective review of records showed that radiologic studies were still available in only 15 of the 49 patients with ITS. All 15 patients had radiographs and plain tomographies, and one patient had a computerized tomography scan of the neck.

Review of the available information showed that idiopathic laryngotracheal stenosis produced focal, 2–3 cm long stenosis at the cervical trachea. The lumen was severely compromised, measuring no more than 5 mm in diameter at its narrowest portion. The stenosis was concentric or excentric, presenting either smooth or lobulated margins.

Grillo's report highlighted the need to pay special attention to the airway in chest radiographs or computerized tomographies when evaluating a patient with a history of prolonged dyspnea and wheezing. It is also important to consider ITS in the differential diagnosis of patients with focal narrowing of the airway.

A recent multicenter study described 23 patients, 96% of which were women aged 45 ± 16 years, endoscopically treated for ITS. Time between first symptoms and diagnosis was 19 ± 18 months. Bronchoscopy showed weblike (61%) or complex (39%) stenosis, located at the upper part of the trachea, mainly at the cricoid cartilage area.

Endoscopic treatment included mechanical dilation only (52%) or associated with laser or electrocoagulation (30%) and stent placement (18%). All procedures were efficient. Follow-up after endoscopic therapy was 41 ± 34 months, showing recurrence of ITS in 30% of patients at 6 months, 59% at 2 years, and 87% at 5 years. Treatment of recurrences ($n = 13$) included endoscopic management in 12 cases [29].

Bronchial Stenosis Post-Lung Transplantation

Since the first lung transplant in 1963, technical advances in thoracic surgery along with new immunosuppressive agents have made lung transplantation a more common indication for those patients with terminal lung disease. However, one of the main problems of this surgical procedure is the development of stenosis at the level of the suture.

Perianastomotic stenosis occurs in 12–40% of patients and nonanastomotic distal bronchial stenosis in 2–4% of all lung transplants [30, 31].

Bronchial stenosis is related to airway inflammation, with mononuclear cell injury to the epithelium and mesenchyme that is further complicated by endothelial injury on a poorly vascularized area. The severe blood-flow impairment may lead to bronchial cartilage ossification, calcification, or fragmentation, leading to stenosis [32].

Other risk factors increase the risk for suture stenosis, such as the use of a simple suture and prolonged mechanical ventilation. There is a very high risk of suture infection also due to low blood flow and the presence of inflammation. Infection should be looked for and appropriately treated before performing any endobronchial manipulation, particularly if a stent placement is considered.

Success depends primarily on the experience of the interventional pulmonology team and the medical resources available

Distal Bronchial Stenosis

As mentioned previously, bronchial stenosis secondary to pulmonary tuberculosis is quite common. Approximately 43% of patients with pulmonary tuberculosis will develop stenosis at the distal bronchi [33, 34] (Fig. 11.2). This number corresponds to approximately 4.1% of all bronchoscopies performed in a hospital.

Another cause for distal stenosis is bronchial anthracosis (called anthracostenosis) [35, 36].

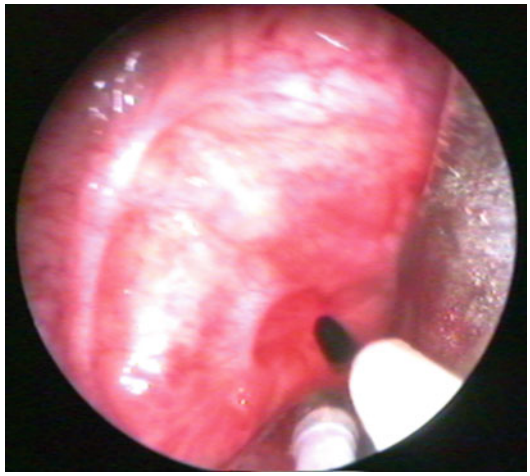


Fig. 11.2 Bronchial stenosis: right upper lobe

As a result of bronchial stenosis, there exists difficult drainage of secretions and recurrent infections distal to the obstruction, with the development of bronchiectasis. In these situations, it is indicated to offer a dilatational therapy that can be performed via balloon dilatation with or without laser application. This treatment is simple to apply and can be easily performed during a short procedure. It has good results, improving secretions clearance which in turn prevents repeated infections. In addition to bronchoscopy, three-dimensional helical tomography of the tracheobronchial tree can be very useful in the evaluation of this condition, since it allows a better distal inspection than bronchoscopy [37].

Another less common cause of airway stenosis is radiation therapy. The incidence of bronchial stenosis has increased following treatment with brachytherapy or external beam radiotherapy of malignant lesions of the airways, with an estimated incidence of 9–12% [38].

Bronchial stenosis is established within an average of 40 weeks after initiation of radiotherapy. Bronchoscopy can show the presence of a whitish-colored membrane covering the mucosa, with important inflammatory response that ultimately results in fibrous stenosis [38]. Radiation therapy rarely compromises the tracheal mucosa.

Diagnosis of Tracheobronchial Stenosis

Symptoms

A careful medical history should be obtained in patients suspected of airway stenosis, since background data is very important. Prior infectious diseases, history of airway intubation, prolonged mechanical ventilation, timing and severity of dyspnea, presence of dysphonia, etc., should be recorded and evaluated.

In most cases, symptoms develop gradually as progressive dyspnea until tracheal stridor appears. When patients present emergently, it is important to offer a therapeutic procedure to reopen the airway to avoid worsening of symptoms and serious complications such as respiratory failure or respiratory arrest. The goal of treatment is to restore and maintain patency of the airway as soon as possible, and then a multidisciplinary team can decide which is the best long-term solution for a given patient.

In clinical practice, most of the patients present with symptoms of stenosis when they are in the fibrous phase of the stenosis, with minimal evidence of inflammation. They frequently have a history of a prior airway intubation or prolonged mechanical ventilation in the past. Many patients have been diagnosed and treated for difficult-to-control asthma, with minimal or no response to asthma therapy.

A significantly smaller number of patients will present within days or weeks from extubation, and in those cases an important airway inflammation can be seen.

Onset of symptoms is very variable. In a work of Marquette et al. describing 58 patients with airway stenosis, 5 of them developed symptoms within 5 days, 23 patients presented symptoms from 5 to 30 days of extubation, 19 patients from 30 to 90 days, and 8 patients took more than 90 days in presenting symptoms. Half of them went to the emergency room with acute respiratory failure [39].

The auscultation of wheezes, especially a fixed one, indicates that the passage of airflow

through the airway is reduced, but its location does not always correlate with the site of airflow obstruction. That means that when a fixed wheeze is heard over the trachea, it does not necessarily indicate that the source of the obstruction is the trachea [40]. When wheezing is unilateral, it often suggests an obstruction of the airway distal to the carina.

The persistence of a fixed unilateral wheezing should always warrant bronchoscopic examination, paying special attention to the distal airway (segmental or subsegmental bronchi). Stridor is always a sign of severe laryngeal or tracheal obstruction and occasionally main bronchial obstruction.

Imaging Techniques

In the study of tracheobronchial stenoses, noninvasive imaging techniques have an important role. They help not only in diagnosing but also in deciding the most appropriate treatment and assessing response to therapy during the follow-up period. These techniques have developed significantly in recent years [41] allowing a better approach to airway stenosis.

Computed tomography (CT) has been the most commonly used imaging test for diagnosis and evaluation of airway stenosis. Although very useful, CT has some limitations, particularly in the assessment of subtle airway stenosis in axial images, underestimation of the craniocaudal extent of the disease, and generation of a large number of images for review [42] (Fig. 11.3).

The introduction of multiplanar reformatting (MPR) CT scans with option to generate three-dimensional (3D) images and virtual endoscopy (VE) provides additional information regarding airway pathology [43] bringing visual data that closely resemble the images obtained from flexible bronchoscopy [44].

MPR CT scan allows the acquisition of thin-slice axial sections of entire body volumes during a single breath-hold, thus eliminating respiratory artifacts [45].

This technique provides information on the length and caliber of the stenosis and the degree of compromise of the laryngotracheal wall. It allows visualizing lesions in depth, showing thickening or thinning of the tracheal wall, fibrous involvement of the submucosa, or disappearance of the tracheal rings. Also, the relationship of the injury to adjacent organs can be better evaluated.

Virtual endoscopy (VE) is a reconstruction technique that exploits the natural contrast between endoluminal air and the surrounding tissue [46], allowing navigation through the tracheobronchial tree with the same endoluminal perspective as an endoscopy [44].

Several authors have demonstrated the high diagnostic accuracy, sensitivity, and specificity of noninvasive, multirow detector CT virtual endoscopy in detecting and grading central and segmental airway stenosis and its close correlation with flexible bronchoscopy [43, 46, 47]. However, it is slightly more accurate at assessing central airway stenosis than segmental airway stenosis [46].

Bronchoscopy

Flexible bronchoscopy remains the primary diagnostic technique [48] in the study of inflammatory tracheal stenosis, allowing direct visualization of the airway lumen. Bronchoscopy offers information at different levels and can assess the mobility and morphology of the vocal cords and arytenoids in subglottic laryngeal stenosis. In tracheal stenosis it allows location of the lesion and evaluation of the degree and length of the stenosis and notes characteristics such as the presence or absence of malacia, mucosal involvement in inflammatory disorders, granulomas, ulcerations, or established fibrosis. It also enables obtaining biopsies, a procedure that should always be performed in tracheal stenosis, to rule out other inflammatory conditions. Bronchoscopy is a minimally invasive procedure, with the additional advantage of not exposing the patient to ionizing radiation. One limitation of this technique is the inability to evaluate the distal airways in severe stenosis, since the bronchoscope cannot be further advanced from the stenotic area.

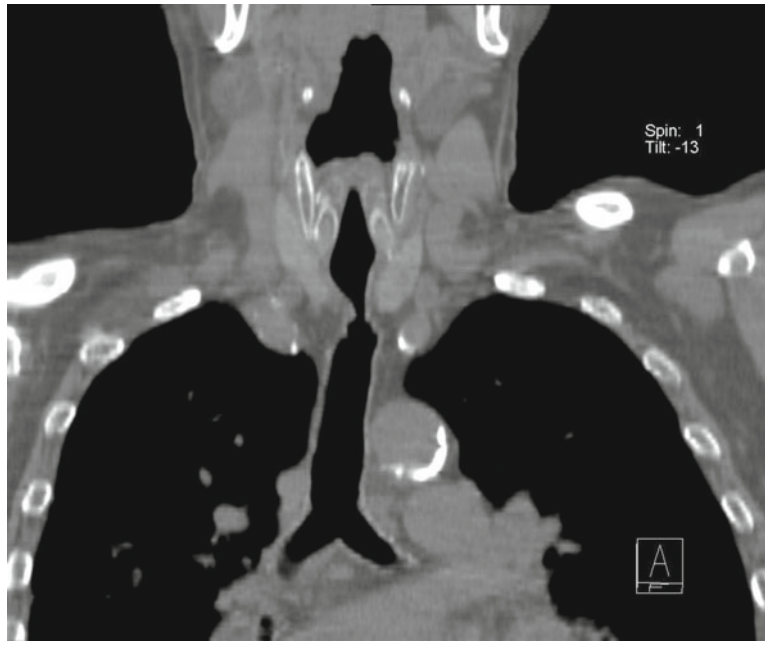


Fig. 11.3 CT scan tracheal stenosis

New bronchoscopic technologies, however, permit more accurate assessment of the airway wall structure and characterization of the stricture before, during, and after treatment, since the correct evaluation of tracheal wall structures is necessary for optimal management of tracheal stenosis.

Endobronchial ultrasound (EBUS) has been introduced as an adjunct to diagnostic bronchoscopy. Radial EBUS helps in evaluating the different tracheal and bronchial wall layers, as well as parabronchial structures. Cartilage damage can be better assessed, influencing the type of treatment that will be offered [49].

Optical coherence tomography (OCT) is a new bronchoscopic imaging technique that has generated considerable interest since it has a much better space resolution than computed tomography. It can provide a micron-level, real-time image of the airway wall structure with a resolution approaching histology [50]. It offers a unique combination of high resolution (1–15 mm) and in-depth penetration of 2–3 mm that is adequate for imaging superficial airway anatomy and pathology. OCT has the potential to increase the sensitivity and specificity of biopsies and create 3D images of the airway to guide diagnostic procedures and may have a future role in different areas such as the study of tracheal stenosis. Some authors hypothesize that this technology may in the future provide a noninvasive "optical biopsy" [51], helping as we said in diagnosis and treatment of a number of conditions.

Anatomic optical coherence tomography (aOCT), a modification of conventional OCT, is a novel light-based imaging tool with the capacity to measure the diameter and lumen area of the central airways accurately during bronchoscopy. This technique can measure tracheal stenosis dimensions, having good correlation with chest CT scan findings and guiding the selection of a proper-sized airway stent [52].

All these new technologies are very promising, and they are currently under active research to define their proper role in the study of airway conditions.

Though flexible bronchoscopy and the different imaging techniques have shown to be useful and reliable in the diagnosis of tracheobronchial strictures, they all have technical limitations that can lead to an inaccurate characterization of airway stenoses [53]. The best way to evaluate these

conditions is to combine different diagnostic approaches in order to correctly define the injury and then plan the best procedure, case by case, based on clinical, endoscopic, and radiological findings.

Pulmonary Function Tests

A simple test such as spirometry can help diagnose and characterize a central airway stenosis. Shape of the flow–volume curve (*F*/*V*), obtained by spirometry and flow resistance (Raw) calculated by plethysmography, can give important information. For instance, flattening of the inspiratory loop with preservation of expiratory flow represents variable extrathoracic obstruction of the central airway. In turn, compromise of the expiratory loop with a normal inspiratory limb indicates variable intrathoracic obstruction. In a fixed obstruction (intra- or extrathoracic), both inspiratory and expiratory curves are affected, presenting with a classic flattening in the *F*/*V* loop.

Another important information that can be obtained with spirometry concerns to the functional status and helps in deciding whether or not the patient is a surgical candidate.

Classification of Benign Tracheal Stenosis

Airway stenoses have been classified following different parameters, in an attempt to design a useful algorithm for treatment.

Cotton et al. [54] used the cross-sectional area of the stenosis in a group of pediatric patients and divided this condition into four grades:

1. 50% obstruction
2. 51–70% obstruction
3. 71–99% obstruction
4. Complete obstruction

In this classification, location and length are noted but without affecting the grading of the stenosis.

In 1999, Brichet and coworkers [8] proposed a classification based on four categories depending on bronchoscopic findings:

- Pseudoglottic stenosis: defined as typically "A"-shaped stenosis due to lateral impacted fracture of cartilages in patients with a history of tracheostomy.
- Weblike stenosis: when it involves a short segment (<1 cm).
- Membranous concentric stenosis: when there is a membrane obstructing the lumen without damage to the cartilages.
- Complex stenosis: all other stenoses, including those with an extensive scar (≥1 cm), circumferential hourglass-like contraction scarring, or malacia, were defined as such.

Moya et al. [55] reviewed 54 patients that underwent surgery for laryngotracheal stenosis and defined findings according to topographic and lesional criteria, incorporating three independent variables: stage of development (S), caliber (C), and length (L). Recently this classification has been modified. It is presented in Table 11.1.

In 2007 Freitag et al. [56] proposed a standardized scheme, presenting descriptive images and diagrams for rapid and uniform classification of central airway stenoses (Fig. 11.4). Classification was based on the type of lesion, degree, and location. They divided airway stenoses into structural and dynamic, and they included malignant causes as well.

The structural group has four major types:

- Type 1: includes exophytic intraluminal malignant or benign tumors and granulation tissue.
- Type 2: stenosis is due to extrinsic compression of all causes, including nonpulmonary tumors.
- Type 3: stenosis is due to distortion, kinking, bending, or buckling of the airway wall.
- Type 4: shrinking and scarring are the predominant features.

Stenoses were further classified in dynamic when a malacic condition that varied with the respiratory cycle was found. They included two different types:

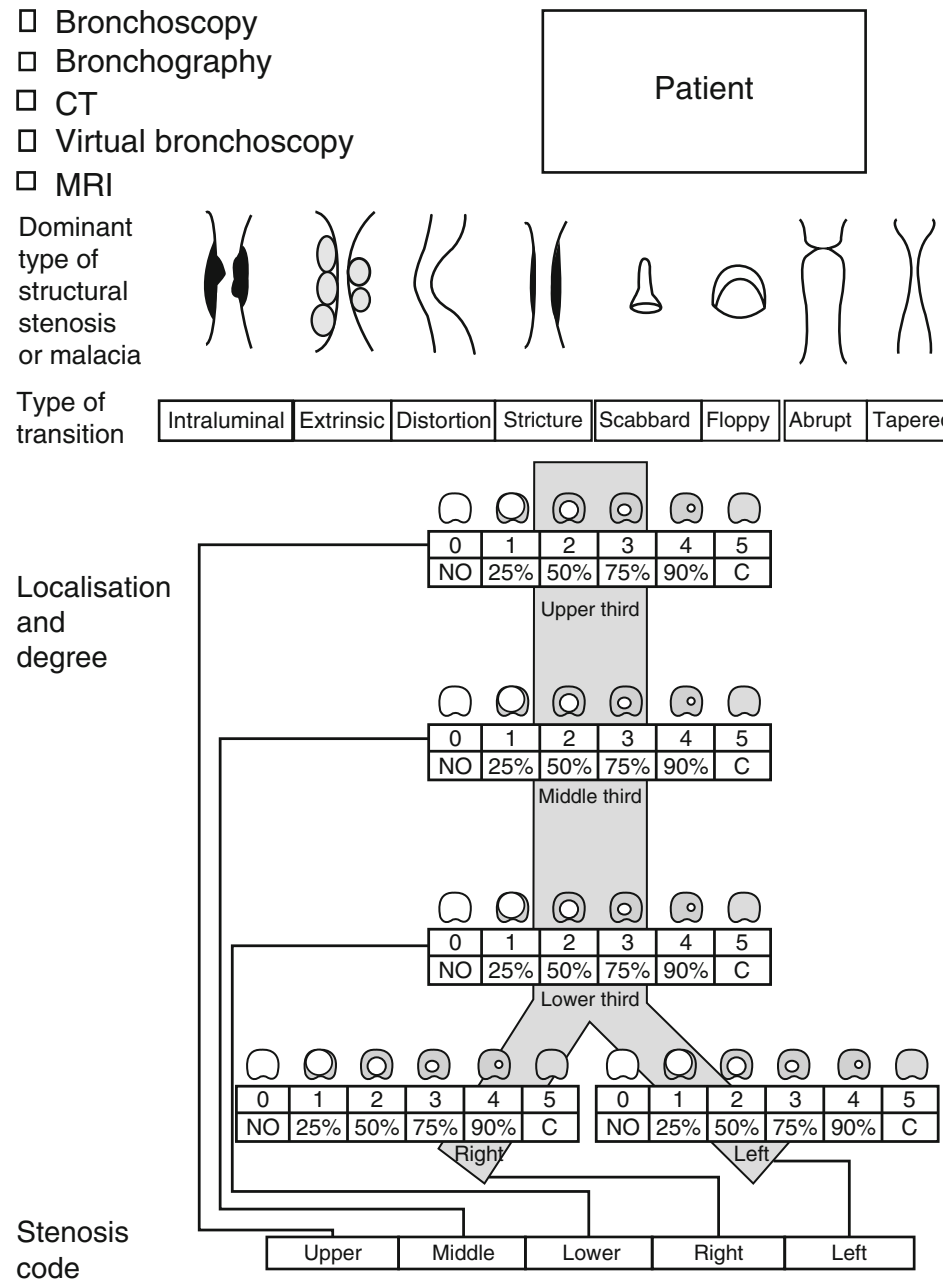
- Type 1: triangular (tent-shaped) benign stenosis in which the cartilage is damaged.
- Type 2: it is the inward bulging of a floppy posterior membrane.

In turn, the degree of stenosis was assigned a numerical code that could be applied to any site:

Table 11.1 Classification criteria for inflammatory stenosis of the trachea

Classification criteria for inflammatory stenosis of the trachea					
Structure (S) Structure of the tracheal wall		Caliber (C) Internal diameter (at the point of smaller diameter)		Length (L) Axis of the larynx–trachea	
S1	Acute–subacute inflammation	C1	>10 mm (area >25 μ)	L1	Stenosis ≤ 2 cm
S2	Organized scar fibrosis	C2	8–10 mm (area 16–25 μ)	L2	2–4 cm stenosis
S3	Malacia	C3	≤8 mm (area ≤ 6 μ)	L3	>4 cm stenosis
S4	Tracheoesophageal fistula				

Adapted from Moya et al. [55]



A worksheet marking the location, degree and type of stenosis. CT: computed tomography; MRI: magnetic resonance imaging; C: complete

Fig. 11.4 Stenosis classification [56]. With permission

- Code 0: no stenosis
- Codes 1: 25% decrease in cross-sectional area
- Code 2: 50% decrease
- Code 3: 75% decrease
- Code 4: 90% decrease

They defined five locations within the central airways:

- Location I: upper third of the trachea
- Location II: middle third of the trachea
- Location III: lower third of the trachea
- Location IV: right main bronchus
- Location V: left main bronchus

In 2008, other authors [1] classified airway stenoses into two groups, according to their morphological aspect in simple and complex, similar to the Brichet's classification. Simple stenosis included granulomas and weblike and concentrical scarring stenosis. All these lesions were characterized by endoluminal occlusion of a short segment (<1 cm), absence of tracheomalacia, or loss of cartilaginous support (Fig. 11.5). Complex stenoses were represented by a longer lesion (>1 cm) with tracheal wall involvement and subsequent scarring contraction of the latter, in some cases also associated with malacia (Fig. 11.6).

The ultimate aim of the various proposed classifications is to define a treatment algorithm accepted and followed by all physicians dealing with these complex conditions. It is also very important to use the same definitions in order to carry out research projects designed to identify the best, type-specific, therapeutic option.

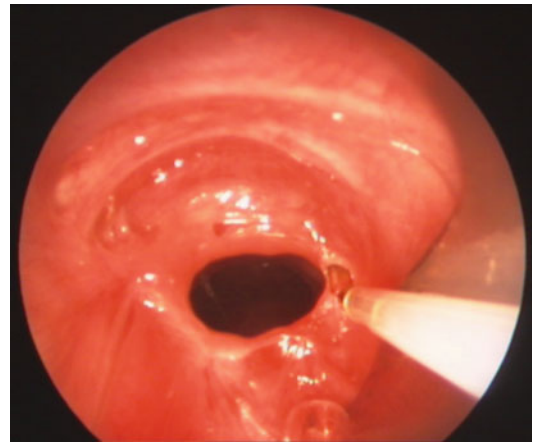


Fig. 11.5 Simple tracheal stenosis

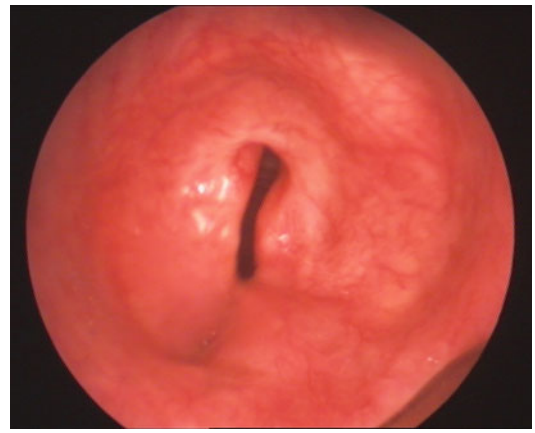


Fig. 11.6 Complex tracheal stenosis

Treatment

Effective management of tracheal stenosis requires a multidisciplinary assessment of patient's overall clinical status and medical history in addition to etiology and morphology of the stricture. When deciding the approach, the dedicated physician has to consider whether or not the patient is a surgical candidate and determine precise intraoperative technique, the extent of the resection, and an estimation of the risk for recurrence. Other treatments to consider are repeated dilatations or the placement of an airway prosthesis. Presentation of patients with an airway obstruction is variable and depends not only on location, severity of the stricture, and the speed of progression but also on underlying medical conditions.

We cannot overemphasize that when an obstruction of the tracheobronchial tree is suspected, a careful review of medical history, patient examination, and review of complementary methods such as pulmonary function testing and imaging studies (chest RX, CT scan) should be performed thoroughly. Virtual bronchoscopy can be used to have a preview of the airway, but it does not replace conventional flexible bronchoscopy as the most useful diagnostic tool to assess the extent of the stenosis as well as its severity

and to determine its cause by direct inspection and biopsies. Patient clinical status is the main parameter in deciding next step, since it will determine how urgent the treatment is needed and which is the most appropriate instrument to perform the procedure.

Endoscopic Treatment

Rigid bronchoscopy under general anesthesia is an essential method in the treatment of severe symptomatic laryngotracheal stenosis. It allows a secure airway and the application of different interventional tools such as balloon dilatation, laser resection, electrocautery, and placement of an airway stent. It is an expedite procedure to reopen the airway and very safe and effective when applied by a well-trained team. The flexible bronchoscope has also an important role, complementary to the rigid bronchoscope during the first approach.

Our recommendation when treating a patient with severe central airway obstruction is to provide appropriate oxygenation and ventilation by intubating with the rigid bronchoscope. The rigid tube serves two purposes: first, it secures the airway, and second, it can be used to dilate the airway. Once successful intubation is achieved, the flexible bronchoscope can be used through the rigid scope to inspect the stenosis and the distal airway and to aspirate retained secretions.

The immediate therapeutic approach depends on the type and severity of the stenosis found. Many times rigid bronchoscopy will resolve the acute situation by dilatating the stricture and will represent a bridge to definitive treatment to be performed electively.

According to the endoscopic findings, several steps can be followed. For instance, simple severe stenosis (concentric membrane) can be immediately resolved with laser resection and dilatation with the rigid bronchoscope. In this particular situation, that may be the only procedure that the patient will need. A close endoscopic follow-up is indicated to detect and treat recurrences.

Complex stenoses represent a different situation. They may be addressed initially with endoscopic therapy to overcome the acute respiratory failure, but the definitive solution is always surgery providing that the patient has a good clinical status.

Patients that present with progressive symptoms can be inspected with both the rigid and the flexible bronchoscope, and a definitive procedure can be planned after discussing the case in a multidisciplinary team, once all information has been collected.

Some treatment algorithms have been recommended in benign tracheal stenosis, according to several defined criteria (Fig. 11.7 and Table 11.2).

Balloon Dilation

As we discussed above, in urgent cases the sole use of rigid bronchoscope causes dilation and enlargement of the airway, improving both extrinsic and intrinsic obstruction. When a rigid bronchoscope is not available, dilatation can be performed by using progressive diameter balloons that are introduced sequentially, thus achieving a greater diameter of the tracheal lumen (Fig. 11.8a, b, and c).

Balloon dilatation does not have long-lasting effects, and it is indicated to relieve the obstruction until a more definitive treatment can be offered.

Laser Therapy

Laser treatment involves application of a laser light to the lesion. The effects of laser are determined by many factors: type of laser applied, distance and surface of application, and target tissue. The most commonly used lasers in interventional pulmonology are the Nd-YAP (neodymium, yttrium, aluminum, and phosphate) and the Nd-YAG (neodymium, yttrium, aluminum, and garnet). Diodos laser can be also applied to airway lesions with similar good results. Dumon published his first large series in 1982 [57]. This author presented 111 patients treated with laser to open the airway for both

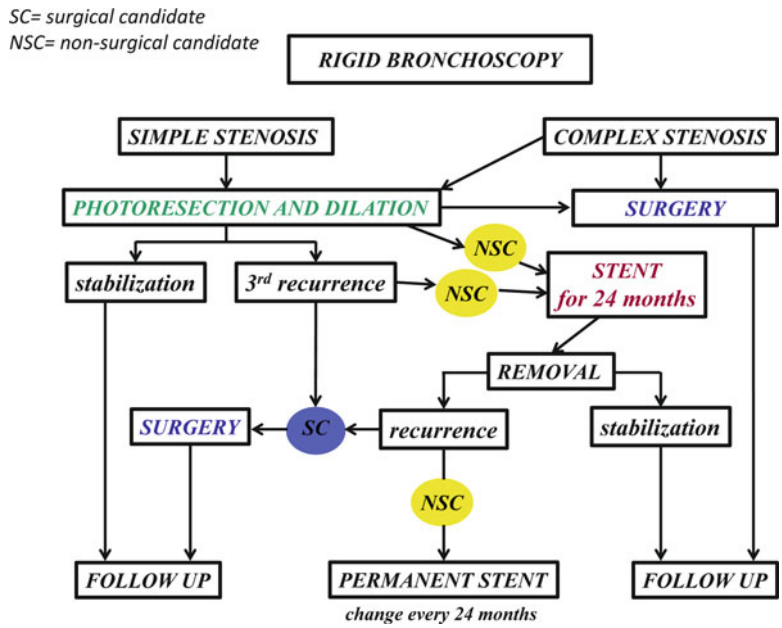


Fig. 11.7 Tracheal Stenoses Treatment Algorithm

Table 11.2 Endoscopic treatment according to morphological criteria [55]

Category	First option	Second option
S1/C1C"C3/L1L2	ET +/– Laser +/– Prosthesis	Surgery
S1/C2-C3/L3	ET +/– Laser +/– Prosthesis	–
S2/C2C3/L1L2	ET +/– Laser	Surgery
S2/C2C3	ET +/– Laser +/– Prosthesis	–
S3/C2C/L1L2	Surgery	–
S3/C1C2C3	Prosthesis	–
S4/C1C2C3/L1L2L3	Surgical correction of fistula + myoplasty	

Moya and colleagues
S = stage
C = caliber
L = length

benign and malignant lesions, 32 of them were benign stenosis. Cavaliere et al. [58] in turn presented their experience on 1,000 patients treated with laser for benign and malignant disease, obtaining cure in 34 of the 81 cases with benign tracheal stenosis treated with laser. We also published our series including 400 cases of benign and malignant disease treated with laser [59]. Ninety-two patients were treated for benign tracheal stenosis and received 113 laser applications. Laser resection was successful in obtaining a 50% increment on the tracheal diameter in most cases.

In another publication, we report our experience with laser resection followed by airway prosthesis placement in 63 patients with benign tracheal stenosis [60]. About 79% of patients obtained definitive cure.

In order to open the airway with laser, we recommend to apply three or four radial cuts at the cardinal points of the stenotic circumference of the trachea (Fig. 11.9a, b, and c) and then to perform careful dilation with the rigid bronchoscope. The flexible bronchoscope can be used to apply laser as well, but we favor the rigid instrument to take advantage of simultaneous dilatation.

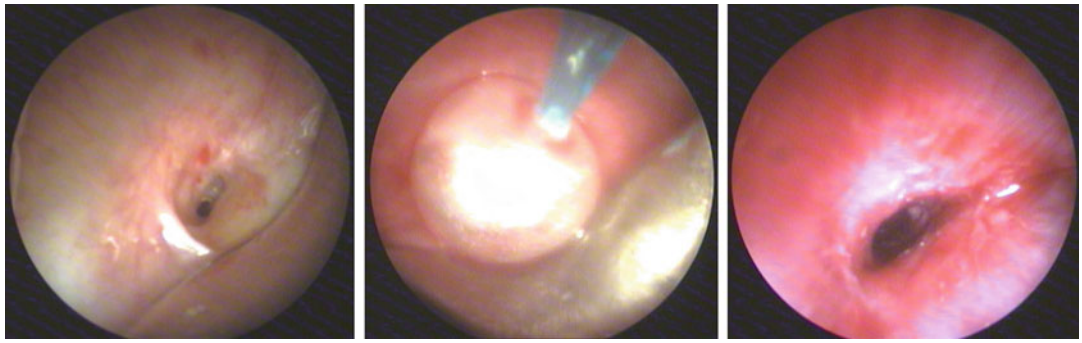


Fig. 11.8 Balloon dilatation (before, during, and after treatment)

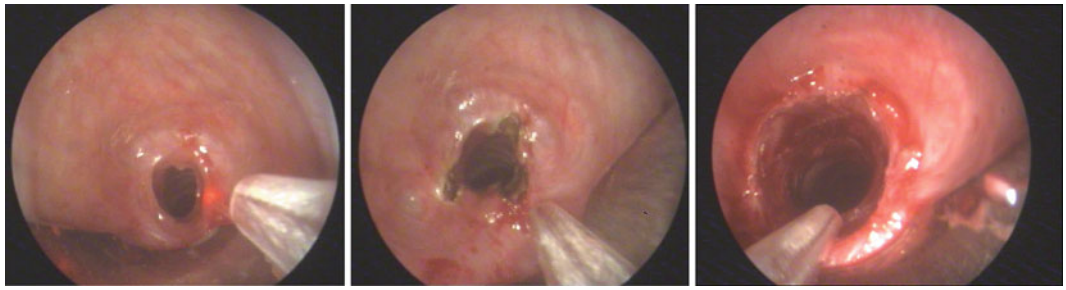


Fig. 11.9 Laser application in tracheal stenosis

Cryotherapy, Electrocautery, and Argon Plasma Coagulation

Cryotherapy, electrocautery (EC), and argon plasma coagulation (APC) are methods that obtain variable outcomes in tracheal stenosis treatment.

Results on the application of these techniques in tracheobronchial stenosis of varied etiology are available. Recently, Fernando et al. [61] treated 35 patients with a median age of 51 (18–81) years with Spray Cryotherapy (SC). Stricture etiology included postintubation, post-tracheostomy, radiation induced, prior surgery, other causes, or unknown etiology. Seventeen patients (49%) required additional SC therapy. Only two complications occurred (3.2%) and these included pneumothorax and intraoperative tracheostomy. Twelve patients were asymptomatic, 16 improved, 4 had no improvement or were worse, and 1 patient died from an unrelated cancer.

They concluded that initial experience with SC for benign airway strictures suggested that this could be used safely and could be effective in improving symptoms and reducing the severity of airway narrowing, but almost half of the patients required re-intervention.

Some authors agree that when applied to postintubation tracheal stenosis, EC and APC can be fibrogenetic, causing more damage and scarring of the mucosa. Cryotherapy is almost ineffective given the paucity of blood vessels in the stenotic area.

These three methods, however, are very useful in granulomas, especially APC [62–64]. Laser therapy still has many advantages over all of them, since it is fast, and it has high coagulation power and a minimal impact on surrounding tissues.

Tracheal Prosthesis

Airway prostheses are tubes of different shapes, sizes, and materials designed to stabilize or reconstruct the lumen of the airways.

Fig. 11.10 Montgomery T-tube

In benign tracheal stenosis, tracheal prosthesis placement may be considered in the following situations:

(a) Treatment failure after dilation of a simple stenosis
(b) First option in cases of complex stenosis as a bridge to surgical treatment
(c) As the only option in unresectable disease (length > 50% of the trachea)
(d) In inoperable patients

Metal, silicone, or other material endobronchial prostheses may be placed in the airways to relieve the obstruction caused by endoluminal tumors or extraluminal tumors that decrease the lumen of the airways by extrinsic compression. Likewise, benign conditions that diminish airway lumen can benefit of an airway stent as well.

Application of prosthesis is most effective when the stenosis occurs in the central airways (trachea or main bronchi). Their indication in distal bronchi stenosis is questionable.

The first airway prosthesis was developed by Montgomery and placed in 1965 [65]. The so-called Montgomery T-tube has an extraluminal portion and requires tracheostomy for placement (Fig. 11.10).

In 1990, Dumon introduced a totally endoluminal silicon-made prosthesis [66] and published his first experience on treating 118 patients with airway obstructions of different etiologies.

Since then, a large number of different airway prosthesis have been developed and are now available for medical use. However, at the moment the ideal stent has not been found yet. Many authors have listed the ideal characteristics for such a prosthesis:

– Easy to insert and remove
– Does not migrate
– Strong to support the airways
– Flexible enough to accompany the normal respiratory movements and cough and to allow adequate clearance of secretions
– Biologically inert (does not produce inflammatory response, avoiding granuloma formation)
– Available in different sizes and lengths

Published articles [60, 67, 68] reporting the application of airway stents in a variety of conditions including malignant and inoperable benign stenosis, tracheomalacia, tracheoesophageal fistula, and post-transplant stenosis showed remarkably positive results in more than 2,000 patients. Stent placement was associated with significant palliative benefits, improvement of dyspnea, quality of life, and performance status. Spirometric results, when available, also demonstrated improvement after placement. Associated adverse effects and complications listed on those reports were migration, granulation tissue formation, retention of secretions, airway perforation, and fatal hemoptysis.

A combined publication from 4 European centers reported the 7-year experience in the application of airway prostheses. A total of 263 patients had benign conditions, and they received an average of 1.6 prosthesis per patient. Duration of stenting ranged from 14 months to 6.2 years. Follow-up demonstrated treatment success in 66% patients, 24% of them had no recurrences after 1 year of stent removal [69].

Both metallic and silicone stents can be used for malignant obstructions of the airway. Silicone stents are favorites, however, since they have a low level of complications along with high efficacy and safety. They have been applied over the last 20 years with very good results.

Metallic stents have the theoretical advantage of being easy to place. In turn, they are very difficult to remove and we discourage their generalized use based on the level of complications they produce [70].

In fact, the FDA advised against metallic stent application in benign conditions in the year 2005 [71]. In malignant diseases, they are still acceptable if the expected survival period is short.

Procedure

Using the Rigid Bronchoscope

Rigid bronchoscopy and laser resection have been used for more than three decades, showing excellent results on the treatment of endotracheal or endobronchial growing tissue.

Concerning treatment of benign stenosis, rigid bronchoscopy laser resection has virtually no morbidity/mortality when the technique is appropriately applied in carefully selected patients.

When implementing this treatment, we recommend to proceed as follows:

1. Careful intubation with the rigid bronchoscope, maintaining the rigid optic lens slightly behind the tip of the bronchoscope in order to have a broad view of the airway as you advance. It is important to perform a planned intubation and to take every possible precaution during the procedure, since these patients often have a history of difficult intubation, and rush maneuvers can damage easily the upper airway, especially at the arytenoids and vocal cords area.
2. Once the lesion is on view, careful inspection of the area should be performed. Anatomic characteristics, extent, degree of compromise of the airway wall, and presence of inflammation should be recorded. It is important to touch the lesion with the tip of the suction catheter in order to test the nature of the stenosis, inflammation, fibrosis, cartilage affectation, etc.
3. When tracheal caliber is equal or greater than half the diameter of the rigid tube in use, the stenosis can be dilated by placing the bevel of the bronchoscope at the beginning of the stenosis and then surpassing the stricture dilating. During the maneuver, a slight rotation movement is applied to the scope as it is advanced through the stenotic area. In case of bleeding, use the bronchoscope to compress the bleeding area for a few minutes. If the lumen diameter obtained after dilatation is not appropriate, it will be necessary to move on to a larger diameter bronchoscope.
4. When the stenosis has a caliber of less than half the diameter of the bronchoscope, laser in cutting mode can be applied, performing three or four cuts at 12, 3, 6, and 9 o'clock of the stenotic circumference. Laser should always be applied parallel to the tracheal lumen, avoiding damage to the posterior tracheal wall and the esophagus that could result in a tracheoesophageal fistula. The anterior tracheal wall can also be accidentally damaged, injuring large vessels placed beyond the wall, such as the innominate artery.

   After several cuts, the stenotic tissue tends to open or is easily removed by the rigid bronchoscope, applying again a rotation pressure and resecting the stenotic membranes. Bleeding rarely occurs or is minimal. Another option is to cut the membrane stenosing the airway with endoscopic scissors, minimizing laser application to avoid burn damage to the mucosa. After the incisions, the rigid bronchoscope is used to dilate the stenotic area.
5. Once the stricture is surpassed, the flexible bronchoscope is passed through the rigid tube to carefully inspect the distal airways and to aspirate retained secretions or detritus.
6. Finally, the rigid bronchoscope is withdrawn above the stenotic area to check that tracheal caliber remains appropriate. Given the case that the lumen remains stenotic, one can assume that there is a complex damage to the tracheal wall such as cartilage disruption or

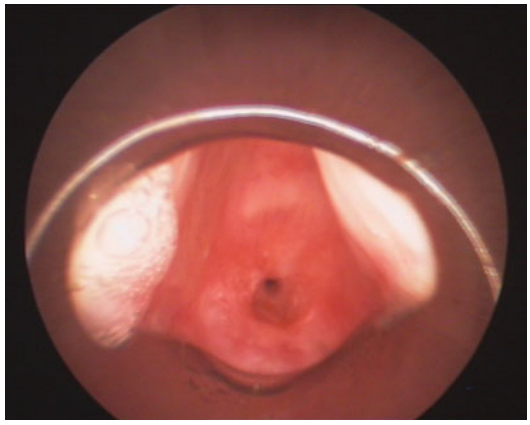


Fig. 11.11 Tracheal stenosis less than 2 cm from the vocal cords

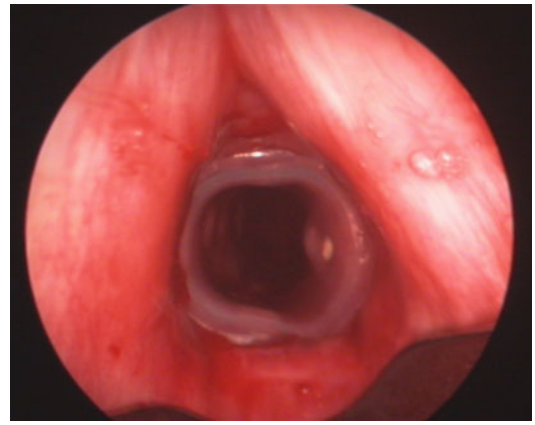


Fig. 11.12 After a Montgomery T-tube placement

malacia. Placement of an airway prosthesis is then the safer recommendation, since it will allow solving the situation avoiding immediate recurrence of the stenosis. Also, it will give time to collect other important information and to discuss the case in a multidisciplinary fashion in order to offer a more definitive solution.

Stent Placement

When placing an airway stent, the first consideration to evaluate is whether or not the prosthesis will really improve the clinical situation or make it worse.

Once risks and benefits have been evaluated and the assessment favored a stent placement, the dedicated physician should inspect the lesion again, noting carefully the size and length of the stenotic area and the characteristics of the surrounding healthy tissue. Two distances are particularly important: vocal cords to the beginning of the stenosis and end of stenosis to carina.

A prosthesis positioned too close to the vocal cords will bring speech problems and will be prone to granuloma formation leading to more stenosis. When the distance to the vocal cords is <2 cm, the best results are obtained proceeding directly to tracheostomy and placing a Montgomery T-tube (Figs. 11.11 and 11.12).

In turn, when a low stent has to be placed, <2 cm from the carina, it is better to offer a Y prosthesis, since a tubular stent will contact and irritate carinal mucosa leading also to granuloma formation and subsequent stenosis.

Our recommendation is to always follow what we call the "cover and respect rule of twos" (Fig. 11.13) for tracheal stents that means:

When considering the vocal cords, stents should:

1. Cover 2 cm proximal to the stenosis.
2. Respect 2 cm from the vocal cords.

   If (1) and (2) are not possible, then a Montgomery T-tube should be placed.

Related to the carina, prostheses should:

1. Cover 2 cm distal to the stenotic area.
2. Respect 2 cm proximal to the carina.

   If (1) and (2) are not possible, then a Y stent is in order.

Summary and Recommendations

Dealing with airway stenoses can be difficult. A variety of methods can be applied in order to relieve the situation. In fact, almost any technique discussed above is useful and can be applied alone or in combination with other methods. A multidisciplinary approach will always bring the best results for patients; important considerations should be thoroughly discussed with the team:

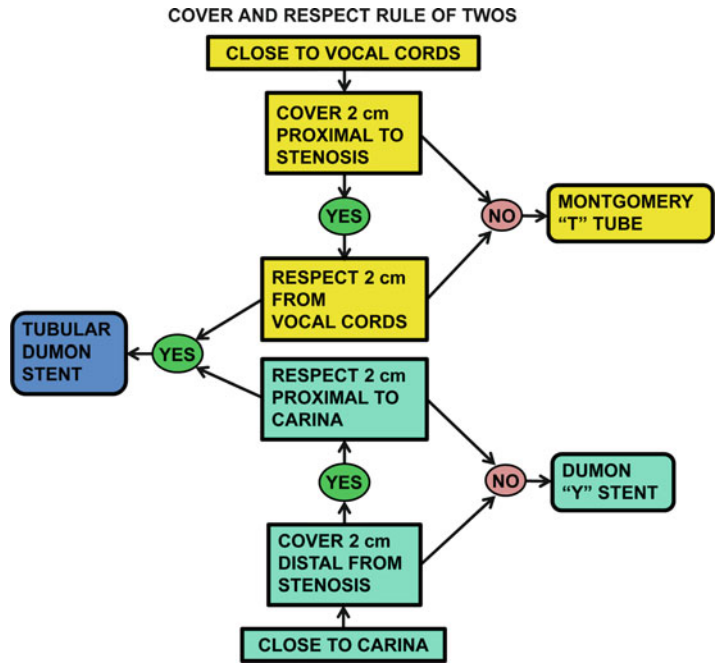


Fig. 11.13 Cover and respect rule of twos

- General status of the patient and his/her wishes
- Type of injury (acute versus chronic, extrinsic or intrinsic obstruction, fixed or dynamic stenosis, benign or malignant stenosis)
- Equipment availability
- Personal experience and expertise on a given method

After that, the "best" approach for a given patient can be offered.

As we said, frequently best results are obtained with a combination of treatments, and better outcomes for the patient are achieved in multidisciplinary, referral centers that have both extensive experience and sufficient equipment to deal with these complex clinical situations. We believe that interventional pulmonologists and thoracic surgeons must discuss thoroughly the indications, contraindications, and possible complications that can arise, case by case. We favor that the interventional team should be well trained and able to apply both the rigid and flexible bronchoscopes and has to be also knowledgeable on handling airway prostheses. The ACCP guidelines to interventional procedures provide useful recommendations including training requirements and number of suggested procedures to become competent and maintain proficiency in all the procedures described in this chapter [72].

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Endobronchial Prosthesis

12

Septimiu Dan Murgu

Abbreviations

CAO	Central airway obstruction
RRP	Recurrent respiratory papillomatosis
EBUS	Endobronchial ultrasound
SEMS	Self-expandable metallic stents
6MWT	Six-minute walk test
MRC	Medical Research Council
BPF	Bronchopleural fistula
ERF	Esophagorespiratory fistulas
QOL	Quality of life
ECAC	Expiratory central airway collapse
EDAC	Excessive dynamic airway collapse
TBM	Tracheobronchomalacia
RP	Relapsing polychondritis
CPAP	Continuous positive airway pressure
EPP	Equal pressure point
Ppl	Pleural pressure
PL	Intraluminal pressure
FLS	Flow-limiting segment
TLC	Total lung capacity
IOS	Impulse oscillometry
R	Resistance
Plat	Lateral airway pressure
CT	Computed tomography
ETT	Endotracheal tube

Introduction

This chapter emphasizes on the indications, physiologic basis, and complications of airway stent insertion. Airway stents have been consistently shown to help patients suffering from benign and malignant central airway obstruction[1] and esophagorespiratory fistulas, by improving their quality of life and potentially survival. These prostheses, however, are foreign objects within the airways and adverse events are therefore expected. The incidence rate of these events depends on patient-related factors and on specific stent–tissue interactions. Prior to inserting such a device, the bronchoscopist should determine the need and expected benefits of this procedure. A first step is to objectively classify the obstruction based on histology, mechanism of obstruction, and dynamic features (Fig. 12.1). An objective assessment of the extent and severity of airway narrowing is necessary as well as an accurate assessment of the impact of the airway narrowing on functional status.

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[1]Central airway obstruction is defined in this chapter as any clinically significant narrowing of the airway from the subglottis to the lobar bronchi.

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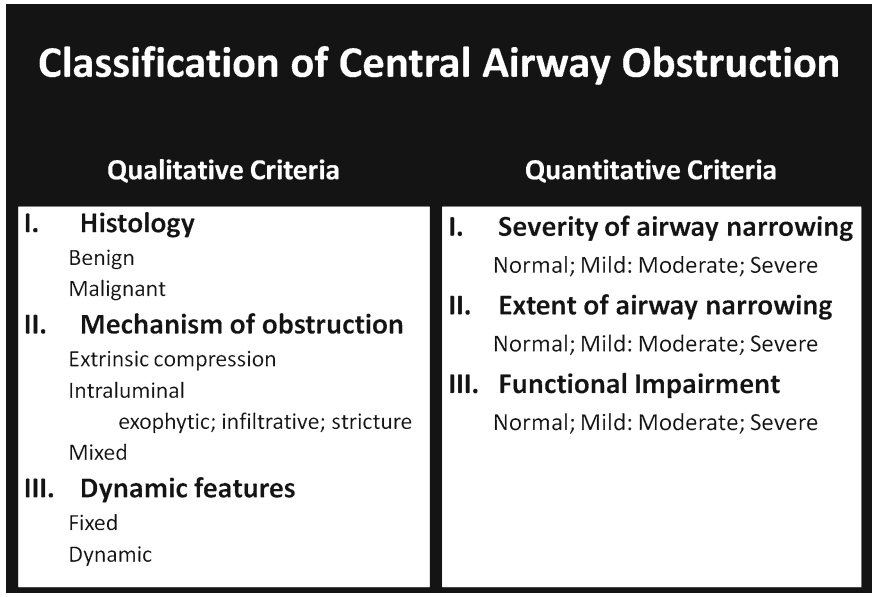

Fig. 12.1 Classification of central airway obstruction based on qualitative and quantitative criteria. Dynamic features refer to the phase of respiration during which there is flow limitation. In a fixed obstruction, there is limitation to flow both during inspiration and expiration, while in dynamic obstruction, only during a respiratory phase, as is the case with tracheomalacia. The quantitative criteria could be objectively assessed. For instance, based on physiologic data, for tracheal stenosis, the severity of airway narrowing can be quantified as mild (<50% narrowing), moderate (50–70%), and severe (>70%); the extent is the vertical length of the stenosis and, based on outcomes from bronchoscopic and open surgical interventions, can be quantified as mild (<1 cm), moderate (1–4 cm), and severe (>4 cm). Functional impairment can be objectively assessed using a variety of validated tools such as MRC dyspnea scale or WHO functional class

Historical Perspective

Since the beginning of documented airway stent insertion at the end of the nineteenth century, tracheobronchial prostheses have been generally made of two types of materials: metal or rubber. As the understanding of airway physiology and its interaction with the prosthetic materials has advanced, the manufacturers take into consideration the biomechanical and biocompatibility characteristics, even though this information is not always or easily available to the practicing bronchoscopist. Clinically used airway stents are currently made of polymers, alloy metallic mesh, or a combination of the two (aka hybrid stents). In general, the pure metallic stents have been abandoned because of severe complications.

The future may see the incorporation of treatment agents such as chemotherapeutic (i.e., mitomycin C), radioactive agents, or bioabsorbable stents [1]. In theory, stents made of bioabsorbable polymers may be ideal, especially in pediatric population, as they can support the airway wall and dissolve after the remodeling process is completed, thus providing temporary airway stiffness, sometimes necessary in infants with tracheobronchomalacia. Such stents have the advantage of potentially avoiding the need for repeated interventions under general anesthesia for removal or revision [2–4]. Only pilot human studies of bioabsorbable stents have been published to date [5]. Bioabsorbable drug-eluting stents have the potential advantage of reducing the risk of stent-related complications, but they have only been studied in animal models of benign tracheal stenosis [1]. Whether these stents will be incorporated into clinical practice remains to be determined. As of this writing, the original described problems of migration, granulation, mucus plugging, infection, and even airway perforation and fatal hemoptysis are still present after stent insertion [6].

Therefore, operators have to carefully review the indications and expected results before inserting such prostheses in patients' airways.

Indications

Airway stents are generally used for symptomatic extrinsic airway compression with or without associated airway mucosal infiltration. Stents can also be used if there is still significant (generally considered more than 50%) narrowing after the intraluminal component of a purely exophytic or mixed type of obstruction has been treated using one or more bronchoscopic techniques[2] [7]. Various stents have been used as well for sealing malignant esophagorespiratory and bronchial stump fistulas. Stents are occasionally used to improve symptoms of severe tracheobronchomalacia or excessive dynamic airway collapse, in patients who are refractory to more conservative measures (i.e., continuous positive airway pressure) and are not candidates for an open surgical procedure (i.e., tracheobronchoplasty for diffuse disease or sleeve resection for focal disease) [8, 9]. Studies performed within the last 20 years have shown that airway stents improve lung function in patients with central airway obstruction. In this section, we will describe the indications of stent insertion based on the mechanism of obstruction.

Extrinsic Compression

Extrinsic compression from benign or malignant thyroid disease, primary lung tumors, mediastinal masses, or lymphadenopathy is the most common indication for airway stent insertion. Rarely, vascular abnormalities such as aortic aneurysm, vascular sling, and double aortic arch may cause symptomatic airway obstruction and may require stent insertion for patients who do not undergo corrective surgery.

Intraluminal Obstruction

Stent insertion may be useful in selected cases of intraluminal exophytic benign central airway obstruction (CAO); this is the case of refractory endobronchial recurrent respiratory papillomatosis (RRP) when medical and other endobronchial therapies fail to restore airway patency. Case reports show that papilloma debulking and silicone stents can offer adequate control of symptoms [10]. However, benign intraluminal obstruction necessitating stent insertion is mostly caused by strictures, either idiopathic or related to other disorders. Wegener granulomatosis, amyloidosis, sarcoidosis, ulcerative colitis, post-tuberculosis, or Klebsiella rhinoscleromatis infection can cause strictures and should be ruled out before making the diagnosis of idiopathic stenosis. The most common cause of benign strictures, however, is post-intubation and post-tracheostomy stenosis, and this section will focus on the role of stent insertion for this process.

For post-intubation or post-tracheostomy strictures, stent placement should be considered only in inoperable patients; in addition, patients need to be symptomatic and the lumen of the airway below half of its normal after other interventional endoscopic techniques have been applied. For example, a simple weblike stricture (extent less than 1 cm) which is dilated and without recurrence will not require a stent [11]; a complex stricture, however, often has associated chondritis, and dilation alone (with or without laser assistance) is not usually successful, and a stent would be required to maintain airway patency [12]. Silicone stents are preferable in these cases and are helpful for splinting post-intubation/tracheostomy stenoses and are considered appropriate to palliate airway narrowing in nonsurgical candidates[3] [12–14]. Stent-related complications, however, are not uncommon in this disease and include migration, obstruction from secretions, infection, and significant granulation tissue

[2]These include rigid or flexible bronchoscopic resection, laser, electrocautery, cryotherapy, photodynamic therapy, or brachytherapy and are described in detail in other chapters in this book.

[3]Coexistent diseases: coronary heart disease, severe cardiac or respiratory insufficiency, or poor general condition.

formation at the proximal or distal extremities of the stent [6, 15]. That being said, silicone stent insertion performed using rigid bronchoscopy under general anesthesia is considered an acceptable alternative to surgery for inoperable patients with complex tracheal strictures.[4] In a study of 42 patients with complex stenoses, only 9 were surgical candidates and 33 were treated with silicone stent insertion, with a success rate of 69% [16]. The success rate of bronchoscopic treatment once stents are removed (usually after at least 6 months) in cases of complex stenosis is reportedly low (17.6%) suggesting the need for long-term indwelling airway stent. A higher rate of airway stability after stent removal (46.8%, in 22 out of 47 patients) was described after stents remained in place for a longer period of time (mean of 11.6 months) [17], with almost 50% of patients (12/22) having their stents for more than 12 months. Predictors of success of bronchoscopic treatments are stenoses less than 1 cm in vertical extent and without associated malacia (i.e., chondritis). Lesion extent (i.e., height) and intubation-to-treatment latency have also been reported to independently predict the success of bronchoscopic intervention. In one study, 96% of patients with lesions <3 cm in height were successfully treated bronchoscopically, but the success rate decreased to 20% for lesions longer than 3 cm. Patients with stenosis present for more than 6 months since the original injury were also less likely to be successfully treated bronchoscopically [18], suggesting that the established fibrotic tissue counteracts the expansile force of the remaining cartilage [19]. In fact, knowing the integrity of the cartilage in post-intubation or post-tracheostomy stenoses is important in the treatment decision-making process. In complex post-intubation/tracheostomy stenosis, cartilage integrity or lack thereof is not always easily assessed on white light bronchoscopy, mainly because of the overlying stenotic hypertrophic tissues [20] (Fig. 12.2). To assess the integrity of the cartilage, one may use high-frequency endobronchial ultrasound (20 MHz balloon-based radial probe) during the bronchoscopic intervention; the EBUS image using this system has a high resolution and allows visualization of the stenotic tissue and the cartilaginous structures and may be a surrogate of gross histology for tracheal stenosis; for instance, in idiopathic tracheal stenosis, the cartilage is known to be normal, but there is clear hypertrophy of the mucosa and submucosa as visualized by EBUS as well. On the other hand, in complex stenoses, there is partial or total destruction of cartilage histologically which can be identified by EBUS [20] (Fig. 12.2).

Silicone T-tubes (Montgomery T-tubes) or tracheostomy tubes are sometimes used for benign tracheal strictures; they should be inserted through the area of stenosis, if possible, to conserve airway not involved by the stenosis lesion. For most patients who do not require mechanical ventilatory support, a silicone T-tube could provide symptomatic improvement [21]. These therapies are warranted in the few patients with critical stenoses who are neither candidates for surgery nor for indwelling airway stent insertion or who develop recurrence after such interventions [12]. T-tubes can also be used when tracheal resection and reconstruction or dilation techniques are either not available or have failed, or as a solution for patients who had silicone stent placement complicated by frequent migrations [15]. In a large case series including 53 patients with complex tracheal stenoses (24 post-tracheostomy), silicone T-tube insertion was effective in 70% of patients with limited complications [22]. The sharper edge of the proximal aspect of the T-tube, in cases when it has to be cut, suboptimal tracheostomy tract (i.e., non-midline stoma), and its placement within 0.5 cm from the vocal cords are known risk factors for granulation tissue development[5] [22]. In addition, airway secretions may become dry and cause obstruction. Patients,

[4]Most studies define complex stenoses as follows: extensive scar ≥1 cm in vertical length, circumferential hourglass-like contraction scarring, or presence of associated malacia.

[5]Granulation tissue formation at the proximal end of the T-tube has also been described, and it is believed that chronic airway irritation incites infection and promotes or aggravates granulation tissue formation.

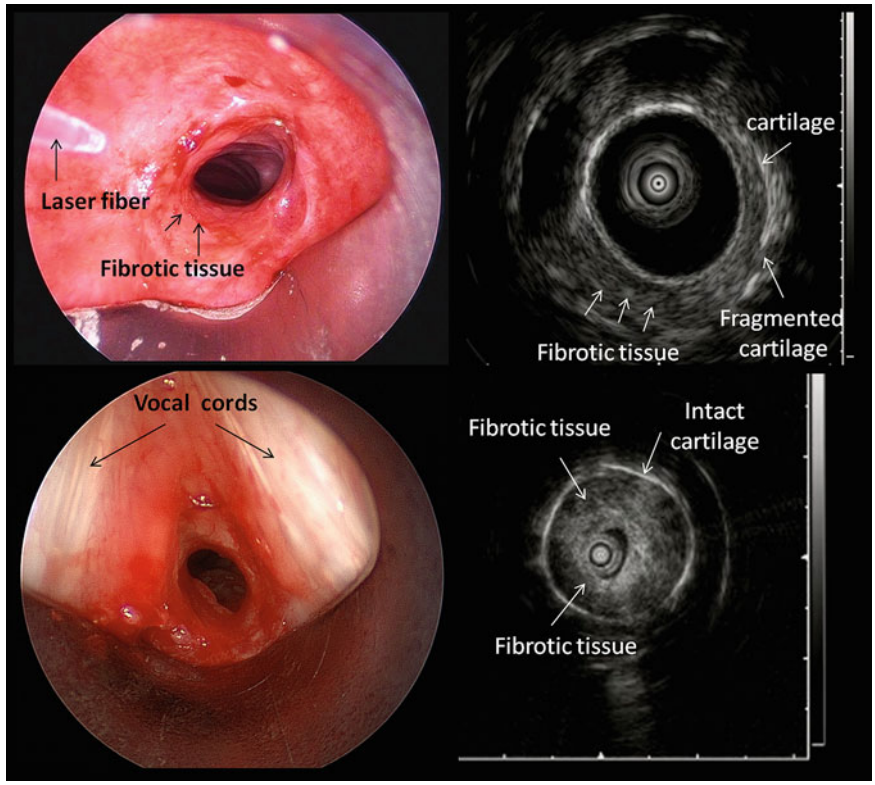

Fig. 12.2 Rigid bronchoscopic and sonographic view of laryngotracheal stenosis. In the *upper panel*, the circumferential post-intubation tracheal stenosis is noted, but on white light imaging, the cartilage cannot be assessed. High-frequency endobronchial ultrasound (20 MHz probe) can identify the cartilage and its disruption. The knowledge that the cartilage is affected could impact management since simple laser-assisted mechanical dilation without stent insertion is unlikely to maintain airway patency in the long term. In the *lower panel*, idiopathic subglottic stenosis at the level of the cricoid is seen on white light imaging, but the intact cricoid cartilage itself is only identified on high-frequency endobronchial ultrasound

families, and referring physicians probably benefit from instruction on how to care for and monitor T-tubes. Frequent bronchoscopies may be necessary to remove mucus plugs, with some investigators performing a 3–4 biweekly bronchoscopies, followed by once every 4 weeks once good stent patency has been documented [22].

Self-expandable metallic stents (SEMS) have been associated with significant complications and are to be avoided, if possible, in benign disorders. Immediate symptomatic improvement is reported and expected, but the long-term complications are common and may be life-threatening [23].

Self-expandable silicone stents, contrary to metal stents, have the advantage of being easily removable. They are, however, placed under rigid bronchoscopy or suspension laryngoscopy. Some of these silicone stents have been studied in benign airway obstruction including tracheal stenosis and malacia [24]. While immediate symptom palliation was established in most cases, the incidence of complications was high (75%) with stent migration occurring in 69% of cases [24, 25].

Mixed Obstruction

Mixed extrinsic and intraluminal obstruction is usually caused by malignant processes. In a series of 172 patients who underwent stent insertion at a tertiary cancer institution, 62.5% of the stents

were placed for mixed disease, while only 16.4% and 14.8% were placed for extrinsic compression and intraluminal obstruction, respectively [6]. In general, for malignant intraluminal obstruction, the principles are the same as for benign disease: if there is still obstruction after removal of the intraluminal tumor or if there is no airway structure (i.e., severe malacia due to cartilage invasion and destruction by tumor), a stent should be placed to maintain airway patency.

Relieving the central airway obstruction due to malignant disease could prevent post-obstructive pneumonia, sepsis, and septic shock; allow extubation; change in level of care; permit initiation of systemic therapy; and potentially improve survival. There is evidence that bronchoscopic therapies often provide acute relief of the obstruction, improve quality of life, and serve as a therapeutic bridge until systemic treatments become effective [26–28]. Subsequent chemotherapy and/or radiotherapy were shown to increase disease-free survival during the first year after restoration of airway patency [26, 29]. Prospective studies show that bronchoscopic intervention for malignant airway obstruction is associated with improvement in the six-minute walk test (6MWT), spirometry, and dyspnea [30]. In addition, studies show that airway stent insertion resulted in significant palliation of symptoms in patients with malignant CAO as evaluated by the Medical Research Council (MRC) dyspnea scale and performance status. Compared with historical controls, a significant survival advantage is apparent in the intermediate performance group, so it is possible that timely stenting of the airway, before the complications of malignant CAO have developed, results in improved survival [31]. In addition, it appears that airway stent insertion followed by adjuvant therapy may improve survival of treatment-naive patients with severe symptomatic airway obstruction caused by advanced lung cancer. In one study, while the performance status and dyspnea scales improved in both treatment-naive and terminal-stage lung cancer, the median survival time and 1-year survival rate after stent insertion were 1.6 months and 5.1%, respectively, in the terminal-stage group and 5.6 months and 25.0%, respectively, in the treatment-naive group [32].

Stump Fistulas

A less common indication for stent insertion is to cover large stump fistulas after lobectomy or, more commonly, after pneumonectomy [33]. In general, management strategies for bronchopleural fistula (BPF) depend on the underlying histology (malignant vs. benign), size, time to fistula formation postsurgery, and health status of the patient. Surgery is the treatment of choice of this condition, but bronchoscopic techniques have been advocated as an option when surgery is not possible or has to be postponed [34]. Surgical repair is not a good option for patients requiring mechanical ventilatory support because postoperative mechanical ventilation is associated with a high failure rate due to persistent barotrauma on the repaired stump [34]. As a general rule, when stents are used for this indication, a large stent must be used to seal the stump fistula as tight as possible in order to prevent aspiration pneumonia and empyema and allow satisfactory single-lung ventilation when the patient requires mechanical ventilation. Stent selection would depend on the size and location of the fistula as well as on the physical properties of the stent and the operator's ability to manage potential stent-related complications. Several case reports and case series of endobronchial stent insertion for isolated fistulas have been published [35]. The effect of case selection is difficult to assess from the limited literature on this topic.

Esophagorespiratory Fistulas

Tracheoesophageal or bronchoesophageal fistulas can be covered by airway stents. While these fistulas can be congenital, the majority are acquired either after esophagectomy, after intubation, or in the setting of malignancy. Benign esophagorespiratory fistulas (ERF) are not expected to improve after stent insertion, and in fact, it should only be considered if there are no operative modalities [36]. Palliation for malignant ERF is usually achieved with endoscopic placement of esophageal, airway, or parallel

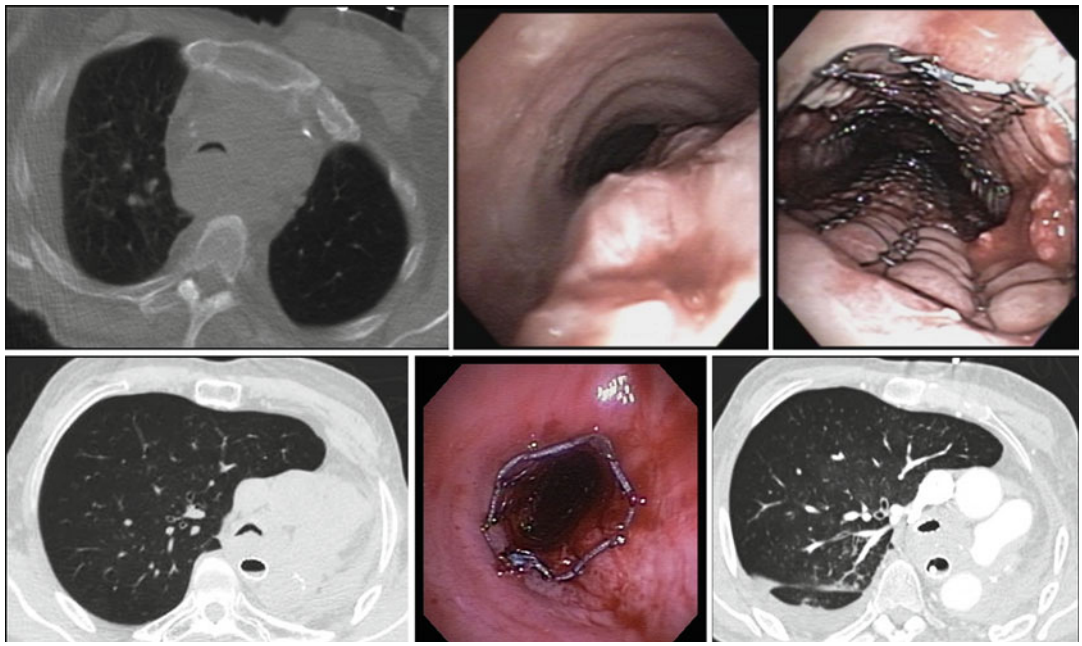

Fig. 12.3 Airway stents in obstruction caused by esophageal tumors. In the *upper panel*, chest computed tomography (CT) shows severe tracheal narrowing from a mediastinal mass, known to be esophageal carcinoma. Bronchoscopy confirmed the CT findings and a partially covered metallic stent was placed to palliate the airway obstruction prior to esophageal stent insertion for dysphagia. In the *lower panel*, severe tracheal and right mainstem obstruction occurred after the insertion of an esophageal stent and resulted in respiratory failure in this patient with poor lung function from his previous pneumonectomy. A partially covered metallic stent was inserted from the lower trachea to the mainstem bronchus, palliating the obstruction and allowing liberation from mechanical ventilation

(dual) stent insertion (in the esophagus and airway). Dual stent insertion appears to work better than a single prosthesis. Particular attention should be paid to airway compression or erosion caused by esophageal stents, prompting operators to initially place an airway stent prior to the esophageal one, if there is concern for significant tracheobronchial obstruction (Fig. 12.3). A dedicated fistula stent, the DJ cufflink-shaped prosthesis, was designed exclusively for closure of malignant ERF secondary to esophageal or lung cancer. It can be sized to the fistula diameter to occlude the abnormal communication [37, 38]. Insertion of silicone Y stents was shown to improve symptoms, reduce infections, and improve the quality of life in patients with malignant ERF. Mean survival of these patients, however, remains dismal and is in the range of 2 months [39]. A conservative palliative approach including only symptomatic control but no palliative interventions (i.e., stent insertion) is not unreasonable especially since interventions in this frail population could be harmful. Without treatment, however, survival may be limited to only a few days [40]. On the other hand, in a recent prospective study of 112 patients with malignant ERF, airway stents were inserted in 65 (58%) patients, esophageal stents in 37 (33%) patients, and both airway and esophageal stents in 10 (9%) patients. Contrary to previous data, the authors found an overall mean survival was 236.6 days (airway stent 219.1 days, esophageal stent 262.8 days, and combined airway–esophageal stent 252.9 days). Since a few patients are operable, currently airway and/or esophageal stent insertion is mainly used with a palliative intent to improve the quality of life (QOL) in patients with malignant ERF [41].

Expiratory Central Airway Collapse

Airway stent insertion has been used to improve cough, secretions, and QOL in patients with expiratory central airway collapse (ECAC) [8, 9]. There are, however, different morphologic types of ECAC, for some of which stent insertion is not physiologically justifiable. Excessive dynamic airway collapse (EDAC) is due to bulging of the posterior membrane within the airway lumen during exhalation that narrows the lumen by 50% or more, and the cartilage is intact in this process. Tracheobronchomalacia (TBM), on the other hand, refers to softening of the airway cartilaginous structures [42]. The decision to insert an airway stent in these processes is complicated by at least two factors: (1) the lack of standardized definitions and cutoff values to define abnormal airway narrowing and (2) the lack of clear understanding if these entities are truly responsible for airflow limitation. In fact, the limit between normal and abnormal narrowing of the central airways has not been physiologically established, and different investigators propose different cutoff values. In addition, there is no standardized way to measure the narrowing in terms of location or respiratory maneuver (Table 12.1) [42]. To illustrate this lack of consensus, a study found that almost 80% of normal individuals met the currently accepted 50% narrowing during forced exhalation criterion [43]. In an attempt to provide a common language for these patients with ECAC, a classification system was proposed based on objective quantifiable criteria which can be applied before and after stent insertion [42].

Studies show that in the short term (up to 10–14 days), airway stabilization with silicone stents in patients with expiratory central airway collapse (malacia and EDAC) improves symptoms, quality of life, and functional status [8, 9]. QOL and functional status scores improved in 70% of patients, and dyspnea scores improved in 91% of patients after stent insertion [9]. Stent-related complications in this case series included obstruction from mucus plugging and migration, and almost 10% of patients (5/52 patients) had complications related to the bronchoscopic procedure itself. Because the dynamic features of expiratory central airway collapse continuously alter the shape of the central airways as well as the surface contact between a stent and the airway wall, stent-related complications may occur more frequently in dynamic forms of airway obstruction than in fixed benign obstruction. Although not life-threatening, these stent-related adverse events required multiple repeat bronchoscopies [8]. In another series of patients with mostly TBM, adverse effects from silicone stent insertion were very common, however, with a total of 26 stent-related adverse events noted in 10 of 12 patients (83%), a median of 29 days after intervention [8]. TBM due to relapsing polychondritis (RP) is one disease for which stent insertion is often necessary due to a diffuse lack of airway cartilaginous support. Both self-expandable metallic stents and silicone stents have been used in patients with malacia from RP [44, 45]. Sometimes, more than one stent may be required if symptoms persist after stent insertion, presumably because of distally migrated choke points [45]. Because airway stents are not the best solution for this disease, a more conservative approach such as continuous positive airway pressure (CPAP) may be safer. CPAP may indeed be considered a "pneumatic stent." The excessive airway narrowing in ECAC and the resulting turbulent flow result in increased airway resistance which requires greater transpulmonary pressures to maintain expiratory airflow. This will increase the work of breathing and result in dyspnea. Thus, noninvasive positive pressure ventilation such as CPAP decreases pulmonary resistance and can be used to maintain airway patency, facilitate secretion drainage, and improve expiratory flow. Small studies showed that nasal CPAP improves spirometry values, sputum production, atelectasis, and exercise tolerance, but its long-term efficiency has not been clearly demonstrated [46]. As of this writing, however, the limited published evidence suggests that QOL and functional status are improved in patients with ECAC undergoing stent insertion, but the lung function as measured by FEV_1 has not been consistently reported to improve after stent insertion or other forms of central airway stabilization (i.e., membranous tracheoplasty) [9]. These facts raise questions about the physiologic basis for stent insertion.

Table 12.1 Summary of classification systems for expiratory central airway collapse

First author/year	Parameters	Comments
Rayl/1965	*Extent*: proximal, mediastinal, and intrapulmonary airways	Collapse during cough on cine-bronchography
Johnson/1973	*Severity*: four degrees and focal type	TM: more than 50% collapse during coughing on fluoroscopy
Feist/1975	*Etiology*: congenital and acquired	TM: more than 50% collapse during coughing on fluoroscopy
Jokinen/1977	*Severity*: mild, moderate, severe *Extent*: TM, TBM, BM	First classification based on bronchoscopic findings
Mair/1992	*Etiology*: congenital, extrinsic compression, acquired *Severity*: mild, moderate, severe	Described for pediatric TBM Empirical severity score
Masaoka/1996	*Etiology* and *extent* criteria Pediatric, adult, and secondary	TBM : >80% collapse during expiration
Murgu/2007	*Functional class* *Extent* *Morphology* *Origin* (*etiology*) *Severity*	Stratification criteria (functional class, extent, and severity are objectively assessed) Morphology: includes EDAC and three forms of TBM[a] Origin: idiopathic or secondary

TM tracheomalacia, *TBM* tracheobronchomalacia, *BM* bronchomalacia, *EDAC* excessive dynamic airway collapse
[a]There are three morphologic types of TBM: crescent type, when the anterior wall is collapsing; saber-sheath type, when the lateral walls are collapsing; and the circumferential or mixed type, when the anterior and the lateral walls are collapsing, as is seen with relapsing polychondritis

Physiologic Rationale for Airway Stent Insertion

In general, for symptomatic patients with fixed tracheal obstruction, a stent is inserted to improve the lumen to <50% obstruction; for symptomatic patients with dynamic obstruction, stents are meant to stabilize the airway at the collapsible segment responsible for flow limitation (aka choke point).

For tracheal stenosis, symptoms depend on the amount of pressure drop along the stenosis; this depends not only on the degree of the obstruction but also on the flow velocity through the airway narrowing. This flow dependence of symptoms explains why different patients with similar degree of airway narrowing have different clinical presentations, depending on their level of activity. These facts highlight the need to individualize treatment based not just on degree of narrowing as assessed by radiographic or bronchoscopic imaging but also on the stenosis impact on functional status. In fact, functional status and dyspnea scales may be more relevant than static lung function measurements which have a weak correlation with the MRC dyspnea scales in laryngotracheal stenosis [47]. In addition to functional status, a classification system for tracheal stenosis should include the extent, the morphology, and the severity of airway narrowing, factors which will impact the decision to insert an airway stent. To quantify the severity of airway narrowing, the cutoff values used in the available systems are 50% and 70% to define moderate and severe stenosis, respectively [48]. These values seem to be justified by physiologic studies in which the investigators found that the effect of the glottis narrowing was noted to be of the same order as that of the 50% stenosis; these data suggests that a 50% or less narrowing may not even be clinically detected or require treatment; however, a significant pressure drop is seen at 75%, 85%, and 90% stenosis, pressure drop which correlates with significant work of breathing [49]. Based on these physiologic data, therefore, one could classify stenosis as mild, when less than 50% narrowing; moderate, from 50 to 70%; and severely narrowed when more than 70% of the lumen is occluded, justifying the practice of improving the airway lumen to less than 50% narrowing, with stent insertion, if necessary.

For expiratory central airway collapse, it is still not clear what degree of airway collapse is physiologically significant; furthermore, as of this writing, there are no accepted noninvasive physiologic tests to predict response to stent insertion. However, when patients have clear inability to raise secretions and recurrent pneumonia or even respiratory failure, then a stent is inserted regardless of the cause of collapse. From flow dynamics standpoint, the clinically relevant question in this process is whether stent insertion improves the expiratory flow. Physiologists proposed a theory to explain expiratory flow limitation, a theory which is useful to understand the role of stent insertion in patients with dynamic CAO such as malacia or EDAC. Physiologic studies showed that once expiratory flow becomes limited at a given lung volume, there would be a region within the intrathoracic airway where intrabronchial and extrabronchial pressures become equal (equal pressure point, EPP) (Fig. 12.4) [50]. At a given lung volume, driving pressure upstream (alveolarward) from the EPP would be equal to lung elastic recoil, because pleural pressure (Ppl) equals the intraluminal pressure (PL); downstream from the EPP (mouthward), airways would be compressed during expiration. This region of compression of intraluminal caliber is referred to as a flow-limiting segment (FLS) or "choke point." As lung volume decreases and pleural pressure (Ppl) increases during forced expiration, the EPP migrates upstream, resulting in a lengthening of the increasingly narrow downstream segment. This increases airway resistance and prevents further increases in expiratory airflow, causing the EPP to become fixed when airflow becomes constant. EPP and therefore the FLS have tracheal location at high lung volumes (TLC), but as lung volume decreases during exhalation, the FLS move peripherally but they still stay in the central airways, in the lobar/segmental, at most subsegmental bronchi [51]. Therefore, if the choke points in humans are often located in the lobar bronchi, a mainstem bronchial or tracheal collapsibility in the form of EDAC, often seen on CT or bronchoscopy, should not result in any pressure drop between the mouth and the choke point and should not affect flow. In fact, physiologists suggest bronchoscopic or radiologic detection of expiratory tracheal or mainstem bronchial compression (EDAC) should trigger a search for causes of airflow obstruction within the lung, not the central airways [52]. Loss of pressure in the abnormally narrowed peripheral airways in patients with asthma, COPD, or bronchiolitis will lead to decreased intraluminal pressure by the time that airflow reaches central airways, so that these airways (trachea and mainstem bronchi) will collapse at the weakest point, which is the posterior membrane. Thus, EDAC is most often a reflection of peripheral airway disease, but it can also be seen with morbid obesity due to increased pleural pressure and possible flow limitation at rest. That being said, some patients may improve their functional status after stent placement in the central airways not only for malacia but also for EDAC; one explanation is that improved central airway stability, regardless of which wall is collapsing, makes the flow less turbulent, similar to heliox, which was shown to improve exercise capacity in patients with moderate to severe COPD, even though these patients typically have choke points in the small airways (of 2 mm or less) [53]. It is possible that in the future, in addition to bronchoscopic and imaging methods, new physiologic or imaging studies may have a role in identifying the choke point physiology in CAO. For instance, using impulse oscillometry (IOS), increased resistance (R) at a low oscillation frequency (5 Hz) reflects an increase in total respiratory resistance suggestive of airway obstruction such as that found in patients with COPD, while increased R at a higher frequency (20 Hz) reflects more specifically increased central airway resistance such as that found in patients with malacia [54]. Until these methods are validated in large studies, a trial and error approach is still clinically used: temporarily place a stent and test whether the patient improves clinically; if they do, a surgeon may perform an external splinting procedure; if not, the stent is removed [55]. Another method, more accurate but invasive, is the intraluminal pressure monitoring using a small pressure catheter. As pointed above, dynamic airway compression causes the formation of FLS in the cen-

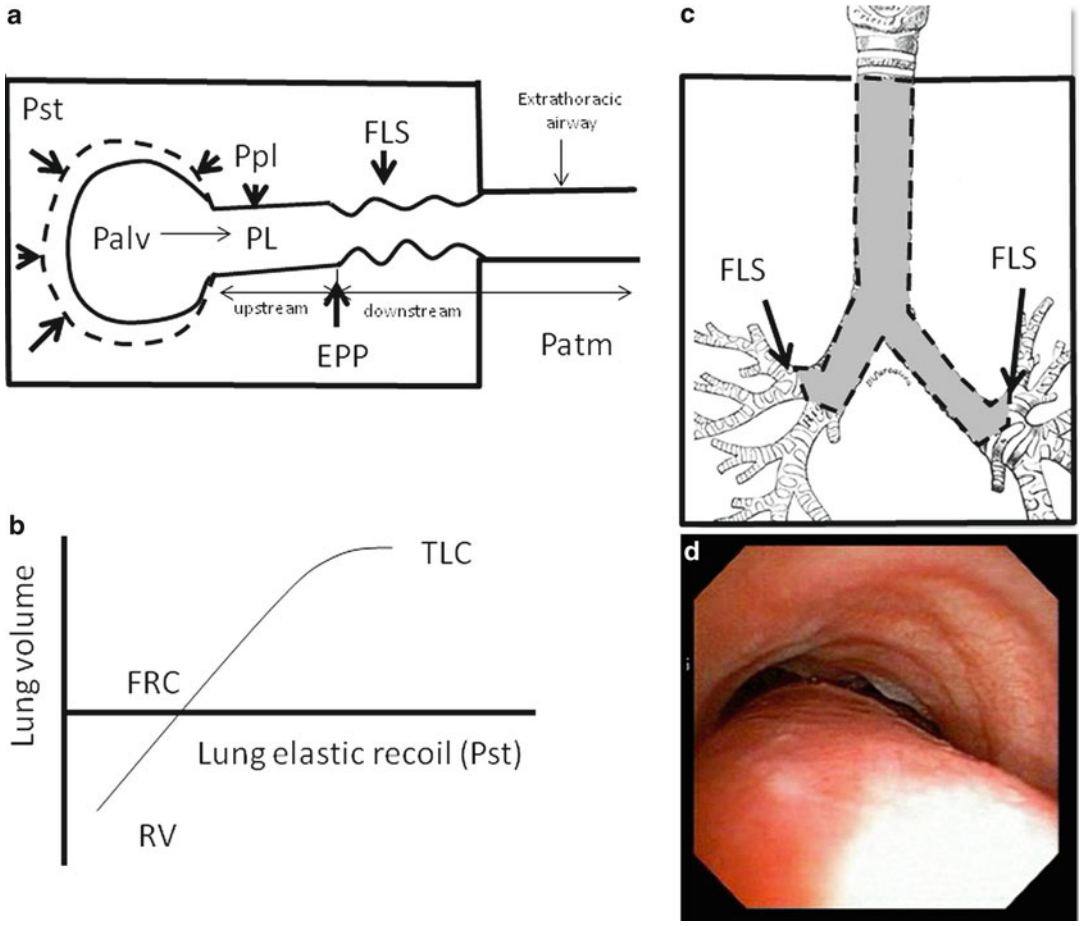

Fig. 12.4 Choke point physiology based on Starling resistor. (**a**) The alveolar pressure (Palv) is the driving pressure that causes gas to flow through airways during expiration and is approximately equal to the recoil pressure of the lungs (Pst) plus the pleural pressure (Ppl): Palv = Ppl + Pst. Normally, a pressure drop is required to accelerate a gas as it moves from an upstream (alveolarward) region of low velocity to a downstream (towards the mouth) region of high velocity. Because of this pressure drop, the intraluminal pressure (PL) eventually becomes equal to pleural pressure (Ppl). The point within the airway at which this occurs is called the equal pressure point (EPP). This equal pressure point (EPP) divides the airways into upstream segments (alveolarward from the EPP) at which transmural pressure is positive and downstream segments (mouthward from the EPP) at which the transmural pressure is positive within the extrathoracic airways and negative within the intrathoracic airways. At a given lung volume, driving pressure upstream from the EPP would be equal to lung elastic recoil, while downstream from the EPP, airways would be compressed during expiration. This region of compression of intraluminal caliber is referred to as a flow-limiting segment (FLS) or "choke point." (**b**) As lung volume decreases from TLC towards RV, the elastic recoil (Pst) decreases as well, and pleural pressure (Ppl) increases during forced expiration. (**c**) Thus, the EPP migrates upstream, resulting in a lengthening of the increasingly narrow downstream segment. This increases airway resistance and prevents further increases in expiratory airflow, causing the EPP to become fixed when airflow becomes constant. FLS have tracheal location at high lung volumes (i.e., TLC), whereas others found FLS in lobar and segmental airways over a range in volume approximating TLC to functional residual capacity (FRC). As lung volume decreases during exhalation, the FLS move peripherally to the lobar/segmental and at most subsegmental bronchi. (**d**) Therefore, if the choke points (FLS) in humans are often located in the lobar bronchi, a mainstem bronchial or tracheal collapsibility should not result in any pressure drop between the mouth and the choke point and should not affect flow. Thus, bronchoscopic or radiologic detection of expiratory tracheal or mainstem bronchial compression (excessive dynamic airway collapse) should trigger a search for causes of airflow obstruction within the lung, not the central airways

tral airways during forced expiration. Both in animal and human studies, these FLS could be located with the use of intraluminal airway catheters by measuring lateral airway pressure (Plat) during induced flow limitation generated by either an increase in pleural pressure or a decrease in downstream pressure. The measurements of lateral pressure in malacia before and after stent insertion show that before stenting, a large pressure difference is seen between the upper trachea and right lower bronchus and carina. After stenting, the pressure difference could vanish for both inspiration and expiration and a regular respiratory cycle is seen [56]. By measuring lateral airway pressure on each aspect of the airway narrowing (proximal and distal) and plotting the two pressures against each other (pressure–pressure curves) during quiet breathing intraoperatively, the site of maximum obstruction and the degree of airway narrowing can be determined quantitatively [57]. Analysis of the pressure difference and the angle of pressure–pressure curve allow intraoperative estimation of the outcomes of a particular interventional bronchoscopic procedure. However, stents may improve flow but the choke points migrate distally. This process can be addressed either by additional stent insertion or by the use of noninvasive positive pressure ventilation. Detection of choke point migration can be demonstrated bronchoscopically or by dynamic computed tomography (CT) in the form of airway wall collapse distal to the stent.

Stent Selection Criteria

Stent retrievability is an important criterion in patients with benign disease and with malignancy for which a temporary stent placement is expected. For example, for patients with malignant CAO who will undergo further systemic chemotherapy and/or radiation therapy and respond to treatment, the stent may become loose, migrate, and require removal [58]. Inserting a stent into the patient is not always the biggest challenge encountered in caring for these patients. It is advisable to select a stent that can be removed if necessary without causing further tissue damage.

Another selection criterion is based on the stent's *morphology and positioning*: for instance, T-tubes require a tracheostomy; straight indwelling stents splint open the trachea and the mainstem bronchi, while bifurcated stents are placed at the main carina and sometimes at secondary carinas. One criterion to consider prior to insertion is the *stent material*. In fact, the traditional way to classify stents was based on material type: metal, polymers, and hybrid stents partially covered or fully covered.

The type of stent, however, should also be decided based on the *biomechanical characteristics* (dependent on the material but also on design and thickness) because stents differ greatly in their elasticity and resistance to angulation [59, 60]. The expansile force (strength) and ability to withhold angulation (buckling) varies among different types of stents. In this regard, the studded-silicone-type stent and Polyflex stents have a high expansile force [60] and may be preferred in obstruction due to severe and extensive airway compression. However, for a distorted, curved airway, angulation properties become important because they determine whether the stent can conform to an acutely angulated airway and still remain patent, such as is often the case in patients with left main bronchial obstruction due to extrinsic compression (Fig. 12.5). In these cases, the Ultraflex stent may be a better choice than a straight silicone stent because of the Ultraflex stent's known resistance to angulation. A study evaluating the role of interventional bronchoscopy for malignant CAO showed that the most common stent used in the trachea and right mainstem bronchi (relatively straight airways) was the Dumon stent, while the most common one for the left mainstem bronchus (curved, tapered airway, often distorted in the setting of malignancy) was the Ultraflex stent, likely because of its better ability to withhold angulation[6] [61]. Therefore, stent biomechanics bench testing data such as the crush (expansile) force, infolding (angulation) properties, and fatigue life, which are

[6]In this study, patients with esophageal carcinoma involving the airway mostly required only stent placement without laser-assisted debulking, probably because the main problem was extrinsic compression.

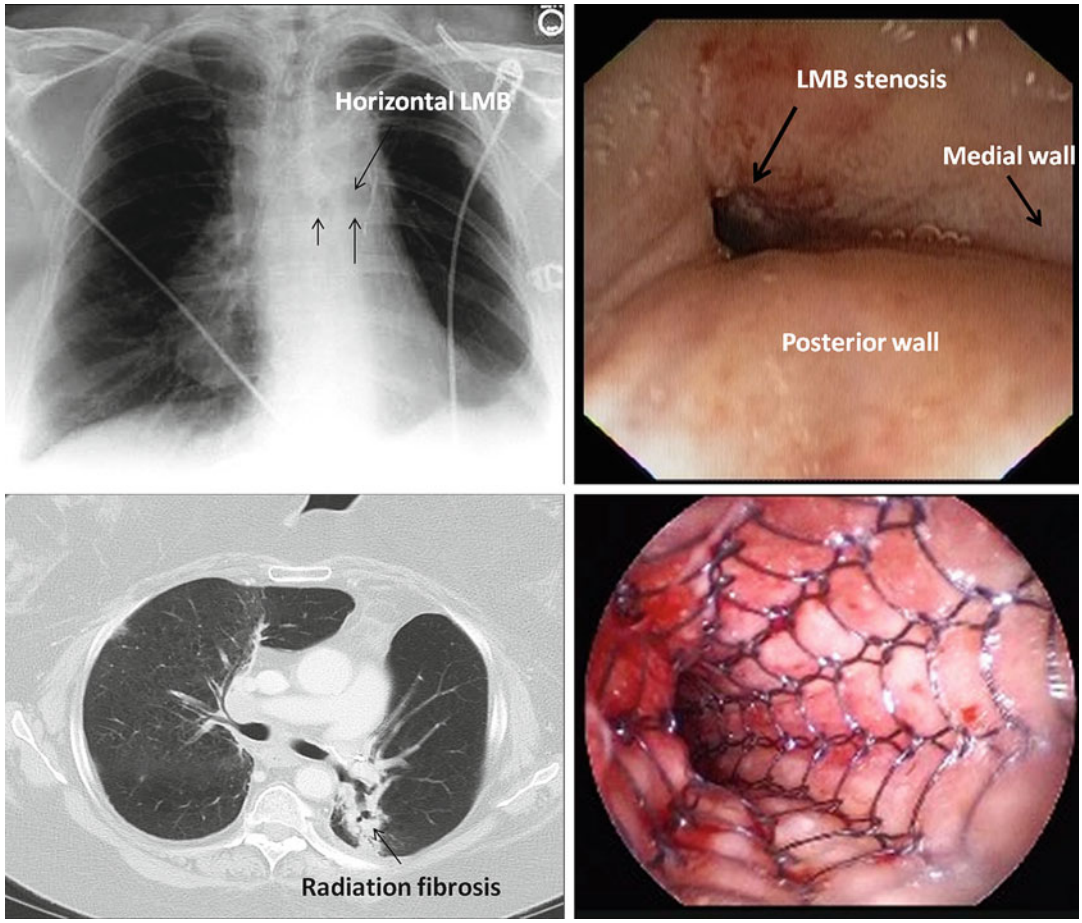

Fig. 12.5 Example of how airway anatomy impacts stent selection. Chest radiograph reveals nearly horizontal left main bronchus (*upper left*). Chest computed tomography shows that this was in part caused by volume loss from radiation fibrosis (*lower left*). Bronchoscopy revealed significant torsion of the left main bronchus and mid-distal left main bronchial stenosis (*upper right*). Due to its resistance to angulation, a partially covered self-expandable metallic stent was inserted to restore airway patency

for the most part considered confidential and proprietary information, may be very useful to the interventional bronchoscopist. For instance, fatigue life may become important in patients with benign etiology of CAO, especially malacia, in which cycled compression of the stent with each exhalation may lead to stent fracture and its associated complications.

In regard to *size*, following dilation, usually a stent with a diameter that is bigger than the remaining stenosis should be inserted. The actual size of the stent could be objectively determined by carefully evaluating the airway diameter using CT, measuring devices, or even radial probe EBUS, or long-range, anatomical optical coherence tomography. Many experienced rigid bronchoscopists, however, do not need or use these technologies and often choose the size of the stent based on the "tactile feedback" resulting from the viscoelasticity property of the airway; in general, the stent is slightly larger (1–2 mm) than the size of the dilating bronchoscope. However, if CT scanning is used to determine the stent size, one should remember that for mainstem bronchi, contrary to trachea, the diameter of the airway on the CT is different than the actual airway diameter and corrections are necessary (Fig. 12.6) [62].

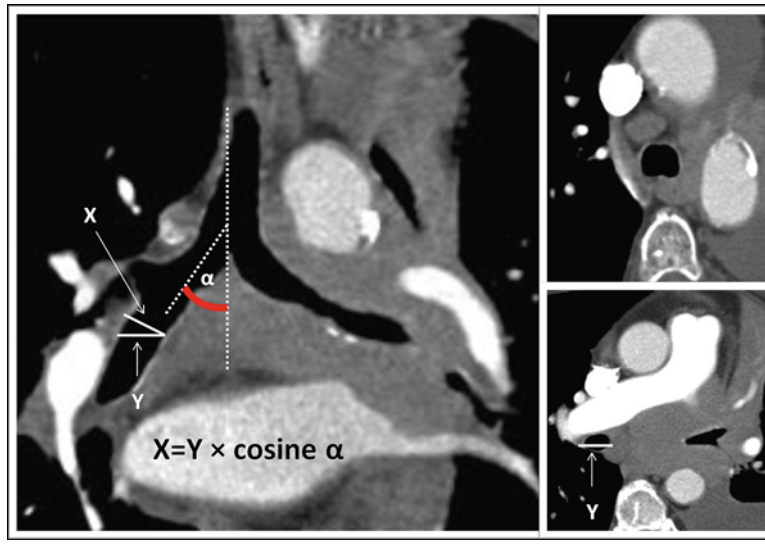

Fig. 12.6 Chest computed tomography use for stent size selection. Contrary to trachea (*upper right*), for mainstem bronchi and bronchus intermedius (*lower right*), the diameter of the airway on the CT (*Y*) is different than the actual airway diameter and corrections are necessary (*right panel*). *Y* represents the measured transverse diameter of the bronchus on chest tomography, and *X* represents the corrected transverse bronchial diameter. α denotes the angle between the central axis of the trachea and bronchus, which equals the angle between *Y* and *X*

Contrary to size, the *length* of the stent does not have an important impact on flow dynamics [49]. That is simply because the resistance to flow is linearly and directly proportional to the length of stenosis and inversely proportional to the radius of the airway narrowing at the power of 4 (for laminar flow). In simulation studies, for instance, long stenoses show a modest difference in pressure profile with a slightly bigger magnitude of total pressure drop than the weblike stenosis of comparable airway narrowing (90%) [49]. The extent of the narrowing is important, however, for surgical decisions and for stent's length selection. In general, the length of the stent should be longer than the actual stenosis, to avoid migration and obviously to properly palliate the airway narrowing. In general the stent should exceed the stenosis by 0.5–1 cm on both sides. This principle may be difficult to apply in short airway such as right main bronchus, when the stent may need to be customized on site in order to provide ventilation to the right upper lobe. The exact length can be measured based on previously performed chest CT scanning for a different indication. Given the risk of radiation and alternative methods, ordering a CT scan for the sole purpose to determine stent size or length may not be warranted or cost-effective. The operator can use the scope itself, the telescope, or the accessory instruments (available sizing devices) to measure the extent of stenosis during bronchoscopy.

All these stent factors (size, length, morphology, material, and biomechanics) become important in selecting a particular stent for a specific type of obstruction. For instance, the dynamic features of TBM can make the selection of the type and size of the stent being inserted problematic. Sometimes very large stents (20–22 mm diameter) are required for those patients with tracheobronchomegaly. In addition, the expansile force has to be high enough to prevent significant collapse during expiration. Even though they rarely migrate, we use Y-shaped stents infrequently because we try to preserve as much normal mucosa as possible and thus decrease the likelihood of stent obstruction by tenacious mucous secretions, a common complication, especially in patients

with chronically inflamed airways. In addition, Y stent insertion in a patient with complete airway collapse and inflamed and friable airway mucosa is not always straightforward and could be complicated by lack of unfolding, airway perforation, and subsequent ventilation, oxygenation, and hemodynamic disturbances.

Technique and Equipment

Airway stents can be placed via flexible (for SEMS) or rigid bronchoscopy (SEMS or silicone). The principles are the same; first, the operator will dilate the lesion (extrinsic compression, stricture, or significant residual obstruction after other endobronchial therapy); second, a stent large enough is deployed inside the airway to prevent migration and properly restore airway patency.

In case of *rigid bronchoscopy*, the scope is introduced through the mouth and then between the vocal cords under direct visualization to assure a secure airway at all times. We usually choose large rigid bronchoscopes (12–13 mm diameter) to allow deployment of a large tracheal/bronchial stents and facilitate easy passage of accessory instruments (large grasping forceps or large suction tubing that may become necessary in severe airway bleeding). The beveled tip of the scope not only facilitates lifting of the epiglottis and atraumatic passage of the scope through the vocal cords but also assists for dilation and removal of exophytic intraluminal lesions (i.e., rigid bronchoscopic debulking). Operators should be familiar with the length of their scope and be able to decide how much the stent introducer should be inserted inside the scope in order to avoid deployment of the stent too distally (beyond the stenosis) or too proximally (inside the rigid bronchoscope). There are two techniques of straight silicone stent insertion, as one can expulse the stent either beyond the stricture and then pull it back or to directly deploy it within the stricture itself. There are also two techniques to deploy a Y stent, and the operator can choose the one he or she is most familiar with: the "push" technique, in which the stent is ejected from the bronchoscope above the carina and then is pushed down with an open rigid grasping forceps placed at stent bifurcation, and the " pullback" technique, in which both bronchial limbs are placed within one bronchus (usually the one involved with most disease), then the stent is pulled back slowly until the shorter limb pops out. While this has not been studied, the "pullback" technique may be safer in patients with abnormal airway wall (friable, infiltrated mucosa, preexistent fistula) because of potential reduced risk of pushing the stent into the mediastinum. Accessory instruments such as grasping forceps may be needed post-deployment to assist with stent unfolding and positioning in the desired location. If the operator works through an open system, he or she may occasionally need to use Vaseline petroleum gauze packing strip or Kerlix gauze roll to pack the nose and the mouth, respectively, in case of significant air leak and subsequent impaired ventilation and oxygenation.

Flexible bronchoscopy is used by many operators to insert SEMS. This procedure can even be performed while the patient is on the ventilator in the intensive care unit. The technique of placing these stents under fluoroscopic guidance is well described [63], but fluoroscopy in the intensive care unit is cumbersome and often unavailable. There are techniques for placing these stents without fluoroscopy, one of which will be described here. First, the bronchoscope is inserted in the mouth through a bite block alongside the endotracheal tube (ETT), after deflating the ETT cuff, and advanced into the space between the tracheal wall and the ETT. The scope is then positioned proximal to the stenosis. A guide wire is inserted through the bronchoscope and passed alongside the lesion, after which the bronchoscope is withdrawn, leaving the guide wire in place. The scope is reinserted into the ETT to confirm guide wire location. A stent delivery catheter is advanced over the guide wire, and the stent is deployed under bronchoscopic visualization. The delivery catheter and guide wire are withdrawn together, leaving the stent in position. If necessary, the stent can be repositioned by grasping its proximal loop with a flexible alligator forceps.

Stent-Related Complications

While rarely reported, procedure-related complications can occur during stent insertion and include perforation of the airway wall resulting in bronchomediastinal fistula, massive hemorrhage (from large vessel laceration), and potentially mediastinal misplacement of the stent and hypoventilation and hypoxemia caused by the large stent not unfolding satisfactorily or by occlusion of the stent with mucus or blood immediately after deployment. This section, however, will address long-term adverse events related to the presence of indwelling airway stent. In this regard, stents are indeed foreign objects inside the airway, and adverse events are therefore expected. Several complications have been identified and reported as incidence proportion[7] [6] in case series, but only recently this issue has been systematically approached using clear definitions and statistics using incidence rate[8] rather than proportions to report these adverse events [6]. Because of different biomechanics, significant differences exist between airway stent types in terms of long-term complications related to stent infection, granulation tissue, mucus plugging, stent migration, and stent fracture which could injure the airway wall or the adjacent mediastinal vessels [64]. While perioperative complications are rare and the immediate effects of stent insertion could be gratifying, both bronchoscopists and patients should be aware that long-term complications are common and potentially life-threatening [65].

Granulation Tissue

This complication may also promote the development of secondary stenoses [66]. The exact prevalence of stent obstruction by granulation tissue versus tumor overgrowth or ingrowth in patients with malignant obstruction is somewhat confounded by the fact that studies tend to report them together rather than separately, but when it occurs may be clinically significant in approximately 25% of patients [67]. The estimated incidence proportion of recurrent obstruction from either granulation tissue or tumor is 9–67% in patients with metal stents and 6–15% in patients with silicone stents [68]. The likely mechanism for granulation tissue formation consists of excessive pressure on the airway wall which may lead to ischemic necrosis due to capillary closure. From physics standpoint, if the expansion force of a stent would be distributed equally over its complete outer surface, this would result in a relatively small contact pressure on the airway wall. However, if the stent wall touches a small portion of the inner tracheal wall (as may be the case with cylindrical stents for stomal, triangular stenoses), then the local pressure at that contact zone would be much higher and would result in considerable impairment of mucosal blood flow promoting further tissue ischemia and damage. This process could be worse if a SEMS is used. Though such a stent may have the same overall expansion force as a silicone stent, it can shut down the mucosal blood flow at spots where the thin wires come in contact with the tissue (Fig. 12.7). Thus, the ciliated epithelium is replaced by fibroblasts and granulation tissue. Oversizing the stent has been suspected as a risk factor especially when stents are placed in the upper trachea or subglottis. In one study, Dumon stent insertion for benign tracheobronchial stenoses showed an incidence proportion of 28% for granulation tissue after a mean period of follow-up of 303 days. The stent-to-airway diameter ratio of 90% was found to be the critical cutoff point for predicting granulation tissue formation (OR: 47.5285) [62]. The optimal ratio between the stent and the airway diameter which would reduce granulation tissue formation has yet to be determined. Friction between the sharp edges of the stent and airway mucosa and the formation of galvanic currents may cause granulation tissue formation; this is especially true if

[7] An incidence proportion is defined as the number of cases with complications divided by the number of cases overall and is an appropriate measure for analyzing immediate perioperative complications [6].

[8] It measures events per person-time at risk [6].

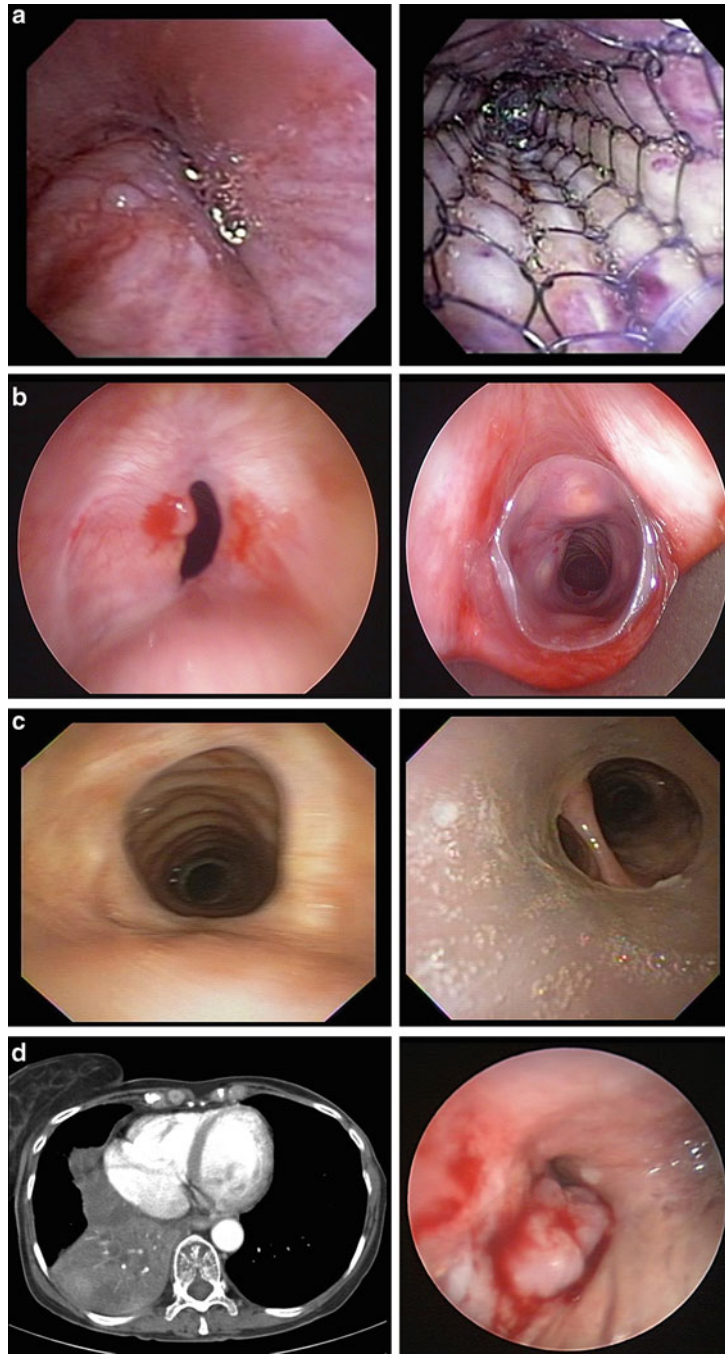

Fig. 12.7 (**a**) Severe, complete left main bronchial obstruction due to extrinsic compression and mucosal infiltration (*left panel*). A partially covered self-expandable metallic stent was inserted which caused blanching spots where the thin wires come in contact with the tissue, suggesting mucosal ischemia from mucosal blood flow compromise (*right panel*). (**b**) Post-tracheostomy-related tracheal stenosis with chondritis and hypertrophic tissues (*left panel*); post-dilation, a straight silicone stent was placed which was well compressed after deployment (*right panel*). (**c**) In the same patient, several months later, bronchoscopy showed that the stent migrated downwards to the main carina (*left panel*); this resulted in significant obstruction of the left main bronchus and inability to clear secretions (*right panel*). (**d**) Computed tomography performed 3 months prior to bronchoscopy showed complete absence of aeration in the right lower lobe, thus precluding bronchoscopic intervention to restore airway patency (*left panel*); bronchoscopy, in this case, showed mucosal infiltration and friability and no evidence of airway patency distal to the obstruction (*right panel*)

electrocautery is used, and these currents are generated[9] around the metal wires [67]. This granulation tissue ingrowth can make removal difficult and result in substantial airway wall trauma [69]. It is likely that factors such as stent kinking or fracture also contribute to granulation tissue formation. Overall, however, granulation tissue formation is not easily predictable but seems to be more common in patients with keloids and in those with chronic airway infection [70]. Management of this problem is complicated by the difficulty of removing metal stents [70, 71]. Interestingly, in one study addressing malignant CAO, compared with Ultraflex stents, both silicone stents and Aero stents seem to be more likely to lead to granulation tissue formation [6]. In the multivariate model, however, only silicone stents (HR = 3.32) and lower respiratory tract infection (HR = 5.69) were associated with increased risk for granulation. It is likely that the observed differences in granulation tissue may be related to repetitive motion trauma and infection.

Stent Fracture

This is a rare complication seen with metal stent insertion, but it may result in airway wall perforation and hemoptysis, potentially fatal events [6, 23, 72]. United States Food and Drug Administration warned that metallic tracheal stents in patients with benign airway disorders should be used only after thoroughly exploring all other treatment options (such as surgical procedures or placement of silicone stents) [23]. The use of these stents as a bridging therapy to surgery is also not recommended, because the removal of these stents is associated with significant complications.

Stent-Associated Lower Respiratory Infection and Mucus Obstruction

When a definition of respiratory infection is based on the presence of clinical findings (fever, increased volume and purulence of sputum, and worsening cough), with or without radiographic evidence of pneumonia but requiring the managing physician to prescribe antibiotics, the incidence proportion of lower respiratory tract infections was 36–39% in patients suffering from cancer [6]. The authors of this study found that respiratory infections led to significant morbidity and mortality: over half the patients were hospitalized, and 23% of patients with respiratory infections died within 14 days of their infection. Respiratory infections were more frequent in patients with Aero stents compared with silicone or Ultraflex. Various degrees of obstruction by mucus are not uncommon. This tends to be more common in patients with ineffective cough and in smokers. In patients with malignant CAO, having a left-sided stent (HR = 3.07), age (HR = 0.97), having a silicone stent (HR = 2.72) versus Ultraflex stents, and having chemotherapy post-stent placement (HR = 0.32) had significant impact on time to mucus impaction. The higher risk with left-sided stents makes sense; because of the sharper angle[10] between the left main bronchus and trachea, the patient may have difficulty in raising secretions. In addition to obstructing the airway, in time this could also lead to halitosis because the stent becomes covered chronically with a biofilm (Fig. 12.7).

Migration

While an oversized stent could cause granulation tissue formation, an undersized stent would

[9] An electrical current in which the electron flow is in only one direction; galvanic currents cause fibroblast proliferation resulting in increase in collagen synthesis, property used for wound healing and also implicated in keloid formation.

[10] Especially in patients with tumors who might have a nearly horizontal left main bronchus due to large subcarinal adenopathy.

likely migrate. In one study, stent migration was 5.26%, 6.06%, and 15.38% in patients in whom the stent-to-airway diameter was between 90% and 100%, 80% and 90%, and <80%, respectively [62]. The migrated stent, in addition to not palliating the airway narrowing for which was initially placed, could result in inability to clear secretions and in continuous friction between the wall of the stent and the airway mucosa and cause granulation as well. Ideally a stent is well compressed once it is deployed, but even if it is sized appropriately and placed properly and sitting tightly at the end of the procedure, it can still migrate later because of the viscoelastic properties of the tracheal tissues (Fig. 12.7). This complication is seen more commonly in benign disease or in patients with cancer undergoing therapy, likely because patients with benign disease survive longer and because of the changes in airway viscoelastic properties (in time the airway stenosis progressively dilates). This probably explains why about 20% of patients with strictures may have their stent removed after ~18 months. For patients with ECAC, silicone stent insertion improves functional status immediately post-intervention but is associated with a high rate of adverse effects with quite frequent stent migration. In fact, in one study of malignant CAO, among various stents (Ultraflex, Aero, and silicone), only silicone tube stents had a significant effect on migration risk with an HR of 3.52 [6]. Stent migration requires a revision procedure to maintain satisfactory airway patency and prevent further complications.

Bronchoscopy is currently the standard for the detection and treatment of stent-related complications and, in nonurgent situations, usually involves a two-step procedure. Initially, diagnostic flexible bronchoscopy is performed to detect and characterize a stent complication; if a treatable complication is detected, rigid bronchoscopy may be required for therapeutic intervention. In this regard, from regulatory perspective, the stent insertion package should probably contain information about stent's biomechanics, sterilization (although this may not affect the infection rate) [6] in addition to reporting indications, expected results, incidence rates of long-term complications, as well as potential contraindications to stent insertion.

Contraindications

There are certain circumstances when stent insertion should not be offered. For instance, in idiopathic or secondary benign subglottic stenosis (within 2 cm from the vocal cords), stents may extend the length of the stenotic segment [73]. This is particularly true for metallic stents. In one study, all patients with laryngotracheal stenosis who had undergone covered or uncovered metallic stent placement developed new strictures or granulation tissue which precluded definitive surgical treatment or required more extensive resections [73]. In fact, some tracheal surgeons believe that SEMS should never be used in patients who are potential candidates for resection, because these are likely to cause additional airway injury and possibly make a potentially resectable patient unresectable[11] [73].

The absence of a functional "distal airway" such as in the case with significant and chronic (usually >1 month) distal parenchymal tumor infiltration or confirmed lack of perfusion of underlying lung is also a contraindication to stent insertion and, for the same reasons, for any intraluminal therapy aimed at restoring airway patency. In patients with CAO (lobar or mainstem bronchi), assessing the functionality of the lung parenchyma distal to the obstruction is useful when considering interventions meant to establish airway patency. Functionality of the lung distal to the obstruction may not be restored in patients who have had chronic complete obstruction and lack of ventilation (Fig. 12.7). Determining whether there is functional airway and lung beyond an obstruction is essential to any successful bronchoscopic intervention,[12] in part

[11] In this regard, histologically benign CAO should be treated surgically or ,for nonsurgical candidates, with silicone stents whenever possible.

[12] Other conditions include experienced bronchoscopist and team, experienced anesthesiologist, control of patient's overall performance status, additional systemic or local therapy still possible, and control of comorbidities.

because significant friability of bleeding from thin infiltrated bronchial mucosa or lack of lung perfusion[13] despite restored airway patency might preclude intervention. In one study, 71% of patients who initiated radiation therapy within 2 weeks after radiological evidence of atelectasis had complete re-expansion of their lungs, compared with only 23% of those irradiated after 2 weeks [74]. Studies pertaining to successful bronchoscopic treatment and time to treatment are lacking. In addition, significant mucosal friability and bleeding of bronchial mucosa might also preclude interventions, because stent insertion may result in bronchomediastinal fistula, loss of the stent within the mediastinum, or hemorrhage (Fig. 12.7).

Follow-up and Patient Education

Immediately after stent insertion, a chest radiograph is performed to confirm its location. Because stents are associated with significant problems, a stent alert card should be given to the patient; this provides information both for patients and for the doctors that may encounter patients with airway stents. They are informed that even though some stents are not radiopaque, one can still identify them on the chest radiographs as straight lines. In addition, the card includes the patient's name; indication for stent insertion; type, location, and size of stent inserted; contact information; and instructions for both patients and physicians in case of stent-related complications. Also, if intubation is necessary for whatever reason, bronchoscopic intubation using a cuffless # 6 ETT to avoid stent dislodgement or mucosal trauma is advisable.

Granulation tissue, secretions, migration, tumor progression, and fistula formation are usually detected during follow-up bronchoscopy or on chest CT. These complications, however, are usually detected by the onset of new respiratory symptoms and do not necessitate systematic (scheduled) routine flexible bronchoscopy. In those patients suspected of having stent-related adverse effects, however, bronchoscopy should be performed for diagnosis and potentially for therapy. While routine follow-up bronchoscopy in the lack of symptoms may not be warranted in all patients after stent insertion, given that most complications occur within 6 weeks post-stent insertion [6, 8, 9], one could choose to perform surveillance bronchoscopy in patients at high risk for complications after stent insertion. There are reports, however, suggesting that time to granulation tissue detection after SEMS insertion is longer in patients with dynamic airway obstruction than in those with structural airway obstruction (396 vs. 95 days $p=0.02$) [66], so a need for prolonged follow-up in these patients may be warranted. Some physicians perform routine bronchoscopy every couple of months, while others only do it when patients complain of new symptoms [75]. Preventive measures for obstruction by mucus such as aerosol therapy, respiratory physiotherapy, and clinical visits are advocated. Also, while not a universal practice, saline nebulization is offered by many bronchoscopists to keep the stent humidified in order to avoid excessive mucus plugging. In fact, severely disabled patients, such as those who are bedridden and with poor cough or impaired metal status, are unlikely to benefit from indwelling airway stents since the risk of obstruction by mucus may outweigh the benefit gained by placing the stent and only temporarily restore airway patency.

Summary and Recommendations

Airway stents improve symptoms of malignant and benign central airway obstruction, esophagorespiratory, and bronchial stump fistulas, but in general, their insertion should be reserved to patients for whom curative open surgical interventions are not feasible or contraindicated. Metallic stents should be avoided in benign disease unless surgery or silicone stent placement is not possible or feasible. For malignant disease, stents are placed with a palliative intent and, as any palliative intervention, should offer comfort

[13] One way to assess the perfusion status of lung parenchyma distal to an airway obstruction is to attempt bypassing the stenosis using a high-resolution EBUS radial probe.

without harming the frail and often terminally ill patient. They should therefore be placed by operators who are able to handle both intraoperative, short-term and long-term complications. Long-term complications after placing such prostheses are not uncommon and can occasionally be fatal. Not all stents are equivalent in terms of biomechanics and stent–tissue interactions. Currently, this information may be considered confidential and proprietary and is not mandated to be reported by regulatory bodies. However, manufacturers should probably describe some biomechanical properties including the resistance to angulation, expansile force, and mechanical failure to help physicians predict successful airway patency restoration and immediate and long-term stent-related complications.

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Part III

Lung Cancer Diagnosis

Early Lung Cancer: Methods for Detection

13

Kazuhiro Yasufuku

Abbreviations

AFB	Autofluorescence bronchoscopy
AFI	Autofluorescence imaging
ASD	Angiogenic squamous dysplasia
CIS	Carcinoma in situ
EBUS	Endobronchial ultrasound
HMB	High-magnification bronchovideoscope
NBI	Narrow band imaging
NADH	Nicotinamide adenine dinucleotide hydrogen
OCT	Optical coherence tomography
PDT	Photodynamic therapy
SCC	Squamous cell carcinoma
WLB	White light bronchoscopy

Introduction

Lung cancer is the leading cause of cancer mortality worldwide [1]. Despite evolving knowledge of lung cancer molecular genetics and improved lung cancer detection technology, the overall lung cancer survival is still quite poor (15% 5-year survival) [2]. A recent study showed a dramatic, 20% relative decrease in lung cancer mortality with low-dose CT chest screening in high-risk groups [3], proving the concept that early lung cancer detection, which allows prompt surgical intervention, offers survival benefit. However, screening CT thorax detects smaller, central, and peripheral lung lesions, but is insensitive for detection of microscopic tumors arising from the airways [4]. Microscopic tumors arising in the central airways require other techniques for early detection.

Squamous cell carcinomas, accounting for approximately 25–30% of all lung cancers, arise in central airways. Pathobiologically, progression from normal bronchial epithelium to squamous metaplasia followed by dysplasia, carcinoma in situ (CIS), and finally invasive carcinoma has been well described [5, 6]. Studies have shown that patients with moderate to severe dysplasia progress to develop invasive carcinoma over the course of 3–4 years. Approximately 11% of patients with moderate dysplasia and 19% to as high as 50% with severe dysplasia develop invasive carcinoma [7–9]. Therefore, prompt detection through screening of high-risk patients (heavy smokers especially) could potentially offer early diagnosis of early preinvasive or early invasive lesions and allow for prompt therapeutic intervention and improved survival. However, conventional airway imaging modality, white light bronchoscopy (WLB) has been shown to be relatively insensitive in inspection of bronchial mucosa with only 30% sensitivity to detect early-stage carcinoma in the central airways [10].

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New bronchoscopic modalities with higher spatial resolution are able to take advantage of intrinsic properties of healthy and abnormal tissues to change appearance when illuminated with different wavelengths of light and have been developed to serve the purpose of more advanced central airway imaging for the purpose of abnormal airway diagnosis. Currently available in clinical practice modalities include autofluorescence bronchoscopy (AFB), high-magnification bronchovideoscope (HMB), and narrow band imaging (NBI). More precise airway inspection can be obtained with radial probe endobronchial ultrasound (EBUS) and optical coherence tomography (OCT) [4]. Confocal fluorescence microendoscopy is another useful technique, allowing in vivo microscopic assessment of the airway basement membrane and alveolar components. Recently, endocytoscopy bronchoscopy system has allowed in vivo microscopic imaging of bronchial mucosa [11]. However, Confocal fluorescence microendoscopy and endocytoscopy system are currently mostly under experimental use.

In this chapter, the advanced bronchoscopic imaging techniques of the airway including AFB, NBI, HMB, and the radial probe EBUS will be reviewed, and their roles in the early diagnosis of lung cancer will be shown.

Autofluorescence Bronchoscopy

AFB improves sensitivity for detection of preinvasive lesions in central airways [10]. It is a technique of advanced mucosal airway examination taking advantage of the property of the normal, pre-, and neoplastic tissues to change appearance when illuminated with different wavelengths of light, depending on differential epithelial thickness, tissue blood flow, and fluorophore concentration. Preinvasive and neoplastic tissues express diminished red and subsequently green autofluorescence compared with normal tissues when illuminated with blue light (440–480 nm wavelength) [12]. Natural tissue chromophores (elastin, collagen, flavins, nicotinamide adenine dinucleotide, nicotinamide adenine dinucleotide hydrogen [NADH]) emit light when their electrons return to ground level after being excited with light of specific wavelength. The low level of tissue autofluorescence cannot be picked up with WLB given the "noise" from high-degree background reflected and backscattered light. However, AFB selectively picks up the subtle changes in natural tissue autofluorescence patterns. Tissue metaplasia, dysplasia, and neoplasia reduce natural concentration of airway chromophores (diminished expression of riboflavin, flavin, and NADH due to increased anaerobic metabolism and lactic acid production) [13]. Higher neoplastic tissue blood flow increases light absorption by the hemoglobin. Malignant tissue proliferation, even if only microscopic at first, results in higher degree of light scattering by tissue hyperplasia. These changes overall result in diminished tissue green autofluorescence with the abnormal tissue assuming a red-brown color [14]. These initially subtle mucosal changes are identifiable by WBL in only less than 30% of cases, even by experienced bronchoscopists. AFB is highly sensitive for detection of preneoplastic and neoplastic lesions; however, it lacks specificity for detection of preinvasive lesions. It often cannot differentiate between the areas of high blood flow and metabolism occurring in chronic inflammatory states like bronchitis.

Different AFB imaging systems have been developed all with slightly different sensitivity for detection of the mucosal abnormalities. Continuous improvement of AFB devices allows for increased specificity. In the SAFE-1000 system (Pentax, Asahi Optical, Tokyo, Japan), xenon lamp replaced used in the light-induced fluorescence endoscopy (LIFE) device laser light. SAFE-3000 system (Pentax, Asahi Optical, Tokyo, Japan) incorporated single-action image switching and simultaneous display. Storz D-light (Storz, Tuttlingen, Germany) and Onco-LIFE systems (Xillix Technologies, Vancouver, Canada) combine autofluorescence and reflected light, all resulting in slightly different sensitivities as compared to WLB for premalignant and malignant mucosal abnormalities detection. Autofluorescence imaging (AFI) (Olympus Medical System Corp, Tokyo, Japan) is a new AFB system. AFI demonstrated improved over

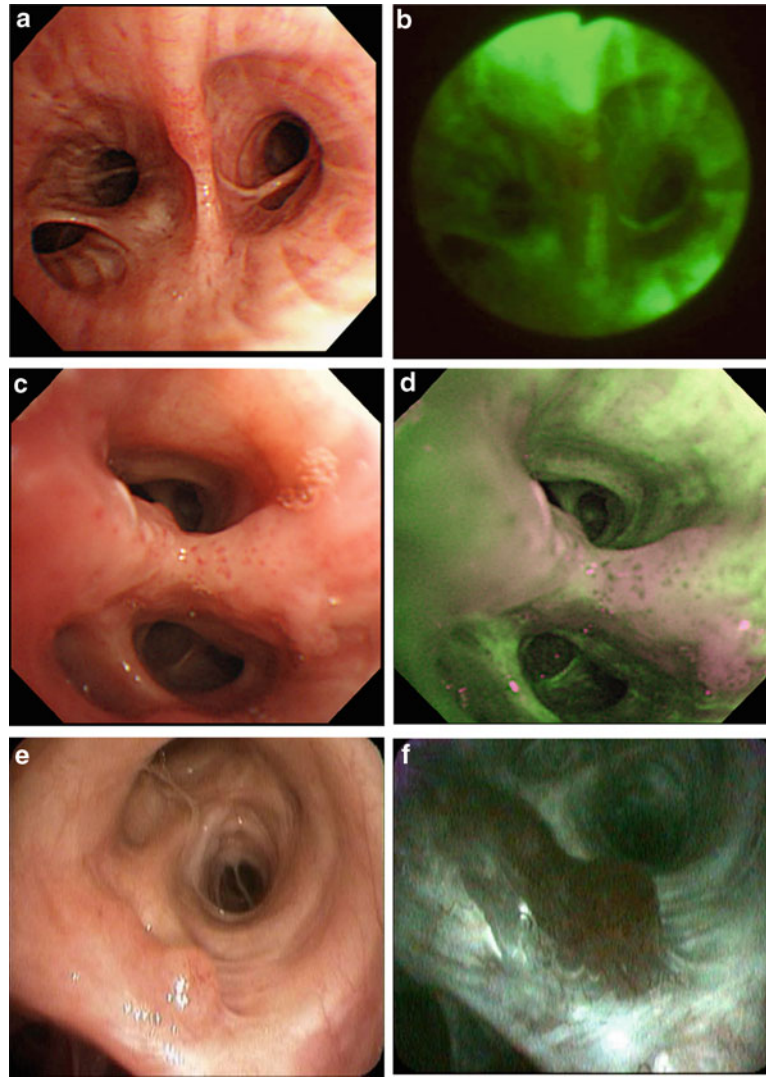


Fig. 13.1 Autofluorescence bronchoscopy images. Representative cases of carcinoma in situ: White light bronchoscopy (**a**, **c**, **e**) and corresponding autofluorescence bronchoscopy images, (**b**) Onco-LIFE systems (Xillix Technologies, Vancouver, Canada), (**d**) AFI (Olympus Medical Systems Corp., Tokyo, Japan), (**f**) SAFE 300 (Pentax, Asahi Optical, Tokyo, Japan)

the LIFE AFB system specificity (83% vs. 36.6%) but slightly lower sensitivity (80% vs. 96.7%) in detection of premalignant and malignant bronchial lesions [15]. Improved discriminatory nature of AFI system results from its ability to integrate three signals: autofluorescence signal with reflected green and red light signals [16]. Composite image displayed depicts normal epithelium as light green; areas of abundant blood flow seen not only in malignant epithelium but also in areas of chronic benign inflammation as dark green and magenta color for malignant tissue [15] (Fig. 13.1).

Multiple studies demonstrated that AFB improves detection of preinvasive central airway lesions and when combined with WLB also of squamous dysplasia, CIS, and early lung carcinoma [10–27]. Recent meta-analysis of 21 studies comparing WLB used with AFB versus WLB alone in diagnosis of intraepithelial neoplasia and

invasive lung cancer, involving 3,266 patients, reported a pooled relative sensitivity of 2.04 (95% CI 1.72–2.42) on a per-lesion basis in favor of combined AFB and WLB approach [16]. However, as documented in pervious individual studies, the sensitivity for detection of CIS and early invasive carcinomas was not superior to WLB alone (the RR of 1.15 at 95% CI 1.05–1.26) [16]. This suggests that while screening for invasive cancer, WLB may be sufficient and more cost-effective.

Use of Raman spectrophotometry system in addition to AFB and WLB may offer improved specificity (91%) in detection of preinvasive lesions, with only minor compromise in sensitivity (96%) as documented by a recent pilot study [28]. Laser Raman spectroscopy (LRS), currently used only in experimental setting, involves exposing the tissue to low-power laser light and collecting the scattered light for spectroscopic analyses [29]. This technology collects spectra nondestructively, and light scattered from tissues with different molecular composition can be easily differentiated. Using this technology can potentially reduce the number of false-positive biopsies for detection of preneoplastic lesions. Use of Raman spectra with AFB and WLB can offer a more objective airway mucosal assessment and detect more preneoplastic lesions. Also, Raman may be able to identify biomolecular changes in histologically preneoplastic and non-preneoplastic lesions that could be markers for development into late-stage malignancy. More studies are needed to assess addition of this technology to armamentarium of tools for endobronchial neoplasia detection.

AFB has also been shown to increase detection sensitivity of recurrent or new intraepithelial neoplasias and invasive carcinomas when added to WLB (from 25% for WLB alone to 75% when AFB is used in conjunction with WLB) in postoperative surveillance of patients who underwent curative resection for NSCLC [30]. AFB combined with CT of the thorax in patients with radiographically suspicious and occult lung cancer has shown to be an effective lung cancer staging and tumor extension assessment modality with impact on therapeutic strategy choice [31, 32].

AFB can become a useful tool in endobronchial premalignant and malignant lesion detection screening, especially in high-risk groups (patients with head and neck cancers, chronic obstructive pulmonary disease [COPD], and smokers), knowing that the incidence of synchronous lesions ranges from 0.7% to 15% and metachronous lesions might occur in as many as 5% high-risk patients annually [33, 34]. However, more studies are needed to determine how the AFB can best be incorporated into clinical practice in an economically efficient way and with reasonable reduction in lung cancer mortality.

Narrow Band Imaging

Narrow band imaging (NBI) is a new optical image technology classified as an image enhancement endoscopy using special blue and green light wavelengths allowing for enhanced visualization of microvascular structures in the mucosal and submucosal layers [35–38]. NBI utilizes wavelengths at 415 nm (blue light) and 540 nm (green light). Narrow bandwidths reduce the mucosal light scattering and enable enhanced visualization of endobronchial microvasculature structure. The 415 nm blue light is absorbed by the superficial capillary vessels whereas the 540 nm wavelength is absorbed by the hemoglobin in the deeper, submucosal vessels. Fine blood vessels appear brown and the deeper vessels cyan (Fig. 13.2).

Beside molecular changes allowing autonomous progression of cell cycle that imparts metastatic potential, cancer cells must also develop extended angiogenic capabilities allowing for rapid growth and invasion. Multistep angiogenesis process has been described in epithelial tumors [39, 40]. To fulfill high metabolic demands of rapidly dividing tumor, neoplastic cells have to develop enhanced angiogenic capabilities. Animal and human invasive neoplasia pathogenesis studies suggest that so-called angiogenic switch is thought to occur in preinvasive lesions prior to invasive tumor formation [41, 42]. Since squamous cell cancer is thought to progress through developmental staged from squamous cell metaplasia to dysplasia and CIS, detection of each of these stages could have a significant impact on therapeutic interventions and prognosis.

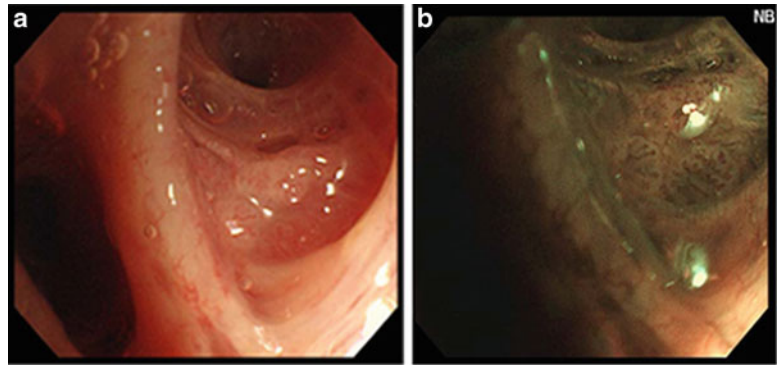


Fig. 13.2 Narrow band imaging. White light bronchoscopy (**a**) and narrow band imaging (**b**) of carcinoma in situ: Dotted vessel and tortuous vessels are identified on NBI

NBI shows higher sensitivity compared to AFB in detection of metaplastic and moderately dysplastic bronchial mucosal squamous lesions. It has equivalent sensitivity as AFB in detection of early preinvasive malignant lesions (CIS) and invasive cancer (ranging between 90–100% for NBI and 83–89.2% for AFB). However, NBI has a higher than AFB specificity for detection of early lung cancer [43].

Combining AFB and NBI increases both the sensitivity (93.7%) and specificity (86.9%) of early lung cancer detection. But the improvement is small as compared to each technique alone. Therefore combining the two technologies in cancerous and precancerous lesion detection does not have significant impact on diagnostic accuracy and may result in unnecessary cost without significant clinical benefit. Judging by the results of the studies, NBI can be used alternatively to AFB in cancerous and precancerous lesion screening of the endobronchial epithelium without compromising sensitivity and with significantly improvement in specificity [44].

Before NBI and AFB can be incorporated into lung cancer screening, few issues need to be addressed. First, natural history of the squamous cell carcinoma (SCC) and bronchial dysplasia must be better characterized. SCC represents a third of all lung cancers diagnosed in the US [1]. It is thought that pathologically, invasive cancer results from a stepwise process that begins with metaplasia then dysplasia followed by CIS and finally invasive cancer. Previous studies showed development of invasive carcinoma in 40–83% of patients with severely dysplastic lesions [7, 45]. However, animal models and human studies show spontaneous regression of some of the lesions [46, 47]. Breuer et al. documented a 9–32% rate of malignant transformation for all dysplastic lesions in 52 patients followed over an 8-year period. Fifty-four percent spontaneous regression of all preinvasive lesions as well as non-stepwise transformation, with development of invasive carcinoma at sites previously characterized as normal in appearance, has also been described. These findings suggest that development of SCC may not always follow classic stepwise transformation pattern [47]. Also, population of patients at risk must be clearly identified and those with highest risk lesions (most likely to progress to invasive cancer) should be screened. Finally, appropriate therapeutic options and follow-up surveillance schedule must be developed based on evidence in order to decrease overall cancer mortality and recurrence [48]. Until all these issues have been addressed, the use of AFB and NBI will be predominantly in research setting.

High-Magnification Bronchovideoscope

HMB is a system that was developed to enhance detailed white light observation of bronchial dysplasia. Increased thickening of the bronchial epithelium and increased vessel growth are thought

to be related to the appearance of areas of abnormal fluorescence, suggesting roles for neovascularization or increased mucosal microvascular growth in bronchial dysplasia. However, the only abnormality seen on WLB in dysplasia is swelling and redness at the bronchial bifurcations. HMB is a direct viewing WLB system that has an outer diameter of 6 mm and can easily be inserted into the tracheobronchial tree. HMB combines two systems—a video observation system for high-magnification observation and a fiber observation system for orientation of the bronchoscope tip. For the video observation system, an objective optical system, in fixed focus mode rather than zoom mode, was used to give an outer diameter of about 6 mm to allow for the bronchoscope and the observation depth of 1–3 mm. Magnification is about fourfold higher than that of the regular bronchovideoscope. The bronchial mucosa is observed minutely on a 14 in. TV monitor at a high magnification of 110 times at the nearest point [49].

HMB has enabled observation of vascular networks within the bronchial mucosa in patients with respiratory disease such as asthma, chronic bronchitis, sarcoidosis, and lung cancer. Areas of increased vessel growth and complex networks of tortuous vessels in the bronchial mucosa that are detected using HMB at sites of abnormal fluorescence may allow clinicians to differentiate between bronchitis and dysplasia. In areas of abnormal fluorescence on AFB, HMB can detect dysplasia more accurately than AFB alone with a sensitivity of 70% and specificity of 90% [49]. HMB observation in patients with asthma showed that the vessel area density and vessel length density are significantly increased compared to control subjects [50].

Using NBI and HMB, previous studies have shown angiogenesis and microvascular structure alteration of bronchial dysplastic lesions at sites detected as abnormal autofluorescence [51]. Using NBI combined with high-magnification bronchovideoscopy, Shibuya et al. showed statistically significant increase in capillary blood vessel diameter occurring as tissue progresses from angiogenic squamous dysplasia (ASD) to CIS, microinvasive cancer, and invasive squamous cell carcinoma [40]. Architectural organization of the vessels also differed between the premalignant and malignant lesions. Classification system was proposed based on vascular appearance of endobronchial lesions of varying invasiveness. It showed high correlation with lesions' histopathologic features [40, 52]. However, more studies using the classification are needed to further validate it (Fig. 13.3).

Endobronchial Ultrasound

Two types of endobronchial ultrasound (EBUS) are currently available for clinical use. The radial probe EBUS first described in 1992 is used for the evaluation of bronchial wall structure, visualization of detailed images of the surrounding structures for assisting TBNA as well as detection of peripheral intrapulmonary nodules [53]. On the other hand, the convex-probe EBUS first described in 2004, has a built in ultrasound probe on a flexible bronchoscope which enables bronchoscopists to perform real-time TBNA of mediastinal and hilar lesions [53].

Premalignant lesions or small intrabronchial radiologically invisible tumors are being detected more frequently as a result of new advanced mucosal imaging technologies. The decision to use endoscopic therapeutic intervention depends on the extent of tumor within the different layers of the bronchial wall. Conventional radiological imaging alone is not capable of distinguishing the tumor extent. The radial probe EBUS is a sensitive method for detection of alterations of the multilayer structure of the bronchial wall even in small tumors. A comparison between the ultrasound and the histologic findings in 24 lung cancer cases revealed that the depth diagnosis was the same in 23 lesions (95.8%) [54]. In another study in a series of 15 patients, EBUS showed a high diagnostic yield of 93% for predicting tumor invasion into the tracheobronchial wall [55]. EBUS also improves the specificity (from 50 to 90%) for predicting malignancy in small AFB-positive lesions that were negative on white light bronchoscopy [56].

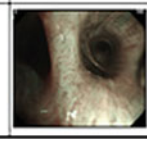
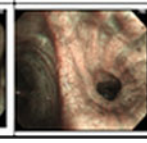
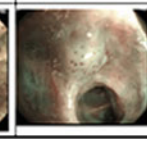
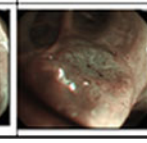
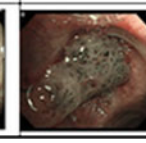
	Squamous dysplasia	ASD	CIS	Micro invasive	Invasive
Tortuous vessel networks	+	+	—	—	—
Dotted vessels	—	+	+	+ +	+ + +
Spiral and screw type vessels	—	—	+	+ +	+ + +
					

Fig. 13.3 Classification of narrow band imaging. Classification of vessel morphology based on narrow band imaging during lung cancer pathogenesis. *ASD* Angiogenic squamous dysplasia, *CIS* Carcinoma in situ

Photodynamic therapy (PDT) is an alternative treatment for selected patients with central type early-stage lung cancer. EBUS was performed to evaluate tumor extent in 18 biopsy-proven early-stage squamous cell carcinomas (including three CIS) [57]. Nine lesions were diagnosed as intracartilaginous by EBUS and PDT was subsequently performed. The other nine patients had extracartilaginous tumors unsuspected by computed tomographic scanning and were considered candidates for other therapies such as surgical resection, chemotherapy, and radiotherapy. Using EBUS, 100% complete remission rate was achieved in the endoluminal-treated group.

Summary

Recent advances in the field of bronchology have allowed bronchoscopists to evaluate the airway with advanced high-resolution imaging modalities discussed in this chapter. Centrally arising squamous cell carcinoma of the airway, especially in heavy smokers, is thought to develop through multiple stages from squamous metaplasia to dysplasia, followed by carcinoma in situ, progressing to invasive cancer. Early detection is key for improved survival. It would be ideal if we can detect and treat preinvasive bronchial lesions defined as dysplasia and carcinoma in situ before progressing to invasive cancer. Bronchoscopic imaging techniques capable of detecting preinvasive lesions currently available in clinical practice including AFB, NBI, HMB, and EBUS were discussed in this chapter.

AFB increases the diagnostic accuracy for squamous dysplasia, carcinoma in situ, and early lung carcinoma when used simultaneously with conventional white light bronchoscopy. However, the specificity of AFB for detecting preinvasive lesions is moderate. AFB displays areas of epithelial thickness and hypervascularity as abnormal fluorescence which suggests a role for neovascularization or increased mucosal microvascular growth in bronchial dysplasia. HMB enables visualization of these vascular networks. HMB can detect increased vessel growth and complex networks of tortuous vessels of various sizes in the bronchial mucosa. To further evaluate the vascular network in the bronchial mucosa, a new imaging technology NBI was developed and is now commercially available.

AFB and NBI are complimentary for the evaluation of preinvasive bronchial lesions. The strength of AFB is its high sensitivity acting as a monitor to pick up potentially neoplastic lesions. However the potential limitation is its moderate specificity. NBI on the other hand enhances the mucosal and vascular patterns which is best suited for detailed inspection of the mucosa. A combination of autofluorescence and NBI into a single bronchovideoscope system would

decrease the time for the procedure as well as unnecessary biopsies. For a bronchoscopist, AFB, NBI, and HMB are just the same as performing a routine WLB without any complicated procedures necessary. Interpretation of the results seems to be fairly straight forward. The radial probe EBUS is an excellent tool for the evaluation of the airway structure which is useful for the determination of the depth of tumor invasion. Minimally invasive treatment may be suitable for selected patients with central type early-stage lung cancer.

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Diagnostic of Lung Cancer: Confocal Bronchoscopy

14

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Introduction

The principle of confocal microscopy, first described in 1957, relies on both the use of a narrow point illumination light source, which focuses on a single spot in the sample, and of a small aperture or pinhole on the detection path, which focuses the light emitted back by the sample onto the detector. This results in the rejection of out-of-focus information from the material above and below a very thin plane of focus. The illumination and detection systems being conjugated on the same focal plane are termed "confocal." As only one point in the sample is illuminated at a time, confocal microscopes make use of systems that scan the sample in both lateral dimensions to produce a two-dimensional image—or "slice"—of a few microns depth, parallel to the sample surface. This principle allows confocal microscopes to provide "optical" sectioning of cells and tissue with micrometric lateral and axial resolutions, without tissue destruction. Confocal microscopes have recently been so successfully miniaturized [1, 2] that they can be integrated into endoscopic systems and used for both animal [3–5] and human in vivo explorations [6–8]. This is achieved by using a small optical device held in direct contact with the area to be imaged. Such systems have recently been applied to the in vivo microscopic imaging of both the proximal [7] and distal respiratory systems [8]. With these recent developments, fiber-optic endoscopy of the respiratory tract has now entered the era of in vivo microscopic imaging.

In general, the aim of confocal endomicroscopes is to produce "optical biopsies," i.e., in vivo microscopic imaging, of a living tissue during endoscopy [9, 10]. Ideally, this direct microscopic imaging could replace tissue sampling or at least allow a very precise targeting of the biopsy area. However, because of optical limitations due to refraction indexes and specular reflexion of the light at the surface of the tissue, *reflectance* (or "white light") confocal endomicroscopes are not currently available. Instead, manufacturers have designed fluorescence confocal devices, where the excitation light can easily be filtered out before the light reaches the detector, to only image the fluorescence emitted from the tissue. Obviously, the main limitations of these systems come from the fact that they exclusively record the signal coming from fluorescent structures in response to appropriate excitation wavelengths. Therefore, besides the unusual "en face view," recorded images may

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appear for the endoscopist quite different from its classical histopathology counterparts or require specific cellular fluorophores. On the other hand, in future applications, fluorescence confocal systems may take advantage of molecular-targeted imaging using smart fluorescent probes.

Confocal Endomicroscopes for Human Exploration

The first confocal endomicroscopic systems for human exploration were available in 2005. Two systems have been commercialized that can be distinguished by the technical approach used to conduct the light to the tissue.

The distal scanning principle is used in the Optisan®/Pentax endomicroscopic system. This system is also called a confocal laser endomicroscope—CLE. In distal scanning, the light is conducted by a single fiber back and forth from the distal tip of the system, and the scanning function is accomplished by a very small scanhead (4.5 cm long × 3.5 mm diameter) which is included in the distal end of the endoscope. Tissue fluorescence is induced by a 488 nm laser wavelength. The sensitivity of the system needs the use of IV Fluoresceine as an external fluorophore. The system has an impressive lateral resolution below 1 μm and produces optical slices of 7 μm for a field of view of 475 × 475 μm. The system offers the possibility to adjust the Z-depth range from 0 to 250 μm below the contact surface, so that three-dimensional structures in the specimen and successive layers of the mucosae can be imaged. However, because of the added sizes of the distal scanhead, working channel, conventional light guide, and CCD camera, the diameter of the distal tip of the endoscope is larger than 12 mm, a size barely compatible with the exploration of the human trachea and large main bronchi, which explains why only a confocal GI endoscope had been launched over the past years. Another limitation is due to the miniaturization of the distal scanhead that results in scanning rates of 1 frame/s, which needs a very efficient stabilization system of the distal tip of the endoscope onto the mucosae, in order to produce crisp microscopic images of the epithelium. In spite of these limitations, Optiscan® endomicroscopic images from the gastrointestinal tract appear very close to conventional histology.

This prototype system is able to provide "en face" imaging of the bronchial epithelium with a lateral resolution of less than one micrometer.

Recently, endomicroscopic images of the proximal bronchial tree of both normal and tumoral epithelium have been obtained by Musani et al. from 5 patients, using a miniaturized prototype of the Optiscan system [11]. The confocal device was composed of a 6.2 mm flexible bronchoscope, devoid of working channel and distal optics, in which the distal end has been replaced by a 4.4 cm scanning device. This prototype was introduced within a 12.5 mm rigid bronchoscope in parallel to the rigid optics. Fluoresceine IV infusion was administered before the procedure. Because of the rigidity of the prototype distal tip, the confocal exploration was limited to the primary and secondary carina of the main bronchus and to an endobronchial mass in one patient. En face images of the respiratory epithelium produced by the system were impressive, with a lateral resolution of less than 1 μm, that allowed clear imaging of the intercellular margins between the normal epithelial cells, as well as imaging of the basement membrane/subepithelial areas due to folds of the epithelium (Fig. 14.1). Motion artifacts were observed in 60% of the frames, which allowed interpretation of the images in all patients.

The second commercially available confocal endomicroscopy system (Cellvizio®, Mauna Kea Technologies, Paris, France) uses the principle of *proximal scanning* in which the illumination light scans the proximal part of a coherent fiber bundle or miniprobe. This bundle conducts the light back and forth from the imaged area at the tip of the miniprobe [12]. The light delivery, scanning, spectral filtering, and imaging systems are located at the proximal part of the device, the distal part being a separate miniprobe, including both the fiber bundle and its connector to the laser scanning unit (Fig. 14.2).

This fiber bundle-based system, also described as "fibered confocal fluorescent microscopy (FCFM)" or more recently "probe-based confocal laser endomicroscopy" or "pCLE," uses very thin and flexible miniprobes (300 μm to 2 mm in

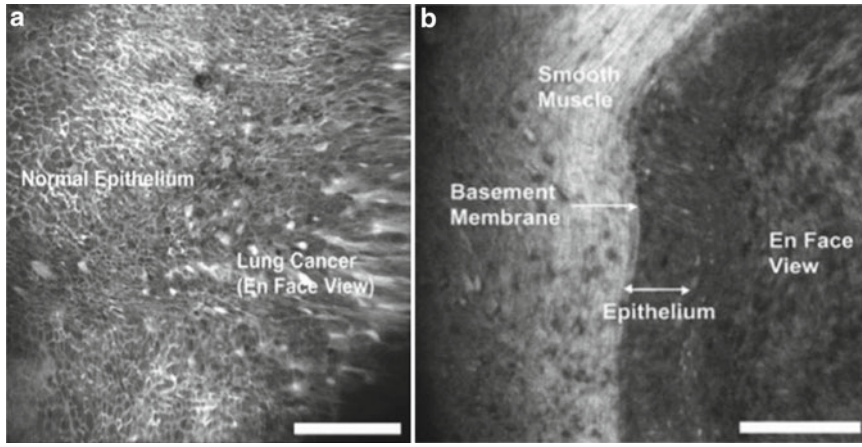

Fig. 14.1 Fluorescein/488 nm in vivo CLE imaging of the proximal bronchus, Pentax prototype. Modified from Musani et al. *J Bronchol Intervent Pulmonol,* 2010

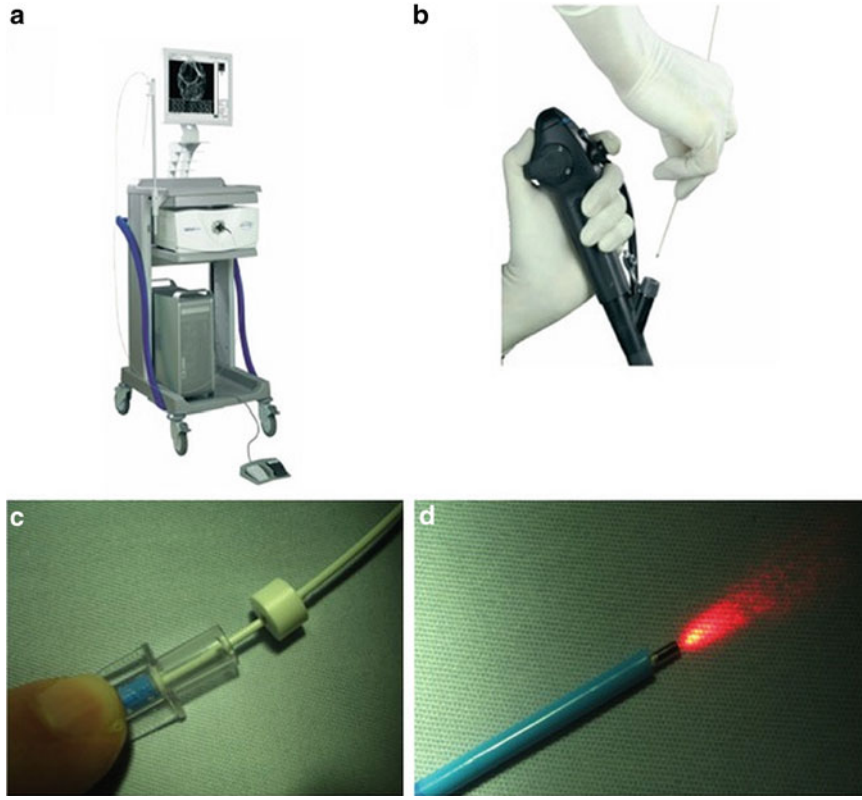

Fig. 14.2 pCLE/Cellvizio system and Alveoflex® miniprobe. (**a**) Cellvizio® and laser scanning unit. (**b**) Alveoflex® entering the bronchoscope working channel. (**c**) Alveoflex® inside the EBUS extended working channel. (**d**) Alveoflex® inside the superdimension extended working channel

diameter) that can contain up to 30,000 compacted microfibers. Similar to bench confocal microscopes, pCLE uses two rapidly moving mirrors to scan the microfibers across the coherent fiber bundle in a raster fashion. Each microfiber, which is scanned one at a time by the laser light, acts as a light delivery and collection system and is, in essence, its own pinhole. The main

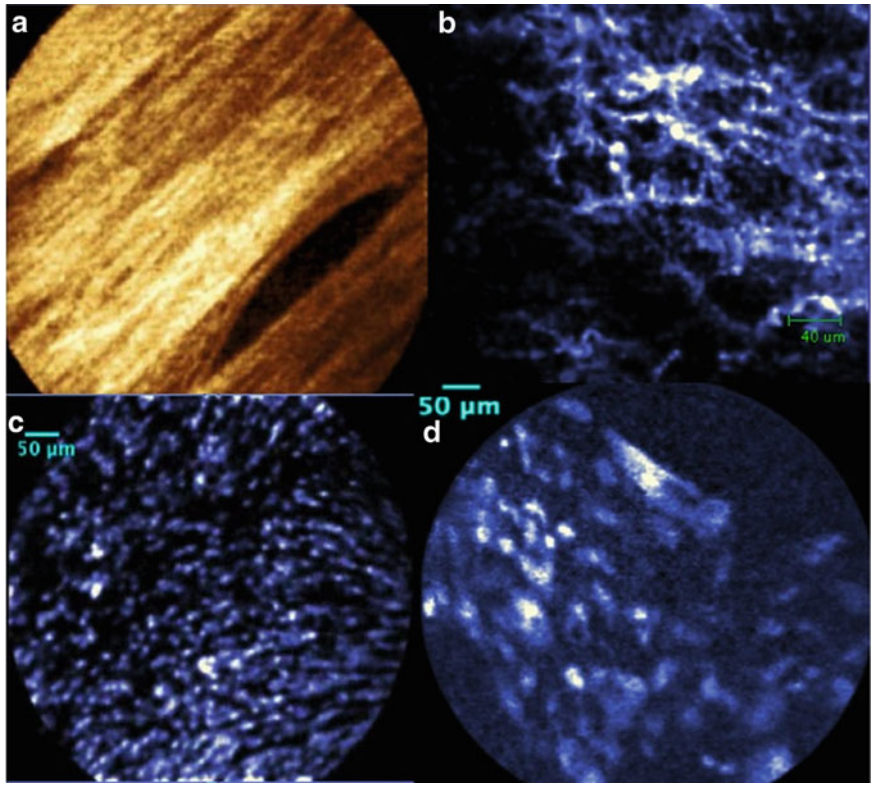

Fig. 14.3 Bronchial confocal microendoscopy imaging. (**a**) Normal elastic-fibered network of the basement membrane zone. (**b**) Disorganized basement membrane zone elastic network at the vicinity of a bronchial CIS. (**c**) Regular normal bronchial epithelium 660 nm excitation FCFM after topical application of methylene blue (0.1%). (**d**) CIS imaging, FCFM at 660 nm and topical methylene blue. Modified from Musani et al. *J Bronchol Intervent Pulmonol,* 2010 [11], with permission of the author

advantages of this design are the very small size and the flexibility of the probe that can reach the more distal part of the lungs [8], as well as the fast image collection speed that helps to avoid artifacts due to tissue movement. The system produces endomicroscopic imaging in real time at 9–12 frames/s.

Specific miniprobes for bronchial and alveolar imaging (Alveoflex®) have a diameter of 1 mm or less that can enter the working channel of any adult bronchoscope. These probes are designed for only 20 uses, at an approximate cost of 5,000 euros/miniprobe. Alveoflex® miniprobes are devoid of distal optics and have a depth of focus of 0–50 µm, a lateral resolution of 3 µm for a field of view of 600×600 µm. Thinner and more flexible probes are available for other applications as for the bile duct exploration (Cholangioflex®) or even probes that can fit into a 19 gauge needle (AQ-Flex®) for endoscopic ultrasound (EUS) lymph node/cysts explorations. Those probes may prove useful in the future for specific intrathoracic applications.

Two pCLE devices using different excitation wavelengths are currently available. The Cellvizio 488 nm is used for autofluorescence imaging of the respiratory tract as well as for fluorescein-induced imaging of the GI tract [7, 8, 13]. Another device at 660 nm excitation can be used for epithelial cell imaging after topical application of exogenous fluorophores such as methylene blue [14–16]. Whereas these two systems are currently sold as separate devices, a dual-band system is currently available for small animal imaging that avoids to disconnect the miniprobe from the LSU in case a dual imaging (488 nm/660 nm with methylene blue) would be indicated.

pCLE Imaging of the Proximal Bronchi

pCLE can easily be performed during a fiberoptic bronchoscopy under local anesthesia [7, 8]. The technique of in vivo bronchial pCLE imaging is simple: the miniprobe is introduced into the 2 mm working channel of the bronchoscope and the probe tip applied onto the bronchial mucosae under sight control. The depth of focus being 50 μm below the contact surface, the system can image the first layers of the bronchial subepithelial connective tissue, presumably the lamina densa and the lamina reticularis [7].

At 488 nm excitation, pCLE produces very precise microscopic fluorescent images of the bronchial basement membrane zone (Fig. 14.3). pCLE bronchial microimaging reveals a mat of large fibers mainly oriented along the longitudinal axis of the airways with cross-linked smaller fibers, as well as larger openings—100 to 200 μm—corresponding to the bronchial glands origins. In vivo, the technique also makes it possible to record high resolution images of small membranous airways, which are recognizable by the presence of the helicoidal imprint of the smooth muscle on the inner part of the bronchiole [7].

Fluorescence properties of the bronchial mucosae at 488 nm excitation are determined by the concentration of various cellular and extracellular fluorophores, including the intracellular flavins, that could originate from the epithelial cells, and specific cross-links of collagens and elastin present in the subepithelial areas [2, 17, 18]. Microspectrometer experiments coupled with pCLE imaging have clearly demonstrated that the main fluorescence signal emitted after 488 nm excitation from both bronchial and alveolar human system originates from the elastin component of the tissue [7, 8, 19]. Indeed, flavin cellular autofluorescence appears too weak to allow imaging of the epithelial layer using 488 nm pCLE without exogenous fluorophore [20]. Similarly, the collagen fluorescence does not significantly affect the pCLE image produced at 488 nm, the fluorescence yield of collagen at this wavelength being at least one order of magnitude smaller than that of elastin.

As a result, 488 nm excitation pCLE specifically images the elastin respiratory network that is contained in the basement membrane of the proximal airways and participates to the axial backbone of the peripheral interstitial respiratory system. In the future, it is possible that a modified pCLE device using several wavelengths [21] or devices based on a multiphoton approach [22–24] may enable imaging of collagen, elastin, and flavins simultaneously.

Distal Lung pCLE Imaging In Vivo: From the Distal Bronchioles Down to the Lung Acini

In the acinus, elastin is present in the axial backbone of the alveolar ducts and alveolar entrances, as well as in the external sheath of the extra-alveolar microvessels [25, 26]. pCLE acinar imaging is easily obtained by pushing forward the probe a few centimeters after the endoscope is distally blocked into a subsegmental bronchi. When progressing towards the more distal parts of the lungs, the entry into the alveolar space is obtained by penetration through the bronchiolar wall. Alveolar fluorescence imaging in active smokers dramatically differs from imaging in nonsmokers. The alveolar areas of smokers are usually filled with highly fluorescent cells corresponding to alveolar fluorescent macrophages [8]. In situ alveolar microspectrometric measurements have been performed in active smokers, which evidenced that the main fluorophore contributing to the pCLE alveolar signal corresponds to the tobacco tar by itself, explaining this difference [8, 19].

Potential Clinical Applications for Lung Cancer Detection in the Proximal Tree Using pCLE

Preliminary studies have shown that per endoscopic pCLE could be used to study specific basement membrane remodeling alterations in benign or malignant/premalignant bronchial alterations [7, 27].

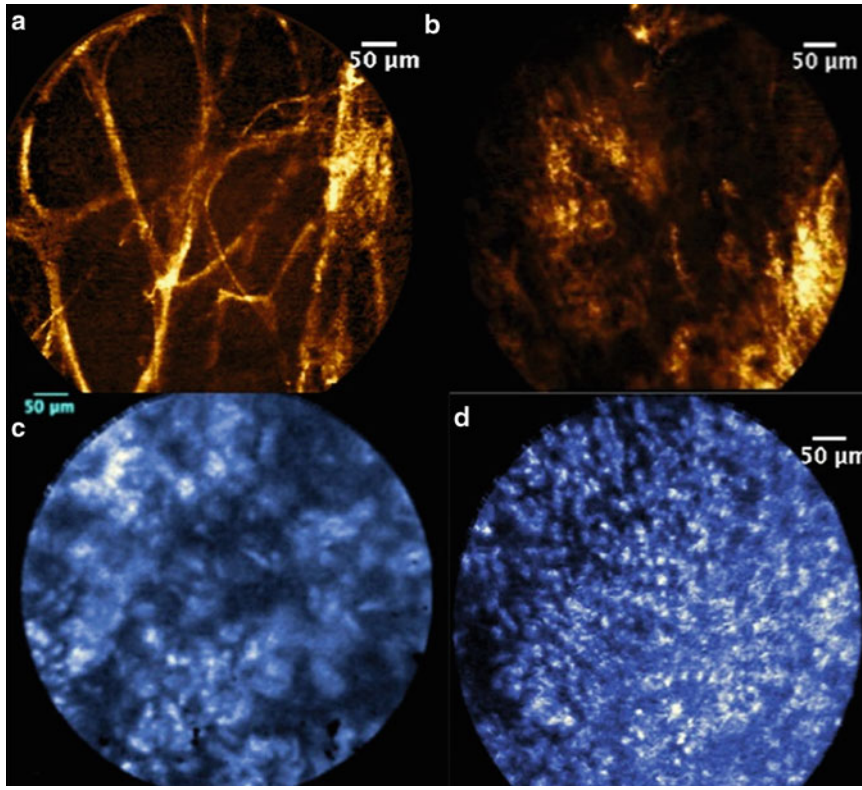

Fig. 14.4 pCLE imaging of normal distal lung and peripheral lung nodule. (**a**) pCLE imaging of normal distal lung. (**b**) Interstitial fiber network disorganization in a peripheral lung adenocarcinoma (488 nm excitation wave length). (**c**) pCLE cellular imaging of a peripheral lung adenocarcinoma (660 nm excitation and topical methylene blue). (**d**) pCLE cellular imaging of a peripheral small-cell lung cancer (660 nm excitation and topical methylene blue)

In the first human study using pCLE in the respiratory tract in vivo, the structure of the bronchial wall was analyzed in 29 patients at high risk for lung cancer that also underwent an autofluorescence bronchoscopy [7]. In this study, the fibered network of the basement membrane zone underlying premalignant epithelia was found significantly altered. This was observed in one invasive cancer, three CIS, two mild and one moderate dysplastic, and three metaplastic lesions. In these precancerous conditions, the elastic fibered pattern of the lamina reticularis was found absent or disorganized (Fig. 14.3). This supported the hypothesis of an early degradation of the basement membrane components in preinvasive bronchial lesions. However, while this observation shed some light on the origin of the autofluorescence defect in precancerous bronchial lesions, the absence of epithelial cell visualization did not allow the technique to differentiate between the different grades of progression of the precancerous bronchial lesions such as metaplasia/dysplasia/carcinoma in situ.

In order to be successfully applied to the exploration of precancerous/cancerous bronchial epithelial layer, the pCLE technique would need to be coupled with the use of an exogenous nontoxic fluorophore. Ex vivo studies have shown that the resolution of the system is not a limitation for nuclear or cellular imaging [7, 8].

A few exogenous fluorophores could be activated at 488 nm.

Acriflavine hydrochloride is an acridine-derived dye containing both proflavine and

euflavine, which binds to DNA by intercalating between base pairs. Acriflavine produces a strong nuclear fluorescence with 488 nm pCLE when topically applicated on the top of the bronchial epithelium ex vivo [7]. Acriflavine has been used in a couple of in vivo study using CLE in the GI tract [28], without demonstrated side effect. Recently, Fuchs et al. [29] have used pCLE imaging of the proximal bronchial tree along with topical Acriflavine. This study demonstrated that the technique is able to differentiate normal from malignant bronchial epithelium. However, comet assay of cells exposed in vitro to acriflavine solution shows significant DNA damage after 2 nm illumination with 488 nm Cellvizio (personal data). This observation needs further studies before acriflavine use for bronchial explorations, especially in patients at risk for cancer. Acriflavine is not currently approved for bronchial use.

Fluorescein has been used in Musani study with some success [11]. However, fluorescein, which does not enter the cells and therefore does not stain the nuclei [30], does not provide cellular imaging using pCLE. This is probably linked to the lower lateral resolution of pCLE compared to CLE and the impossibility to distinguish intercellular space with pCLE. Recently, Lane et al. have used a confocal microendoscope prototype at 488 nm excitation and topical physiological PH cresyl violet to provide cellular contrast in the bronchial epithelium both in vitro and in vivo [31].

Methylene blue is a nontoxic agent which is commonly used during bronchoscopy for the diagnostic of broncho-pleural fistulae. MB is also used in gastroenterology for chromo-endoscopic detection of precancerous lesions [32–34], as well as for in vivo microscopic examination of the GI tract and bronchus using a novel endocytoscopic system [35, 36]. MB is a potent fluorophore which enters the nuclei and reversibly binds to the DNA, before being reabsorbed by the lymphatics. In order to give a fluorescent signal, MB needs to be excited around 660 nm and is therefore accessible to FCFM intravital imaging using this excitation wavelength. In our hands, no DNA damage could be observed using comet assay from lymphocytes exposed to methylene blue in vitro and 660 nm Cellvizio for 2 min.

Human preliminary study has demonstrated that Cellvizio 660/topical methylene blue makes it possible to reproducibly image the normal and tumoral epithelial layer of the main bronchi [16, 37]. Unpublished data from our center also show that the technique easily differentiates small-cell lung cancer from non-small-cell lung cancer in vivo and normal epithelium from CIS (Fig. 14.3). Future studies using this technique have to show whether the technique allows to differentiate normal, premalignant, and malignant alterations at the microscopic level. If this strategy is successful, FCFM may become a very powerful technique for in vivo diagnostic of early malignant and premalignant conditions of the bronchial tree, allowing the analysis of both the epithelial and subepithelial layers during the same procedure.

pCLE for the Exploration of Peripheral Lung Nodules

Potential applications for in vivo distal lung imaging using pCLE appear wide. Some limitations of the technique could be predicted from its basic principles, such as artifacts linked to fragile parenchymal lung structures compression, as well as difficulties of interpretation of an imaging technique mainly based on elastin network assessment. However, preliminary results are encouraging in specific diffuse or focal lung diseases, such as in pulmonary alveolar proteinosis [38], diffuse emphysema [39], drug induced lung diseases [40], or peripheral lung nodules.

Coupled to electromagnetic navigation or radial EBUS, pCLE has the potential to image microstructural and cellular patterns of peripheral solid lung nodules in vivo at both 448 nm and 660 nm [15, 16] (Fig. 14.4). After navigation bronchoscopy to the peripheral nodule has been achieved and the peripheral nodule located, the Alveoflex® miniprobe can enter the extended working channel of both radial EBUS or superdimension system, except for the posterior and apical segments of the upper lobe due to the relative rigidity of the miniprobe. In such case, a smaller probe such as the Cholangioflex® should be used.

Confocal imaging of the peripheral nodule can be performed at either 488 nm (autofluorescence) or 660 nm after distal deposition of a few microliters of methylene blue for cellular imaging.

Recently, Arenberg et al. made use of pCLE at 488 nm to explore peripheral lung nodule in 39 patients from two centers [41]. Three investigators with different pCLE experiences met to develop descriptive criteria through a consensus review of 5 teaching and 5 training cases. Twenty-nine randomized pCLE sequences of lung nodules were secondly blindly reviewed and scored. The more reliable criteria for lung cancer diagnostic was the "solid" or "compact" pattern (Fig. 14.4). Interobserver agreement for this item was moderate (0.54). Using this single item, the sensitivities of detection of cancer are 70%, 70%, and 80% for the three observers, with specificities of 58%, 58%, and 74%, respectively. Future studies will assess the technique as an aid to localize the peripheral nodule and to differentiate benign from cancerous lesion.

Besides autofluorescence solid pattern at 488 nm, we have shown that topical methylene blue/660 nm pCLE makes it possible to image the cellular organization of peripheral lung nodules [15] and to differentiate small-cell lung cancers from the other histological type (Fig. 14.4). Again, more studies are needed to determine if the technique has a place in the clinical assessment of peripheral nodules.

Conclusion

Confocal fluorescence endomicroscopy is an emerging fascinating technique that allows optical microimaging of both the proximal and distal bronchial tree. Potential applications for lung cancer diagnosis include the exploration of both basement membrane alteration and epithelial layer of the proximal airways, as well as peripheral nodule assessment. Until now, pCLE only used endogenous autofluorescence or simple fluorescent contrast agents. In the future, the use of fluorescent molecular compounds will make it possible to extend applications of the technique. Pilot studies exploring this strategy have recently been published that provided specific confocal imaging of molecular probes in precancerous conditions of the oral cavity ex vivo [42] and of colonic dysplasia in vivo [43], and even invasive fungal diseases [44]. Coupled to FCFM, molecular imaging may help in the future to enable early diagnosis, rapid typing of molecular markers, and assessment of therapeutic outcome in many lung diseases.

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Optical Coherence Tomography

15

Norihiko Ikeda and Stephen Lam

Introduction

Optical coherence tomography (OCT) is a promising technique for clinical diagnosis of various types of tissue, because high-resolution tomography is easily obtained by its compact imaging optics.

The fundamental principles of OCT evolved from optical one-dimensional low-coherence reflectometry, which uses a Michelson interferometer and a broadband light source.

Due to the additional transverse scanning (B-scan), two-dimensional imaging was obtained, and this technique was named OCT by Fujimoto and rapidly expanded to numerous biomedical and clinical applications [1, 2].

The mechanism is similar to ultrasound imaging but uses light rather based on the low-coherence interferometry. In ultrasound, the imaging is accomplished by measuring the delay time (echo delay) for an incident ultrasonic pulse to be reflected back from structures within tissue. Because the velocity of sound is relatively slow, this delay time can be measured electronically. However, since the velocity of light is 200,000 times that of sound, measurements of delay cannot be performed directly by electronic techniques. Therefore, a technique known as low-coherence interferometry is used [1, 3–5]. Tomographic images are produced in a manner similar to radar, by scanning the optical beam across the sample, and represent a cross-sectional image of the optical reflectance properties within tissue.

Thus, the resolution of OCT, in both the axial and the lateral dimensions, is more than an order of magnitude higher than that of ultrasonic examination; therefore, OCT can be used to obtain the high-resolution cross-sectional images of microstructure of biological tissues which is comparable to histology [3–5].

Figure 15.1a shows a schematic diagram of the time domain OCT (TD-OCT). Low-coherence light, or light containing many different wavelengths, is generated from the source. The light is split evenly, toward the sample and toward a moving mirror; thus, the reflected light comes from both within the sample and from the mirror. If the distance traveled by light from both directions is nearly identical, interference will occur when the light reflected from the sample and the light reflected from the reference arm mirror recombine at the beam splitter. The coherence length is analogous to the pulse length in ultrasonic imaging systems. The position of the moving reference mirror is precisely controlled electronically. Moving the mirror allows interference (back reflection) information to be obtained from different depths within the sample, because the distance traveled by light in the reference

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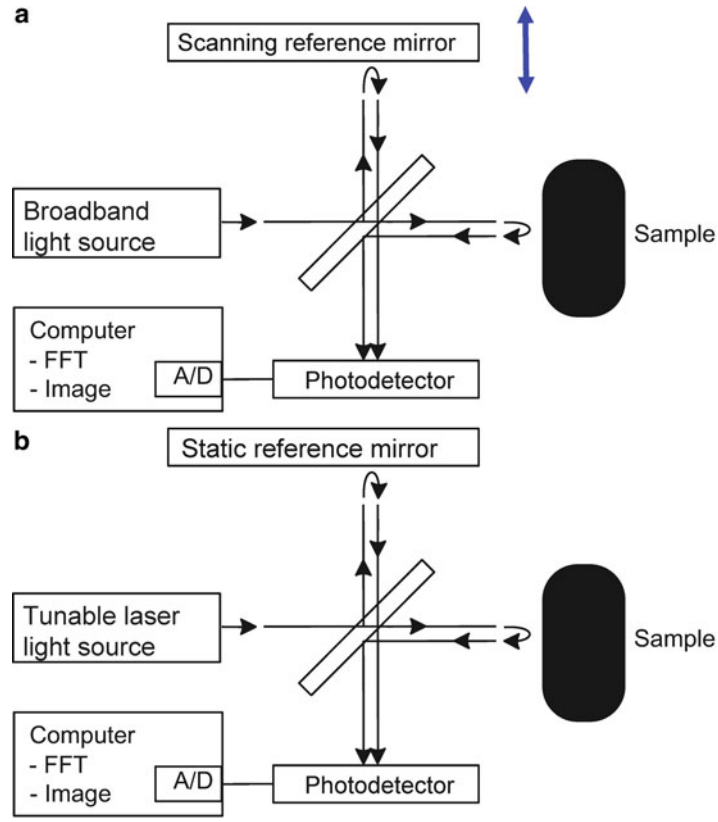

Fig. 15.1 (**a**) TD-OCT. (**b**) FD-OCT

mirror arm changes. In A-mode ultrasound, the intensity of back reflection is displayed on a gray scale map as a function of depth.

As the different layers of the tissue have different optical properties, they produce different image patterns on OCT [3, 4].

In recent years, Fourier-domain OCT (FD-OCT) (Fig. 15.1b) has been extensively employed due to its significantly higher imaging speed. FD-OCT has much higher A-scan rates because it requires no mechanical scanning of the reference path length. The spectral response of the interferometer measured is then encoded as an interferogram in optical frequency space. A Fourier transform of this interferogram reveals the reflectivity profile of the sample [5]. The application of FD-OCT to endoscopic OCT requires the use of a Swept-source OCT (SS-OCT). With a tunable narrow-band light source, a sweep over a broad range of optical frequencies is performed [5].

Historical Perspective

In ophthalmology, the first application of OCT involved imaging the transparent structures in the eye [6]. Recent clinical studies have shown that OCT provides tomographic images of the retina with 10-μm resolution and can be used to diagnose a wide range of retinal macular diseases [7]. OCT is accepted as a clinical standard for diagnosing and monitoring the treatment of a number of retinal diseases.

In dermatology, OCT has been employed for monitoring inflammatory diseases. It is useful in visualizing subsurface structures of normal skin, including the epidermis, dermoepidermal junction, dermis, hair follicles, blood vessels, and sweat ducts. Therefore OCT has been employed to diagnose vascular skin lesions, skin malignancy, psoriasis, keratosis, and so on [8].

As OCT is based on sophisticated technology used in optical communication, it can be constructed with common optical fiber components; thus, it is well suited for intralumenal diagnosis.

A key technology that is necessary for the application of OCT for endoscopy is a catheter–endoscope that is capable of delivering, focusing, scanning, and collecting a single spatial-mode optical beam. In addition, the catheter must be flexible and have a smaller diameter than the working channel of the endoscope [9, 10].

Numerous other possible applications of OCT in the field of medicine have been investigated to evaluate their potential in the clinical environment.

OCT is endoscope-compatible and is thus well suited to examining hollow organs like the gastrointestinal tract, the bronchi, and the coronary artery. Gastroenterologists have found that in vivo OCT scanning accurately detected disease features of ulcerative and cancerous lesions in gastrointestinal tract as well as colon segments with high sensitivity [11–13].

In the field of cardiovascular disease, diagnostic assessment of coronary atherosclerosis under OCT-guided coronary intervention has been performed. OCT provides the clear image of the stenotic lumen of the coronary artery caused by the atherosclerosis, which can support interventional procedures [14, 15].

Equipment

Figure 15.2 shows the OCT system developed in collaboration between LightLab Imaging (Boston, USA) and Pentax (Tokyo, Japan).

The catheter is part of the sample arm and is attached externally to the probe interface unit (PIU). The axial resolution of the OCT system is proportional to the coherence length, which is inversely proportional to the bandwidth (wavelength distribution) of the source. In this study, the source used had a bandwidth of 70 nm and power output of 10 nW.

The lateral or transverse resolution is determined by the diffraction limit of the OCT endoscopic catheter [4].

Application to Pulmonary Disease

Endoscopic OCT examination provides high-resolution images of the bronchial surface enabling detailed examination of intraepithelial lesions. Figure 15.3 shows an OCT image of squamous cell carcinoma located in the left upper lobe. Due to the limitation of light penetration, the normal structures observed in the current OCT system are the boundaries of layers between the epithelium, basement membrane, and cartilage. As most bronchial lesions originate from this area, this method is extremely

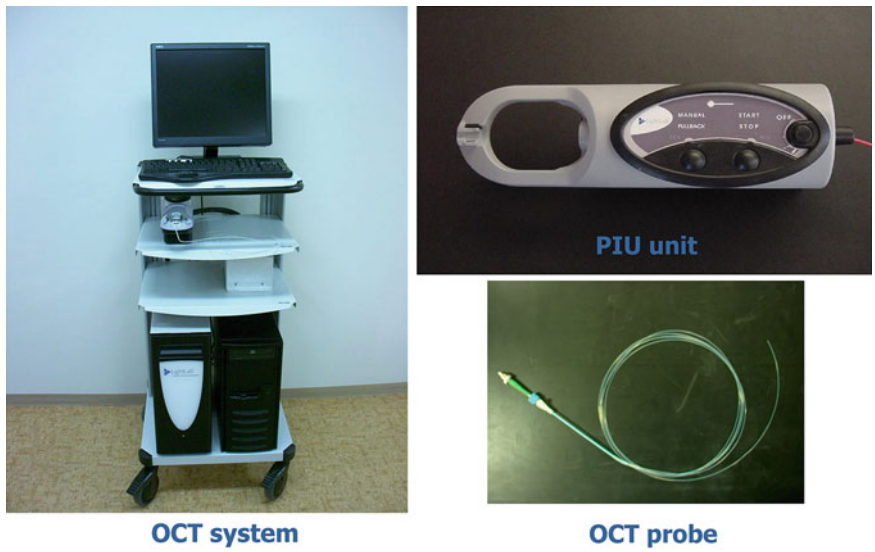

Fig. 15.2 OCT unit

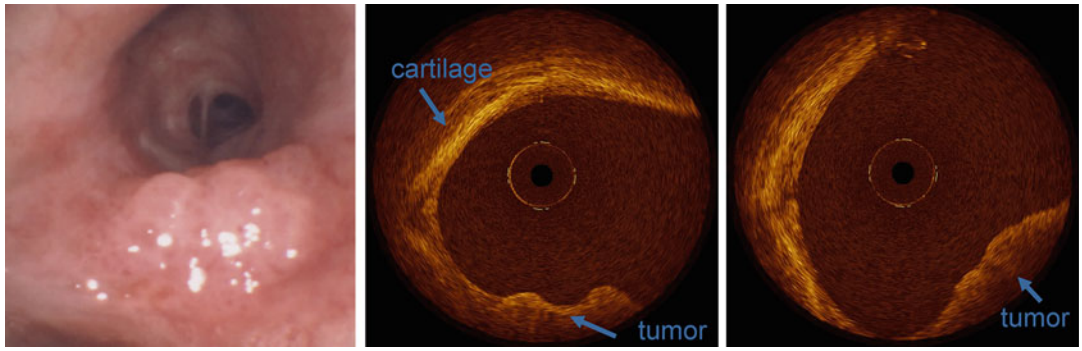

Fig. 15.3 Bronchoscopic and OCT images of squamous cell carcinoma in the left upper lobe (Tokyo Medical University)

useful in capturing the loss of normal structures of the bronchial surface due to tumor invasion by OCT (Fig. 15.3). Also OCT is helpful in evaluating the depth of invasion of bronchial tumors, which is especially useful in selecting the optimal treatment of endobronchial malignancies [3, 4, 16]. Endobronchial ultrasonography (EBUS) is often employed for the same purpose; however, the resolution of the EBUS image is not as good as that of the OCT. Also, the requirement of a transducing medium can make ultrasound difficult and often impractical for routine integration with endoscopy. Furthermore, because OCT is based on light, imaging is possible through air and does not require a transducing medium or direct contact with the object.

OCT is presently used for only investigational purposes, but improvement of this device will enable diagnosis of lesions without invasive biopsies as well as evaluation of the depth of lesions [16]. In a recent study by Lam, using radial scanning endobronchial OCT imaging, the bronchial epithelial thickness of invasive lung carcinoma was reported to be significantly greater than that of carcinoma in situ [16]. Although increased epithelial thickness can be an important feature of lung malignancies, other OCT features may be equally important in distinguishing lung malignancies from normal bronchial mucosa. Michel postulated that some OCT characteristics of malignancy included the loss of normal, identifiable epithelial and subepithelial microstructures, and possibly subepithelial optical fracture [17].

In the future, when cellular-level OCT resolutions are obtained, even greater uses for OCT in thoracic diagnostics can be envisioned. However, at present, the depth of penetration of OCT is relatively shallow (1–2 mm) and is likely to remain limited due to the degree of scattering inherent in complex biologic tissues of the lung and thorax, and thus, major advances in depth of penetration are unlikely, unless more advanced intratissue focusing devices can be developed [18].

OCT might be particularly useful in malignancies such as adenoid cystic carcinomas in which tumor spread tends to occur in the submucosal plane well beyond the observed lumenal component of the tumor. Application of OCT in this and similar settings would allow for possible detection of indistinct margins that might otherwise be overlooked in gross examination and could assist in the accurate determination of resection margins, as well as assessing operability [18]. Autofluorescence bronchoscopy (AFB) aids in screening and localizing preneoplastic and neoplastic lesions; AFB alone cannot be used to study the natural history of these lesions without biopsy confirmation. A combination of multiple imaging modalities can provide an increased and more accurate diagnostic yield from bronchoscopy.

OCT can be applied to evaluate the degree of airway remodeling such as occurring COPD, and there is a strong correlation between CT and OCT measurements of lumen and wall area [19]. In addition to an increase in airway wall thickness, differences in the subepithelial matrix and number of alveoli attached to the airway wall can be shown. OCT can capture the real-time changes in airway lumen diameter between maximal inspiration and tidal breathing which may correlate with the degree of COPD, and the wall measurement of airway relates to the value of forced expiratory volume [20].

Figure 15.4 demonstrates the 3D image of a terminal bronchiole from a smoker without COPD (Fig. 15.4a) and that with adjacent

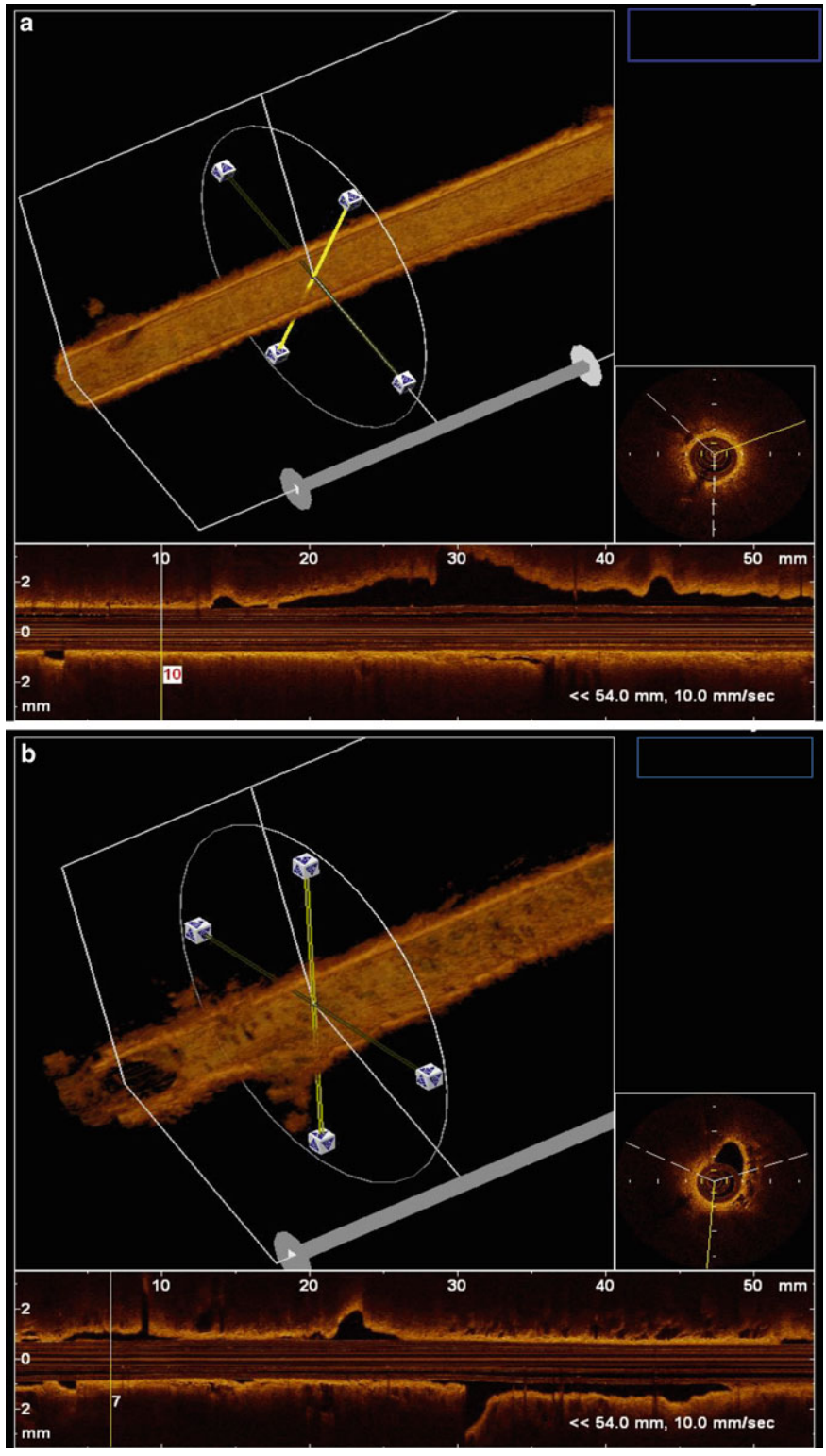

Fig. 15.4 (**a**) 3D image of a terminal bronchiole from a smoker without COPD (British Columbia Cancer Agency). (**b**) 3D image of a terminal bronchiole with adjacent pulmonary emphysema with destroyed alveolar walls in a smoker with COPD (British Columbia Cancer Agency)

pulmonary emphysema with destroyed alveolar walls in a smoker with COPD (Fig. 15.4b). The difference of alveolar structure is precisely demonstrated by OCT.

Summary and Recommendation

OCT imaging is likely to become a powerful tool in diagnostic pulmonary medicine, not only in the early detection of lung cancer but also in the evaluation and monitoring of bronchial microstructures that are affected by other inflammatory or invasive disease processes. It could potentially be used in conjunction with endobronchial ultrasound, autofluorescence bronchoscopy, or narrow band imaging to determine the location of biopsies.

The discrimination of carcinoma in situ, dysplasia, and chronic inflammation should become possible by OCT image soon, although at present, these cannot be definitively diagnosed without biopsy. With further improvement in resolution, contrast, acquisition, display, and processing and the development of specific thoracic probes, OCT might offer a significant advance for the diagnosis and treatment of patients with thoracic diseases.

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Electromagnetic Navigation

16

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Introduction

Flexible bronchoscopy (FB) is primarily used to sample pathologic lesions involving the tracheobronchial tree as well as lung parenchyma. It is the most commonly performed invasive procedure by the pulmonologists. The procedure is frequently used to diagnose the nature of pulmonary nodules (PN). However, when it comes to the nodules located in the peripheral one-third of the lung, the procedure is of limited value and establishing the diagnosis remains challenging [1]. Percutaneous needle aspiration of such lesions is frequently marred by pneumothorax, requiring chest tube placement and hospitalization in half of the subjects with the complication [2, 3]. Obviously, even the video-assisted thoracic surgery (VATS) in all patients with PN suspected to be malignancy would not be a practical approach.

Studies have demonstrated that Solitary PNs are seen 1 in 500 chest X-rays and are caused by a variety of conditions ranging from infectious granulomas to lung cancer [4]. Approximately 150,000 new Solitary PNs are discovered each year in the United States and even more if screening computerized tomography (CT) of the chest is considered [5]. Based on a variety of factors, 10–70% of these lesions could be malignant [6]. The prevalence of malignancy in PNs depends upon its size and is in the range of: 0–1% for the lesions less than 5 mm in size, 6–28% for the lesions 5–10 mm in size while 64–82% for lesions larger than 20 mm in diameter [6–11].

Diagnostic yield of FB in PNs is limited by its inability to guide endobronchial accessories directly to the lesion. Its diagnostic yield depends on the size and location of the lesion and ranges between 20 and 84% [12–18]. For PNs less than 20 mm in diameter, the yield is 14% for those located in the outer third of the lung, and it goes up to 31% for the lesions located in the central two-thirds [19]. If the CT reveals a positive "bronchus sign," the yield of FB increases up to 90%; unfortunately not a common occurrence for smaller lesions [20]. Similarly the diagnostic yield of FB for mediastinal lymph nodes using transbronchial needle aspiration (TBNA) is reported to be between 15 and 83% [21]. Newer adjuvant technologies such as endobronchial ultrasound (EBUS) and CT fluoroscopy [22–26] have been proposed to guide the tissue sampling to further the yield. Bronchoscopy under CT fluoroscopy has a success rate of 70%; however, the drawbacks of radiation exposure and the necessity of finding CT time for the procedure are considerable [23, 26]. On the other hand,

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EBUS technology is demanding, expensive, and technically limited as the ultrasound probes cannot be easily steered beyond the visible portions of the airways [24, 27].

Real-time guidance and the ability to steer biopsy instruments to the peripheral lesion are critical for a successful FB procedure. Electromagnetic navigation (EMN) is a novel technology that facilitates approaching peripheral lung lesions as well as mediastinal lymph nodes which are difficult to sample with conventional FB. Following is a concise review on the present-day experience with EMN.

What Is Electromagnetic Navigation?

The navigation system involves creating an electromagnetic (EM) field around the patient's chest and then directing endoscopic accessories using a microsensor placed upon previously acquired CT images. In other words, EMN is an image-guided localization device which assists in placing endobronchial accessories in the target areas of the lung. The principles and the components of the EMN are provided below [27–31]:

Electromagnetism

EMN operates on the principles of electromagnetism. Electromagnetic location board (EMLB) produces low-frequency EM waves. The board is 1 cm thick and 47×56 cm in dimension. It is placed under the cephalic end of the bronchoscopy table mattress to produce EM field over the patient's chest (Fig. 16.1).

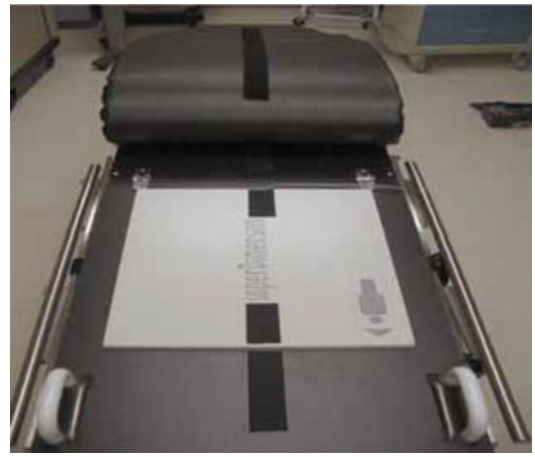

Fig. 16.1 Electromagnetic location board placed at the cephalic end of the bronchoscopy table

A retractable sensor probe, 1 mm in diameter and 8 mm long, is mounted on the tip of a flexible cable locatable guide (LG) (Fig. 16.2). This microsensor is the main feature of the system. Once placed within the EM field, its position in *x*, *y*, *z* axes as well as in motion (roll, pitch, and yaw) is captured by the EMN system and displayed on the monitor in real time at a rate of 166 images/s, superimposed upon previously acquired CT images.

Fig. 16.2 Microsensor, 8 mm long and 1 mm in diameter

Steerable Guide

The LG also has a feature that allows its distal end to be steered in 360°, in 45° increments. The terms steerable and locatable guide are used interchangeably. Four separate wires control the movement of the distal end of the probe from the proximal end of the device using a rotating knob and control lever. The LG also provides a socket for connecting a wire, which relays the information from the sensor to the main computer (Fig. 16.3).

Extended Working Channel

An adult-size flexible bronchoscope usually cannot be advanced beyond the fourth or fifth

Fig. 16.3 Proximal end of the locatable guide. Computer wire is connected at the black socket. *Red arrow* on the rotating knob is positioned in the direction indicated by the navigation system, and the handle is squeezed to change the direction of the microsensor

Fig. 16.4 Extended working channel (*blue*) with locatable guide in place. Both accessories are navigated to the peripheral lung lesions once the tip of the scope is wedged in place

generation bronchus. Hence, the LG is inserted into a 130-cm-long, 1.9-mm-diameter flexible catheter, serving as an extended working channel (EWC) (Fig. 16.4). Once the tip of the bronchoscope is wedged into the segmental bronchus of interest, the LG is advanced along with the EWC under the guidance provided by the navigation system. Upon reaching the desired target, the LG is withdrawn leaving the EWC in place. Endobronchial accessories are inserted through the EWC to sample the target.

Computerized Tomography

To overlay the patient's radiographic information on the patient's anatomy in the electromagnetic field, a high-resolution spiral CT scan of the chest is performed (with or without the contrast) and reconstructed with a protocol specific to the scanner manufacturer. This recommended reconstruction protocol will optimize CT images suitable for planning and navigational purposes. DICOM (Digital Imaging and Communications in Medicine) images from a low-dose CT scan can be accepted and viewed in the planning module; however, the detail and quality of the images produced may not be suitable to enable the advanced features of the ENB system.

The information is gathered in the DICOM format and placed either on a compact disk or directly downloaded on the system's laptop from the PACS system.

Computer Interphase

The electromagnetic navigation system is provided with two separate computers, a laptop with a dedicated program for "planning" and a main system computer used for "registration" and "navigation."

Upon receiving the CT chest information, the planning software program provides images of the chest in coronal, sagittal, and axial fashion as well as a virtual bronchoscopic image and a three-dimensional representation of the patient's tracheobronchial tree and pleura. These images are used to plan all aspects of the procedure. Upon completion of the plan, the information is uploaded in to the system's main computer using an external memory device. The main computer software and the monitor allow the bronchoscopist to view the reconstructed images of the patient's anatomy together with superimposed graphic information depicting the position of the LG as well as position of the target lesion.

ENB System

A new generation of the EMN bronchoscopy system was introduced in 2009. Improvements include a new software platform with a simplified planning and navigational system that improves ease of use and further enhances visualization for

the physician. The virtual 3D bronchial tree made possible with the technology extends deep into the lungs and enables several automated features such as automatic registration, automated pathway planning, and airway sync. Further, the customized high-definition views offer physicians multiple navigation perspectives to improve detection and diagnosis. A 26 in. high-definition wide-screen format allows six viewports to be displayed simultaneously, including one video input, enabling the physician to evaluate positional data and optimize central and peripheral guidance within the lung.

Procedure

The procedure of EMN is performed in the following steps:

Computerized Tomography Imaging

A spiral CT scan of the chest is performed with the patient supine, immobile, and performing a full inspiration breath hold. The scan type can be of the chest, lung, or for pulmonary embolism (PE). The scanner type should be a multi-slice, 4-detector or greater with 16-detector or greater preferred. Reconstruction parameters are recommended by manufacturer type to optimize generation of a 3D map.

Planning Module Overview and Workflow

The digitized information from the CT scan is downloaded into the software of the dedicated laptop. This information is used to reconstruct graphic axial, coronal, and sagittal views of the chest a virtual bronchoscopic image (Fig. 16.5), and a three-dimensional representation of the patient's tracheobronchial tree and pleura. Utilizing these views, a plan is created that will be used during the procedure.

Procedure planning comprises four phases:

(a) Registration planning:
Registration is the process of matching the patient's CT images to the patient's body. A 3D map extending to the fourth generation of tracheobronchial tree is required to enable automatic registration. Planning is not required for automatic registration. If a 3D map is not available, manual registration points are marked using the CT cross sections and the virtual view. These registration points are matched to actual anatomic landmarks in the patient during the procedure. Anatomical locations that are easily recognizable and that can be accurately located during the procedure registration process are selected. Five (or more) Registration Points are advised, specifically the Main Carina as well as two points in each lung, one in the lung upper lobe and one in its middle/lower lobe.

(b) Marking target locations and dimensions:
Targets are identified by scrolling through the CT cross sections. Once identified, the location of the target(s) is marked using the CT cross sections and the target dimensions are set.

(c) Pathway planning:
If a 3D map is available, one or more automatic pathways to each target can be constructed to assist in navigation. The automatic pathway is constructed using the 3D map as a reference (Fig. 16.6). A review of the automatic pathway should be completed utilizing the CT cross sections and the 3D tree. Additionally, a virtual navigation of the pathway can be performed using the pathway preview feature. The suggested pathway can be modified, extended with waypoints or it can be accepted for use as is.

(d) Saving the plan and exiting:
When the procedure plan is complete, it is exported to a CD, a removable disk (USB), or to a network storage location for transfer to the procedure system.

Registration

The information gathered during the planning stage is uploaded into the system's main computer using the external memory device. FB is

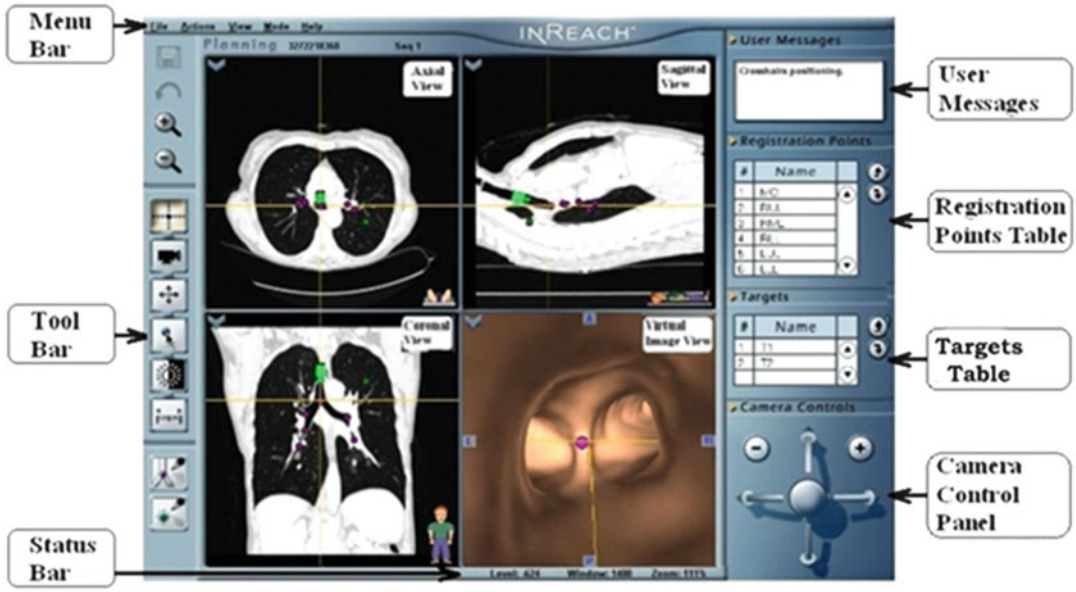

Fig. 16.5 Computer interphase: Dedicated program on the laptop provides coronal, axial, and sagittal views of the chest along with virtual bronchoscopy. Planning involves selecting the target (*green*) and the anatomical landmarks (*purple*)

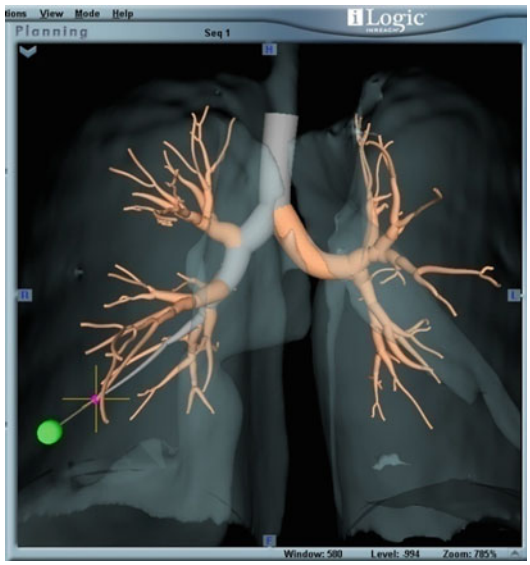

Fig. 16.6 Automatic pathway

performed in the bronchoscopy suite where the EMN system is mapped for its surrounding metallic objects. The procedures can be performed under general anesthesia or with moderate sedation. When the patient is placed on the examination table, three reference electrodes are fixed on the chest wall to accommodate for respiratory motion and nominal patient movement. FB is performed in a usual fashion. The LG is inserted via the working channel of the scope.

During the automatic registration process (Fig. 16.7), the system records the location of the LG while the physician performs a bronchoscopic survey of the lungs, creating a virtual cloud of navigation points that approximates the tracheobronchial tree. The system completes the registration process by matching the navigation cloud to the 3D map. The virtual bronchoscopy (VB) will appear during the bronchoscopic survey when the system has collected the minimal amount of data needed to match to the 3D tree. After completing the balanced survey and visual verification, the registration is accepted and the navigation phase of the procedure begins.

In a small percentage of procedures, the CT images will not support generation of a 3D tree. In this case, manual registration will be required. The radiological landmarks (registration points) selected on the virtual bronchoscopy images in planning are identified in vivo and touched with

Fig. 16.7 Automatic registration

the tip of the LG to register their location in the system's main computer to establish radiographic–anatomic alignment. Registration of all the above information into the computer software automatically synthesized a navigation scheme to approach the lesion with precision. Accuracy of navigation depends upon this radiographic–anatomic alignment also referred as "average fiducial target registration error" (AFTRE), which defines registration quality. The AFTRE can be improved or corrected by repositioning the misplaced landmark or by eliminating that with the greatest deviation. The registration error of 5 mm or less can be considered acceptable.

Real-Time Navigation

Following a successful registration, the scope with the LG in place is advanced towards the segmental bronchus of interest.

The navigation screen consists of six different viewports. The configuration of viewports is customizable with eleven different viewports available. Each viewport provides information that is meaningful at different points in the navigation procedure. The targets and pathways defined during planning will be available for selection during navigation. Once a target and pathway have been selected, the available views are used to guide the LG to the target.

The following are the viewports available to aid navigation:

- Planar CT axial, coronal, and sagittal image (Fig. 16.8). The views show the selected target and, optionally, the selected pathway and waypoints.
- Static 3D map (Fig. 16.9). A view of the 3D map showing the selected target, selected pathway, waypoints, and real-time location of the LG tip.
- Dynamic 3D map. A view of the 3D map showing the selected target, selected pathway, waypoints, and real-time location of the LG tip. The 3D map is automatically rotated, panned, and zoomed during navigation.
- Tip view (Fig. 16.10). A graphical representation of the steering wheel on the LG handle. This

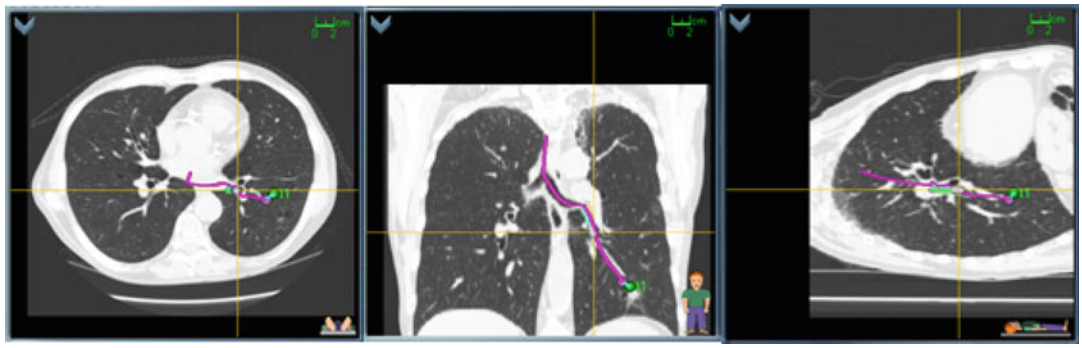

Fig. 16.8 CT cross sections

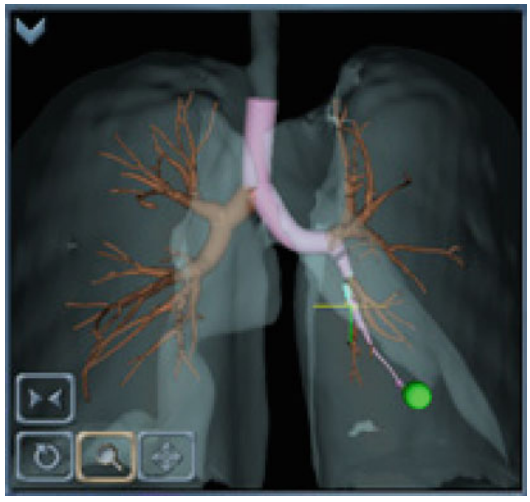

Fig. 16.9 Static 3D map

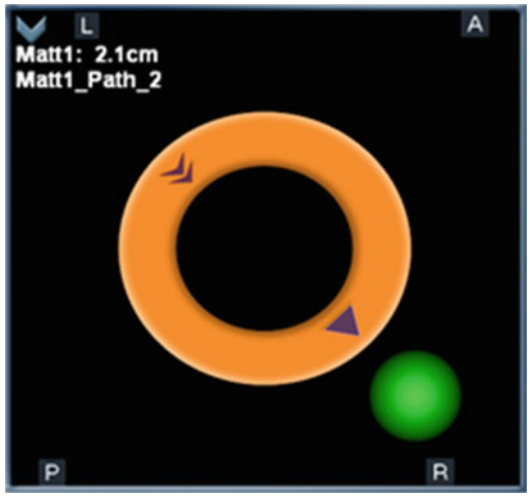

Fig. 16.10 Tip view

view shows the direction to rotate the steering wheel to turn the LG towards the selected navigation object (target, pathway, or waypoint).

- 3D CT. A planar projection of the CT volume located directly in front of the LG tip.
- Video bronchoscope. Live display of the video input feed, typically used to show the bronchoscope video.
- Virtual bronchoscopy. A live display of the virtual bronchoscopy showing the real-time location of the LG tip. The selected pathway, waypoints, and 3D map centerlines can be overlaid on the view.
- Local view. A planar CT image located at and aligned with the LG tip. The view shows the selected target, selected pathway, waypoints, and 3D map branches.
- MIP (maximum intensity projection). A pseudo-three-dimensional projection of the CT volume below the LG tip. MIP shows high intensity structures, such as blood vessels and lesions.

Navigation guidance to the target is primarily given through the selected pathway. The pathway is displayed in the 3D map, local view, virtual bronchoscopy, and CT cross sections. The objective during navigation is to steer and advance the LG along the pathway.

In addition to pathway guidance, steering directions are provided to specific navigation objects using the tip view. Navigation objects include targets, the automatic pathway, and waypoints, and are represented by spheres in all views.

The lesion is represented as a green sphere on all of the system viewports. As the LG gets closer to the lesion, the green dot continues to get larger in a relative fashion. Once the LG reaches the desired target location, the EWC is fixed at the proximal end of the biopsy channel of the bronchoscope by a special locking mechanism, and the LG is withdrawn. Fluoroscopy can be performed to view the LG in the desired location before its removal. Bronchoscopic accessories such as a biopsy forceps, transbronchial aspiration needle, and endobronchial brush can be inserted via the EWC to obtain a tissue specimen. An endobronchial ultrasound probe can also be inserted for additional location confirmation.

Result

A number of studies have been published establishing effectiveness of the EMN in the diagnosis of peripheral lung lesions [27–40] (Table 16.1).

Schwarz et al. [28] performed the first animal trial to determine the practicality, accuracy, and safety of the real-time EMN in locating peripheral lung lesions in a swine model. The study proved that EMN was accurate when added to the standard bronchoscopy to assist in reaching peripheral lung lesions. Artificially created lung lesions were sampled without difficulty or complications, using conventional accessories.

Becker et al. [27] published results of a pilot study in humans. They obtained biopsies of the peripheral lesions under the guidance of EMN in 30 adults. Evaluation was possible in 29 patients; definitive diagnosis was established in 20 patients (69%). EMN added 9 min of time to the bronchoscopy procedure. There was one pneumothorax requiring chest tube insertion. They concluded that EMN is feasible and safe as an aid to obtaining biopsies of peripheral lung lesions.

Hautmann et al. [30] performed a prospective evaluation of an EMN system for the diagnosis of peripheral infiltrates or solitary PNs. In all of the pulmonary infiltrates and solitary PNs, the navigation system was able to guide the sensor tip to the center of the lesion, despite some being undetectable by fluoroscopy. All the lesions were reached by EMN, and tissue was sampled successfully for the histological examination. The biopsy results in three of five solitary PNs were positive for carcinoma, whereas normal lung tissue was obtained in the two remaining cases. All "masses" were positive for carcinomas. Biopsy results for infiltrates were diagnostic in five cases. In the remaining three, histological findings were nonspecific. There were no complications. Overall, EMN was well tolerated and proved to be safe and useful in localizing small and fluoroscopically invisible lung lesions with an acceptable level of accuracy.

Then Schwarz et al. [29] also performed a human study following their animal trial on unreachable peripheral lung lesions (15–50 mm in size) under EMN guidance. The diagnostic sensitivity of the procedure was reported as 69%. This success rate was felt to be due to the road map created by the navigation system which reduced trial and error attempts during the use of endobronchial accessories. No complications were reported.

A prospective, single center, pilot study was conducted by Gildea et al. [31] to determine the ability of EMN to sample peripheral lung lesions and mediastinal lymph nodes. Sixty subjects were enrolled and the diagnostic yield was 74% for the peripheral lesions and 100% for mediastinal lymph nodes. A diagnosis was obtained in 80.3% of bronchoscopic procedures with EMN. The lesions were accessed in all subjects. Two patients developed pneumothorax. There was no significant relationship between diagnosis and size or the location of the peripheral lesions or lymph nodes.

Prospective studies were undertaken by Makris et al. [32] and Eberhardt et al. [33] to determine the yield of EMN without using fluoroscopy in the diagnosis of peripheral lung lesions. The diagnostic yield was found to be 67% and 62.5%, respectively, and was independent of lesion size. There were 3 and 2 incidents of pneumothoraces, respectively. The EMN yield was found to be 77.2% if AFTRE was less than 4 mm [32]. Diagnostic yield was lower for the upper lobe lesions probably due to the acute angle of the corresponding bronchus as well as for the lower

Table 16.1 Diagnostic yield of EMN-aided FB

Reference	Technique	*N*	Size (mm) Range or mean	Diagnostic yield (%)	AFTRE (mm) (mean ± SD) or range	Procedure duration (min) (mean ± SD) or range	Flouro	PNX % (*N*)
Becker (27)	EMN+flouro	29	12–106	69	RE: 6.1 ± 1.7	NT: 7.3 RT: 2	+	3.3 (1)
Hauttman (30)	EMN+flouro	16	22±6	Not given	4.2	NT: +3.9 min	+	0
Schwarz (29)	EMN+flouro	13	15–50	69	NE: 5.7	TPT: 46 min	+	0
Gildea (31)	EMN+flouro	58	PL: 22.8 LN: 28.1	PL:74% LN:100%	RE: 6.6 ± 2.1 NE: 9 ± 5	RT: 3 ± 2 NT: 7 ± 6 TPT: 51 ± 6	+	3.4 (2)
Wilson (37)	EMN+flouro+ ROSE	248	PL: 2.1 LN: 1.8	70–86%	RE: 0.5 ± 0.02	Not given	+	1.2 (3)
Makris (32)	EMN	40	23.5	62.5	RE: 4 ± 0.15 NE: 8.7 ± 0.8	Not given	–	7.5 (3)
Eberhardt (33)	EMN	89	24	67	RE: 4.6 ± 1.8 NE: 9 ± 6	RT: 3.2 ± 2.3 NT: 4.5 ± 3.4 TPT: 29.9 ± 6.5	–	2.2 (2)
Eberhardt (35)	EMN+EBUS	40	26	88	Not studied	Not studied	–	6[a] (3)
Lamprecht (38)	EMN+PET-CT+ROSE	13	30	76.9	Not studied	TPT: 60	–	0
McLemore (36)	EMN+EBUS	48	23 (6–60)	90	Not studied	Not given	–	2.1 (1)
Seijo (39)	EMN+ROSE	51	25 (15–35)	67	RE: 4	Not given	–	0
Eberhardt (40)	EMN+EBUS	53	23.3 (11–29)	75.5	3.6 (1.8–5.7)	RT: 2.9 (1–9) NT: 3.5 (0.3–14) TPT: 25.7 (16–45)	–	1.9 (1)

EMN Electromagnetic navigation, *ROSE* Rapid on-site examination, *EBUS* Endobronchial ultrasound, *PL* Peripheral lesions, *LN* Lymph nodes, *RE* Registration error, *NE* Navigation error, *NT* Navigation time, *RT* Registration time, *TPT* Total procedure time

[a]When only EMN was done

lobes, probably related to the diaphragmatic movement [33]. Both studies concluded that EMN can be used as a stand-alone procedure (without fluoroscopy) without compromising diagnostic yield or increasing the risk of pneumothorax.

It has also been established by a prospective, randomized trial that combination of EBUS (endobronchial ultrasound) and EMN improves the diagnostic yield of FB in peripheral lung lesions without compromising safety [35]. In this particular study, 72% of all 118 patients recruited had a positive diagnostic yield via FB. Combined EBUS/EMN had a significantly higher diagnostic yield of 88% compared to that of EBUS (69%) and EMN (59%) alone. The diagnostic yield from the lower lobes was significantly lower, consistent with the previous study by Eberhardt [33]. The improved yield of the joint procedure ascribed to combining the ability of EBUS to directly visualize the peripheral lung lesions with the precise navigation capabilities of EMN. The overall pneumothorax rate was 6% (7 patients) and 6.3% (5 patients) when EMN was used. Four of the 7 patients required a chest tube placement. Although this combination provides a higher diagnostic yield compared to either one of them alone, the issues of cost and training need to be addressed.

In another report using the combined EBUS/EMN approach, 48 patients with peripheral lung lesions were studied [36]. Successful navigation was possible in 42 patients. The diagnostic rate was 90% with 45% true positive and 45% true negative rate. Five out of the six failed procedures were because of mechanical limitations of the EMN (lesions in the upper lobes). The authors calculated that with the concomitant use of EMB and EBUS, 32 thoracotomies were averted at the expense of only 1 pneumothorax.

A retrospective, single center study was carried out to evaluate the diagnostic yield of bronchoscopy, guided by EMN plus the rapid on-site evaluation (ROSE) of the cytology specimens [37]. Of 248 subjects, 65% received a definitive malignant or nonmalignant diagnosis on the day of the procedure. During the follow-up, 12 patients (5%) were confirmed to be free of malignancy, and 8 patients (3%) were confirmed as having malignant disease. Sixty-seven patients (27%) were lost for follow-up (inconclusive). Thus on the day of the procedure in 173/248 (70%) of all patients, correct information was gathered. If all inconclusive cases are treated as nondiagnostic (worst-case scenario), the yield was 70%, but if all inconclusive cases were treated as diagnostic (best-case scenario), the estimate was 97%. The diagnostic yield probably ranged between 70 and 97% based upon the assumptions made regarding the outcome of the cases that had an inconclusive diagnosis on the day of the procedure. In this particular study, pneumothorax was encountered in 3 patients and a few other minor complications yet none of the latter were related to the use of EMN. It was concluded that combination of EMN and ROSE can provide a better diagnostic yield in patients with a peripheral lung lesions.

Recently the combination of EMN, PET-CT, and ROSE was further studied for the routine diagnostic workup of peripheral lung lesions [38]. EMN was performed in 13 subjects, where the PET-CT scans were the part of the diagnostic workup. In 76.9% of the patients, EMN resulted with a definitive diagnosis. No pneumothorax or any other complications related to the procedure were encountered. Patients with peripheral lung lesions, EMN in combination with ROSE and prior PET-CT was shown to be safe and highly effective.

The influence of having CT bronchus sign on the yield of EMN was evaluated in a study of 51 patients with pulmonary nodules [39]. The overall diagnostic yield of EMN was 67% (34/51). EMN was diagnostic in 79% (30/38) of patients with a bronchus sign on chest CT, but only in 4/13 (31%) with no discernible bronchus sign. Both univariate and multivariate analysis identified bronchus sign as statistically significant variable. No procedure-related complications were observed.

Catheter aspiration was compared to the traditional forceps biopsy technique of small pulmonary nodules suspicious for malignancy using EMN [40]. Both tools were used to sample suspicious malignant lesions in 53 patients. EBUS was

used to verify the accuracy of target lesions as well. Diagnosis was obtained in 75.5%. Sampling by catheter aspiration was associated with a higher diagnostic yield than sampling by forceps biopsy alone ($p=0.035$). When EBUS verified the lesion location after navigation, the diagnostic yield was 93% compared to only 48% when lesion location was not confirmed [40]. There was 1 pneumothorax, treated conservatively.

Therapeutic Interventions

EMN is a promising technology not only in diagnosing the peripheral lung lesions and mediastinal lymph nodes but also may provide a means for treating patients with possible lung cancer.

Localizing non-visible and non-palpable peripheral lung nodules during thoracoscopic resection can be challenging. A variety of techniques have been described to mark the pleural surface in the vicinity of these nodules to guide the surgeon. The use of EMN has been reported in 2 cases were subpleural fiducial markers were placed under EMN guidance [41]. This was followed by successful VATS wedge resection during the same procedure.

In external beam radiation of lung cancer, the metallic fiducials are usually implanted transcutaneously under CT or fluoroscopic guidance. Kupelian et al. compared this method to transbronchial placement of metallic fiducials using EMN [42]. Eight of 15 patients who had the implantation transcutaneously developed pneumothorax, and 6 of them required a chest tube. No pneumothorax was observed in the 8 patients who underwent placement using EMN bronchoscopy. The implanted markers were stable within the tumors throughout the treatment duration regardless of implantation method.

Recent advances in minimally invasive thoracic surgery have renewed an interest in the role of interstitial brachytherapy for lung cancer [43–46]. One of the studies has described the principles of navigated brachytherapy for treatment of a medically inoperable peripheral non-small cell lung cancer patient [46]. A right upper lobe lesion was treated with external beam radiotherapy and navigated endoluminal brachytherapy. After successful localization of the lesion, EBUS was performed and a brachytherapy catheter was placed within the tumor. After the application of high-dose-rate brachytherapy, EBUS and CT demonstrated a partial while histology showed a complete remission of the tumor. This finding advocates that navigated brachytherapy for peripheral pulmonary tumors not responsive to conventional treatment is achievable [46].

Studies have demonstrated that a minimally invasive robot-assisted (MIRA) lung brachytherapy system produced results that are equal to or better than those obtained with VATS and comparable to results with open surgery for peripheral, malignant lung lesions [45]. Following this findings, an integrated system involving modified EMN, EBUS, and MIRA is being evaluated for brachytherapy for the peripheral lesions. It appears that EMN with an improved robotic controller may help to perform minimally invasive robot-assisted lung brachytherapy which may have better outcome than standard VATS [44].

Stereotactic radiosurgery (CyberKnife) is a treatment option for patients who are medically unfit to undergo lung tumor resection [47]. This technology has been complimented by more targeted chemotherapeutic regimens, novel methods of administering more accurate and more concentrated doses of radiation therapy, and innovative local excisional methods. For an exact tumor ablation, CyberKnife requires fiducial marker placement in or near the tumor. In the past, it was being carried out via transthoracic route under CT guidance with obviously high risks of pneumothorax. When the fudicials are placed via standard bronchoscopy, they have a tendency to dislodge [48]. In a single study, a total of 39 fiducial markers were successfully deployed in 8 of 9 patients using EMN guidance without any complication [49]. This finding supports the notion that EMN can be used to deploy fiducial markers for CyberKnife radiosurgery, safely and accurately.

A recent study described the use of coil-spring fiducial markers in nonoperative patients with isolated lung tumors planned for CyberKnife treatment [50]. A total of 52 consecutive patients

underwent fiducial markers placement using EMN bronchoscopy. Of these, 4 patients received 17 linear fiducial markers, and 49 patients with 56 tumors received 217 coil-spring fiducial markers. A total of 234 fiducial markers were successfully deployed in 52 patients with 60 tumors. At CyberKnife planning, 8 (47%) of 17 linear fiducial markers and 215 (99%) of 217 coil-spring fiducial markers were still in place ($p=0.0001$). Of the 4 patients with linear fiducial markers, 2 required additional fiducial placements while none of the patients with coil fiducial markers required additional procedures. Three pneumothoraces (5.8%) occurred in peripheral lesions (2 of them needed a chest tube). The bronchoscopy procedures were done under moderate sedation in an outpatient bronchoscopy suite.

A novel EMN system that provides tracking for percutaneous procedures has been introduced to aid radiologists in their different pulmonary interventions [51, 52]. The tracking is done percutaneously without using bronchoscopy. This system did not show any benefit in terms of reducing CT fluoroscopy time or radiation dose when compared to the traditional percutaneous CT fluoroscopy-guided biopsy of small lung lesions [51]. This EMN system was also evaluated to determine its potential to reduce the number of skin punctures and instrument adjustments during CT-guided percutaneous ablation and biopsy of lung nodules [52]. This early experience suggested a low number of skin puncture and instrument adjustments when using the system.

Complications

Pneumothorax is the most common complication encountered with the use of EMN and occurs in the range of 0–7.5% [27, 29–34, 40]. In the published studies related to EMN effectiveness in the diagnosis of peripheral lung lesions, 18 patients have developed pneumothorax (Table 16.1). Four of these patients needed chest tube drainage, while in the remaining 14 it resolved spontaneously**.** Theoretically the rate of pneumothorax could be affected by AFTRE, as an error of even a few millimeters could be crucial in these small peripheral lesions, especially if the fluoroscopic guidance is not utilized.

Self-limiting bleeding may be encountered in some cases [27, 37]. It is believed that the EWC also facilitates to tamponade the bleeding by allowing the scope to remain wedged at the subsegmental bronchus throughout the process [31, 35].

There is also a possibility of EWC being dislodged from its primary site during sampling of the tissue, requiring repeat navigational stage of the procedure [31]. Use of fluoroscopy during the sampling of the tissue can help identify the problem. In a single case, repeated insertion and removal of biopsy forceps perforated the EWC [33].

Limitations

We believe that major obstacle to the wide-spread use of the EMN is its cost and the need for expensive disposable LG and EWC. Medical economics will certainly limits its use in developing and third world countries.

Summary

Electromagnetic navigation is a novel tool which aids diagnostic yield of flexible bronchoscopy for the peripheral lung lesions and mediastinal lymph nodes. The procedure is safe, effective, and easy and can be performed with or without the use of fluoroscopy. It plays a complementary role with endobronchial ultrasound. It has a potential to be a helpful tool in improving outcomes from thoracoscopic resections, external beam radiotherapy, interstitial brachytherapy, and CyberKnife treatment. Its upfront cost and that associated with the disposable LG could hinder its popularity.

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17 Lung Cancer Screening and the National Lung Screening Trial (NLST)

Fabien Maldonado and Eric S. Edell

Introduction

Lung cancer remains the most common cause of cancer-related deaths in the USA and worldwide. An estimated 220,000 new cases are diagnosed, while nearly 160,000 patients die from lung cancer each year in the USA alone, accounting for more cancer-related deaths than the next three most common cancers combined: colon, breast, and prostate [1, 2]. In spite of major advances achieved in lung cancer diagnosis, medical, surgical treatment, and palliative care, the overall 5-year survival for lung cancer has not noticeably changed over the past 20 years and is estimated around 16% [3]. These dismal statistics compare poorly with those of other common cancers such as colon, breast, and prostate cancers characterized by 5-year survival rates of 65%, 88% and 99%, respectively. Among the many potential explanations advanced to explain such differences, the lack of effective screening for lung cancer is often contrasted to what are generally assumed and accepted screening strategies for those other malignancies. Lung cancer is in the majority of cases diagnosed at advanced stages, as symptoms prompt patients to seek medical attention, when curative therapeutic options are at best limited.

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The high case-fatality rate of lung cancer, its relatively high prevalence, a tendency to primarily affect easily identifiable "at-risk" individuals, and a prolonged preclinical phase are characteristics that should theoretically position lung cancer as an ideal candidate for some type of screening [4]. Indeed, the recently published results of a large randomized controlled trial, the National Lung Screening Trial (NLST), suggest that in a closely defined high-risk population, annual screening with low-dose high-resolution chest computed tomography (LDCT) results in a 20% relative reduction in lung cancer mortality [5]. These results undeniably represent the most significant advance in lung cancer research achieved over the past 20 years and should inform future recommendations for lung cancer screening. However, many unanswered questions wilI need to be addressed before such a screening strategy for lung cancer can be implemented on a larger scale. A consistent finding in all studies on LDCT as a screening tool for lung cancer is the excessive number of "false-positive" studies. This highlights the need for further research aimed at defining appropriate management strategies for screen-detected lung nodules, a substantial proportion of which will likely require the diagnostic tools available to most interventional pulmonologists. While many of these questions will most certainly be addressed by further analysis of the NSLT data in the years to come, important insight can be gained from considering previous studies on lung cancer screening that paved the way to the NLST and from understanding the

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biases inherent in screening that are systematically introduced and affect the significance of their results.

Early Attempts at Screening: Chest Radiography and Sputum Cytology

Chest radiography is an appealing option for lung cancer: it is simple, inexpensive, available to most medical providers, and only exposes patients to a small amount of radiation (0.1 mSv, the equivalent of 10 days of background radiation). While some would argue that the effectiveness of chest X-rays (CXR) for lung cancer screening remains to be clarified, most experts agree that the available evidence argues against it. In the early 1970s, the National Cancer Institute (NCI) sponsored three large randomized controlled trials designed to address the value of frequent sputum cytology screening (every 4 months for 6 years) in addition to the historically "accepted" screening strategy consisting of an annual CXR [6–8]. Both the Johns Hopkins Lung Project and the Memorial Sloan Kettering Lung Project enrolled approximately 10,000 subjects each and showed no difference in lung cancer mortality between experimental and control arms.

The third study, the Mayo Lung Project (MLP), was slightly different in that patients were randomized after an initial round of screening by CXR in an attempt to exclude prevalent cancers. Furthermore, the value of intense CXR screening in addition to sputum cytology (every 4 months for 6 years) was compared "routine care" which at the time consisted of a rather loose recommendation for annual CXR for at-risk patients [6]. A total of 9,211 subjects were randomized, with 206 patients diagnosed with lung cancer in the experimental arm vs. 160 in the control arm. The 5-year survival rate clearly favored more intense screening, estimated at 35% vs. 15% for the control arm, consistent with historical estimates for lung cancer. However, lung-cancer-specific mortality was not significantly different between the experimental and control arms, estimated at 3.2/1,000 person-years and 3.0/1,000 person-years, respectively. Furthermore, long-term data of the MLP with a median follow-up of 20.5 years confirmed the absence of lung-cancer mortality benefit [9]. While substantial limitations of the MLP have been described in detail, this study was arguably the most influential in informing healthcare policies and in providing evidence against CXR for lung cancer screening.

Among the reported limitations of the study are the poor compliance in the experimental arm (approximately 75%) and a relatively frequent CXR screening in the control arm, the exclusion of lung cancer patients after the initial screening round (so that all patients underwent by design some screening), and the fact that intense screening with CXR was addressed rather than annual CXR screening. Nonetheless, CXR screening was largely abandoned based on these data. It is important to realize that several case–control studies have conversely added support for CXR screening [10–14] and that the equipoise provided the rationale for yet another NCI-funded study exploring the role of CXR in lung cancer screening among other screening interventions, the prostate, lung, colorectal, and ovarian cancer trial (PLCO), the results of which were recently published and support abandoning CXR for the purpose of lung cancer screening [15].

Survival Is a Tricky Endpoint in Screening Studies

The apparent contradiction between survival and mortality observed in the above-mentioned studies deserves further comments. Screening systematically introduces a number of biases that need considered as one tried to make sense of the available data. The heated debate that has surrounded lung cancer screening and provided the scientific rationale for the NLST, which will likely remain one of the largest and most expensive screening studies ever performed (53,454 subjects and more than 200 million US dollars), has largely revolved around the concepts of lead-time and length-time biases and, possibly, overdiagnosis [16]. While the former (lead-time and length-time biases) are

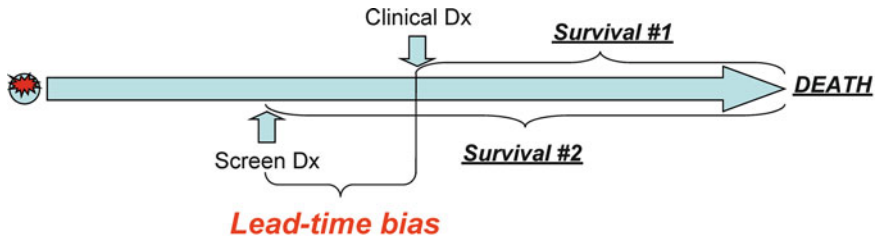

Fig. 17.1 Lead time represents the interval of time between screen detection and symptom-driven detection of cancer

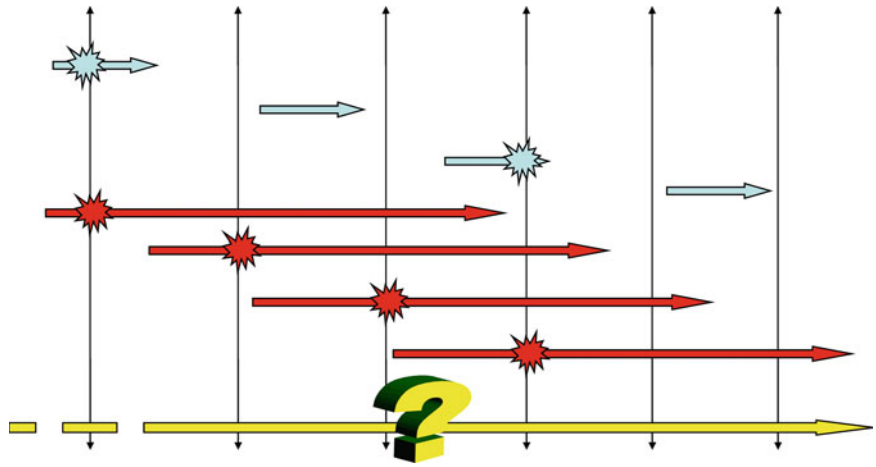

Fig. 17.2 Length-time bias is introduced by the propensity of screening to identify cancers (*red*) more indolent than their clinically detected counterparts (*blue*). Overdiagnosis (*yellow*) is an extreme form of length-time bias and is due to cancers detected by screening that never would have become apparent otherwise

universally accepted as potential confounders in lung cancer screening, the concept of overdiagnosis in lung cancer remains a source of intense controversy.

While a comprehensive review of this topic is clearly beyond the scope of this chapter, a brief description is helpful in order to understand some of the questions raised by the NLST. The self-evident purpose of screening is to detect cancer before it becomes apparent. The interval of time between a screening diagnosis and a clinical diagnosis (when symptoms prompt clinical investigations) is called lead time. The inclusion of lead time will therefore prolong survival from the time of diagnosis in the absence of any therapeutic interventions, which could be misinterpreted as benefit of screening, i.e., lead-time bias (see Fig. 17.1). The concept of length-time bias relies on the premise that not all lung cancers are "created equal." Some lung cancers are biologically more aggressive than others, as clearly shown for lung cancer by varying volume-doubling times on imaging studies. Hence, a screening strategy consisting of regular screens at regular intervals of time is more likely to intercept more indolent cancers than the most aggressive ones that may elude screening (i.e., interval cancers, see Fig. 17.2). Hence, if survival associated with screening is based on a population of cancers in which indolent tumors are overrepresented, it will also appear falsely prolonged, so-called length-time bias. An extreme form of length-time bias is overdiagnosis, which simply stated represents the bias introduced when screening identifies cancers that would never have become clinically apparent, a concept that has been well described

in other cancers such as prostate or thyroid cancers but remains highly controversial in lung cancer. What is less controversial is the observation that subjects at risk for lung cancer are also at risk for a host of other potentially life-threatening conditions (such as cardiovascular diseases or emphysema) and that indolent lung cancers may in some cases be of little clinical significance for patients more likely to die from these other conditions (see Fig. 17.2). For obvious reasons, length-time bias and overdiagnosis are more likely present when considering the first round of screening, as a significant proportion of these indolent cancers should be intercepted and excluded from further rounds of screening.

These concepts emphasize the importance of considering mortality as an endpoint rather than survival in lung cancer screening; this will be discussed further in a following chapter (limitations of LDCT screening for lung cancer, see below).

Low-Dose Computed Tomography: The Way of the Future?

Conventional chest radiographs have a poor sensitivity for lung cancer when compared to high-resolution computed tomography (HRCT), particularly with early lung cancers. The probability of identifying stage I lung cancer with CXR has been estimated around 16%. The use of HRCT for the screening of lung cancer has long been hampered by the excessively stringent technical requirements of HRCT (acquisition times of several minutes with multiple breath holds using single-row detectors machines) and the amount of cumulative radiation exposing patients to possible long-term risks of secondary malignancy (7 mSv, the equivalent of 2 years of background radiation). Low-dose computed tomography, however, has a sensitivity for lung nodules similar to that of conventional HRCT, but with a fraction of the radiation (1.5 mSv, equivalent to 6 months of background radiation). In addition, multi-row detector CT scans now allow full chest scans in less than 15 s with a single breath hold.

Numerous single-arm noncontrolled observational prospective studies using LDCT for lung cancer screening have been performed to date and have been reviewed elsewhere [17]. These studies have consistently reported a high detection rate of lung cancer at early stages, with excellent curability and survival rates. One of the most influential studies in that regard combined the results of the Early Lung Cancer Action Project (ELCAP) initiated in 1993 with those of the International Early Lung Cancer Action Project (I-ELCAP), an ongoing multicenter collaborative effort distributed across North America, Europe, Israel, and East Asia [18]. A total of 31,567 asymptomatic subjects at risk for lung cancer (including a minority of nonsmokers at risk from occupational exposure or secondhand smoke) were screened from 1993 to 2005. A clearly defined protocol was made available to participating centers to guide management of screen-detected lung abnormalities. A total of 484 subjects were diagnosed with lung cancer based on positive screening LDCT. The vast majority of these subjects (412 subjects, 85%) had clinical stage I lung cancer (77% were pathologic stage I), and the estimated 10-year survival for these patients was 88% and 92% for those undergoing surgical treatment within 1 month of diagnosis. The actual median follow-up was 40 months. It is noteworthy that 84% of these 412 subjects had lung cancer diagnosed on the first screening round (i.e., prevalent cancer) and that the vast majority of these cancers belonged to the adenocarcinoma spectrum of disease (71%), a subset of lung cancer known to include more indolent tumors than in other cell types. Nonetheless, these encouraging results were in line with previously reported similar, though smaller in size, observational noncontrolled studies and supported the notion that LDCT may indeed represent an attractive strategy for lung cancer screening.

Another influential report published shortly after the I-ELCAP study reached apparently opposite conclusions. Using two validated lung cancer prediction models, Bach and colleagues collated the results of three other single-arm observational prospective studies on LDCT screening for lung cancer and compared overall

lung cancer diagnoses, lung cancer surgical resections, advanced lung cancer diagnoses, and lung cancer deaths observed in these studies to what could have been expected in the same population in the absence of screening [19]. Similar to what had previously been described in the CXR studies, more lung cancers were identified (three times more) leading to ten times more surgical resections, but the numbers of advanced lung cancers and lung cancer deaths were not significantly different. Limitations of this study included a relatively short follow-up (median 3.9 years), a relatively wide 95% confidence interval (allowing for up to a 30% relative reduction in lung cancer mortality), and the reliance of prediction models rather than true control groups. This study suggested that overdiagnosis may indeed be a potential limitation of LDCT screening and that at least some of the screen-detected lung cancers could be fundamentally different than their clinically detected counterparts. If anything, these results reemphasized the importance of waiting for the long-anticipated NLST results before considering profound changes in recommendation for lung cancer screening.

Interestingly, another prediction model-based study using the Mayo LDCT screening trial data based on a different prediction model, the Lung Cancer Policy Model, reached conclusions very similar to those observed in the NLST [20]. This model differed from those used in the previous study in that it simulated survival based on individual disease characteristics, explicitly modeled benign disease and, perhaps more importantly, incorporated competing causes of death, an important consideration as described above. Using the screening regimen used in the Mayo LDCT screening trial (five annual LDCT), the predicted relative reduction in lung cancer mortality was 28% at 6 years (number needed to screen to save one patient from lung cancer, or NNS = 205), while the relative reduction in overall mortality, including lung cancer mortality, was 3.6% at 6 years (NNS = 262). The discrepancy between lung cancer and overall mortality was attributed to the frequent coexistence of severe comorbidities, potentially lessening the impact of lung cancer screening in a population at risk not only for lung cancer but also for a host of other life-threatening conditions.

The National Lung Screening Trial

The NLST was a large randomized controlled trial that enrolled 53,454 subjects at high risk for lung cancer at 33 US medical centers [5]. At-risk subjects were defined as being between 55 and 74 years of age with a significant smoking history (30 pack years, having quit less than 15 years prior to enrollment for former smokers). Subjects were randomized to an experimental arm consisting of three annual screening LDCT or a control arm, consisting of three annual screening CXR, with a median follow-up of 6.5 years. The rationale for using CXR in the control group rather than the "standard of care" (i.e., no screening) was that the yet-to-be released results of the PLCO could potentially show some benefit of CXR screening, in which case a study comparing LDCT to no screening would have been of lesser value.

A positive LDCT scan consisted of lung nodules of 4 mm or more (adenopathy or pleural effusion could also be considered a positive result), while any visible nodule or mass on CXR was considered positive. Overall, LDCT yielded positive results in 24.2% of cases, while CXR were considered suspicious for lung cancer in 6.9% of cases. A total of 1,060 lung cancers were diagnosed in the LDCT group, 649 of which were diagnosed after a positive screening. In the CXR group, 941 cancers were diagnosed, 279 of which were identified after a positive CXR screen. Early stage lung cancers were more frequent after a positive screening test, in both the LDCT and CXR groups. Stages I and II represented 70% of LDCT-detected lung cancers. Perhaps more importantly, stage IV lung cancers were less frequent in the LDCT than in the CXR group, supporting real stage shift, a sine qua non attribute of effective screening.

A total of 356 lung cancer-related deaths were observed in the LDCT group vs. 443 in the CXR group, representing a 20% relative reduction in lung-cancer-specific mortality (NNS = 1/320). A statistically significant relative reduction in

overall mortality of 6.7% (including lung cancer mortality) was also observed. Contrary to the explanation advanced in the Lung Cancer Policy Model study described above, the calculated NNS for overall mortality is only 220. While the significance of this observation deserves further study, one possible explanation is that LDCT may have additional health benefits that remain to be characterized.

While no clear guidelines for management of suspicious lesions detected on LDCT or CXR were provided to participating centers, the frequency of invasive investigations was low, most of the follow-up consisting of further imaging studies, and the complications from invasive investigations or surgery were rare (1.4% with at least one complication in the LDCT group and 1.6% in the CXR group). A total of 16 patients died within 60 days of an invasive procedure, six of whom did not have evidence of lung cancer. Bronchoscopy was performed in 76 of the 649 lung cancers identified by LDCT, resulting in four deaths, and 227 of the 17,053 subjects without lung cancer but abnormal LDCT, also resulting in four deaths.

These results arguably represent the most significance advance in lung cancer management achieved over the past 20 years, and LDCT screening will likely be implemented in clinical practice based on these results. Clearly, LDCT screening allows for at least some clinically relevant lung cancers to be identified and treated earlier, resulting in significant improvement in mortality. However, a number of problems and unanswered questions will need to be addressed before the full benefits of LDCT screening may be appreciated.

Limitations of Screening with Low-Dose Computed Tomography and Clinical Implications

The relative reduction in lung-cancer-specific mortality of 20% reported in the NLST is a compelling argument for integrating LDCT in a screening program for lung cancer, particularly when contrasted with existing mass screening programs such as mammogram for breast cancer, associated with conservative estimates for number needed to screen of 1/2,500 (vs. 1/320 in the NLST) [21]. A number of important questions not directly answered by the NLST will however need to be addressed before implementation of LDCT screening on a larger scale can be adopted. These include the questions of cost-effectiveness, the high frequency of false-positive studies, the persistent question of overdiagnosis, and the long-term risk of exposure to ionizing radiations. The question of false-positive management and overdiagnosis will be discussed here.

The frequency of false-positive studies observed in the NLST was high in both LDCT and CXR (control) groups, respectively, 96.4% and 94.5%. This was an expected finding as this high frequency of abnormal LDCT scans in high-risk individuals has been a consistent finding in the majority of previous LDCT studies. Prior observational single-arm noncontrolled studies on LDCT have reported screen-detected lung nodules in 5–51% of the cases [22]. Randomized controlled trials, including the NSLT, have yielded similar results. The rate of false-positive studies appears to be a direct correlation of LDCT slice thickness (collimation), with more nodules detected with thinner slices. In addition, one needs to consider that some investigators (including the NSLT investigators) have decided to call nodules <4 or 5 mm negative studies in order to limit false positives but thereby also increasing the number of false negatives [5, 18].

The vast majority of these nodules eventually prove benign (96.4% in the NLST). This raises understandable concern for the applicability of this strategy at a population level in the absence of validated and standardized management strategy aimed at keeping unneeded invasive interventions to a minimum. As previously noted, unnecessary invasive interventions were rare in the NLST, as appropriate imaging follow-up was recommended for the majority of screen-detected lung nodules. Indeed, only 671 bronchoscopies were performed after positive LDCT screening result in the three screening rounds, as well as only 322 percutaneous examinations/biopsies and 713 surgical procedures (mediastinoscopy,

thoracoscopy, or thoracotomy). Mortality within 60 days of an invasive procedure was very low in patients without confirmed lung cancer, with only six deaths. The NLST data on nodule size is not yet available, but considering prior studies, these observations can easily be understood. In the Mayo LDCT screening trial, 3,356 nodules were identified over a 5-year period in 1,520 participants with only 68 cancers eventually confirmed, representing 98% false-positive studies. Only 284 (8%) of these nodules were >8 mm in size, and therefore realistically amenable to some type of invasive diagnostic procedure, the vast majority only requiring additional follow-up [23, 24].

If the NLST screening strategy was to be endorsed by professional societies, approximately eight million Americans would fit the strict NLST inclusion criteria. This would translate into approximately 200,000 bronchoscopies if we assume that similar management strategies would be applied, more if screening was extended to other populations at risk for lung cancer. However, participants in the NLST were enrolled in large academic tertiary centers with significant expertise in management of lung nodules, and it is possible that less-experienced providers would recommend more aggressive approaches, resulting in significantly more invasive procedures, and consequently more complications. Interventional pulmonologists are likely to become actively involved in the management of screen-detected pulmonary nodules. An understanding of the limitations of LDCT screening will be crucial to extend our role beyond that of proceduralists to inform and discuss appropriate management strategies with referring providers and carefully select appropriate candidates for more invasive procedures.

This issue is further complicated by the concept that LDCT-screen-detected lung cancers are likely to include a subset of tumors more indolent than their clinically detected counterparts. Studies analyzing volume-doubling times (VDT) of screen-detected lung cancers show a wider distribution of VDT than either clinically identified or CXR-screen-detected lung cancer, with an average doubling time exceeding 400 days, a usual threshold beyond which lung cancers are assumed to be of limited clinical relevance [25]. Clinically relevant lung cancers are, however, detected by LDCT screening, as confirmed by the positive results of the NLST, arguing against a strictly bipartite model of the natural history of lung cancer previously described. A bipartite model of lung cancer suggests that all or most screen-detected lung cancers are biologically different than clinically detected ones and likely overdiagnosed [26, 27]. This contrasts sharply with the other extreme position that all histologically proven lung cancers are likely to become clinically relevant and should be aggressively managed. The truth likely lies somewhere in the middle, but if not all LDCT-screen-detected lung cancers need surgically resected, evidence-based strategies aimed at stratifying screen-detected lung cancers in order to recommend optimal management will need to be developed and validated. This latter point would be of even more significance if lung cancer screening is offered by providers less experienced than those involved in the NLST.

These more indolent tumors typically belong to the adenocarcinoma spectrum of disease. The recently published new classification of lung adenocarcinoma is based on the concept that specific histologic criteria appear to be accurate predictors of biological behavior [28]. Higher percentage of lepidic growth (neoplastic growth that respect the underlying lung architecture) and limited invasion (≤5 mm in greatest dimension) correlate well with indolent behavior. By definition, this assessment implies resection of the tumor and cannot be made on limited biopsies obtained either bronchoscopically or via percutaneous cytology sampling or biopsy. The corollary to this observation is that noninvasive methods of assessment of underlying histology and future behavior are needed and currently lacking and that the role of interventional pulmonologists is in that regard limited by the size of biopsies achievable by bronchoscopic techniques.

Conclusion

Interventional pulmonologists are likely to become significantly more involved with the management of lung nodules as LDCT screening is likely to be endorsed by major professional societies and recommended to subjects at risk for lung

cancer. In order to move the field beyond that of a strictly proceduralist service, the limitations and questions raised by the recently published NLST results need to be understood and studied further. Interventional pulmonologists have to seize the opportunity to contribute scientifically to the development of optimal strategies for the diagnostic management of screen-detected lung nodules and continue to be actively communicating with referring physicians in order to provide guidance on the possibilities and limitations of available diagnostic tools. Major advances in bronchoscopic techniques have been achieved over the past decade which has led to an ever-increasing diagnostic yield, but the landscape of lung cancer is also rapidly evolving and interventional pulmonologists should strive to remain at the forefront of the ongoing debate surrounding lung cancer screening. Only then may we be regarded not only as skilled proceduralists but also as valuable partners in the necessary multidisciplinary approach to lung cancer screening.

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18 Tissue Acquisition in Patients with Suspected Lung Cancer: Techniques Available to the Pulmonologist

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Introduction

The method of diagnosis of suspected lung cancer for the most part depends on the type of lung cancer, small-cell lung cancer (SCLC) or non-small cell lung cancer (NSCLC); the size and location of the primary tumor; the presence of metastasis; and the overall clinical status of the patient [1]. Although it is reassuring that the accuracy of differentiating between SCLC and NSCLC generated by various diagnostic techniques is excellent [1], treatment of NSCLC now relies on accurate histopathologic diagnosis and molecular characterization of the tumor. In recent years, we have witnessed a revolution in our understanding of the molecular genotype of lung cancer, and certain molecular determinants not only guide treatment decision-making but also have a prognostic and predictive function.

NSCLCs are clinically, pathologically, and molecularly heterogeneous tumors. In the last decade, paradigm shifts in the treatment of NSCLC have emerged as the result of clinical trials that have shown us that NSCLCs respond to different therapeutic agents based on histologic phenotypes and molecular characteristics. Histology is recognized as a potential predictive factor in advanced NSCLC treated with chemotherapy [2]. In a study by Scagliotti et al., a significant interaction was reported between treatment by histology and response/survival in non-squamous NSCLC treated with pemetrexed and cisplatin compared to squamous cell cancer (SCC) [3]. In a study by Ciuleanu and colleagues, maintenance pemetrexed plus best supportive care was well tolerated and offered improved progression-free and overall survival compared with placebo in patients with advanced non-squamous cell NSCLC [4]. Targeted therapy with bevacizumab added to first-line chemotherapy produces modest improvement in outcomes [5]. However, patients with squamous cell histology are not candidates for treatment with bevacizumab because of increased risk of hemorrhagic complications [5, 6]. Patients with advanced NSCLC whose tumors carry activating epidermal growth factor receptor (EGFR) mutations have been shown to have improved progression-free survival with acceptable toxicity when treated with first-line therapy with EGFR tyrosine kinase inhibitors (EGFR TKI), gefitinib or erlotinib, as compared with standard chemotherapy [7, 8]. On the basis of the results of five phase III trials, the American Society of Clinical Oncology (ASCO) provisional clinical opinion on EGFR mutation testing states that "patients with advanced NSCLC who are being considered for first-line therapy with an EGFR TKI should have their tumor tested for EGFR mutations to determine whether an EGFR TKI or chemotherapy is the appropriate first-line therapy" [9]. Oncogenic

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fusion genes consisting of EML4 and anaplastic lymphoma kinase inhibition (ALK) are reported to be present in 3–7% of adenocarcinomas of the lung [10]. The inhibition of ALK rearrangement in lung cancers with the orally available small-molecule ALK–TK inhibitor crizotinib results in dramatic response rates and stable disease in most patients [10]. A recent study reported response to crizotinib in NSCLC cell lines positive for a new driver mutation, the ROS1 translocation [11].

The ability to detect driver mutations in patients with lung cancer and administering agents targeting those molecular lesions has revolutionized the treatment of adenocarcinoma of the lung. The current treatment strategy is personalizing therapy based on an individual tumor histology and molecular profile in order to optimize efficacy and treatment outcomes. The clinician evaluating the patient with suspected lung cancer must understand that obtaining adequate amounts of tissue at the time of diagnosis is essential so that accurate histologic differentiation (squamous cell vs. adenocarcinoma) can be achieved and, when applicable, the tissue can be evaluated for driver mutations (K-Ras, EGFR, EML-4 ALK, and ROS1 translocations).

Ideally, one would like to obtain core or surgical biopsies in patients with lung cancer in order to accurately define histology and obtain molecular analysis. However, the majority of patients with NSCLC present with unresectable advanced disease that means that small biopsies or fine needle aspirations (FNA) for cytologic specimens are usually the primary means of diagnosis. Obtaining adequate amounts of tissue can be challenging especially in current clinical practice when minimally invasive procedures such as endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) are more commonly utilized, but the clinician must remember that limited tissue acquisition contributes to the difficulty of accurate molecular and histologic subtyping. For this reason, multidisciplinary thoracic oncology teams, which include pulmonologists, thoracic surgeons, chest radiologists, medical and radiation oncologists, and pathologists, must collectively decide how best to obtain tissue and then optimally utilize the available tissue by performing the minimal immunohistochemical stains needed to diagnose the likely NSCLC subtype (squamous cell vs. adenocarcinoma) so that more tissue is available for molecular diagnosis [12].

Table 18.1 Bronchoscopic procedures available for tissue diagnosis of lung cancer

1.	Conventional flexible bronchoscopy with forceps biopsy, bronchial brushing, and washing
2.	Conventional transbronchial fine needle aspiration (TBNA)
3.	Endobronchial ultrasound (EBUS)-guided TBNA
4.	Endoscopic ultrasound-guided (EUS)-TBNA
5.	Electromagnetic navigational bronchoscopy (ENB)-guided forceps biopsy
6.	Radial probe endobronchial ultrasound

Diagnostic Bronchoscopic Procedures for Tissue Acquisition

There are several procedures available to the pulmonologist to obtain tissue for diagnostic and biomarker analyses in patients suspected of having lung cancer (Table 18.1). The sampling technique should be chosen on the basis of tumor location (central vs. peripheral), local expertise, safety, availability, ease, diagnostic accuracy, and patient preference [1]. Once tissue is obtained, multiple tests must be performed in order for the pathologist to accurately provide histology, immunohistochemical profile, and molecular characterization of the tumor.

Flexible Bronchoscopy

Traditionally, the diagnosis of lung cancer has been made with flexible bronchoscopy (FB) and its attendant procedures: bronchial washings, endobronchial or transbronchial brushes, bronchoalveolar lavage (BAL), transbronchial biopsies, and conventional transbronchial fine needle aspiration (TBNA) of mediastinal lymph nodes.

The sensitivity of bronchoscopic biopsy for central, endobronchial lesions has been reported

to be very high; however, the yield for peripheral lesions is not so promising. In a review of 30 studies that reported diagnostic yield, the diagnosis of central, endobronchial tumors by bronchoscopy showed the highest sensitivity for endobronchial biopsies (0.74) followed by bronchial brushing (0.59) and washing (0.48). The sensitivity for central tumors for all modalities combined was 0.88. For peripheral lesions, cytobrushing demonstrated the highest sensitivity (0.52), followed by transbronchial biopsy (TBB) (0.46) and BAL/washing (0.43). The overall sensitivity for all modalities for peripheral lesions was 0.69 [13]. The diagnostic yield of bronchoscopic sampling procedures is very much dependent on tumor visibility during bronchoscopy, the location of the bronchoscopically visible tumors, and in the case of peripheral lesions, the size of the lesion (diagnostic yield higher for lesions greater than 3 cm in size) [1]. Another critical factor in the diagnostic yield of bronchoscopic biopsies is the forceps size and the number of biopsies obtained [14]. Forceps of 2-mm open diameter are felt to be the most useful in order to decrease artifacts that can impede the correct diagnosis. The more biopsies obtained, the better; however, increasing the number of biopsies taken results in increased risk of bleeding [14]. It is reported that between one third and one half of the bronchial biopsies taken from visible endobronchial tumors contain no viable tumor [15]. Cryobiopsies may be a more effective way to obtain larger biopsies, but the technique is not yet widely used in clinical practice [14].

Transbronchial Needle Aspiration

Conventional TBNA (without endobronchial ultrasound) can be performed during flexible or rigid bronchoscopy in order to sample endoscopically visible bronchial abnormalities especially when there is evidence of extrinsic compression, submucosal infiltration, or exophytic mass [16] as well as sampling hilar and mediastinal lymph nodes for staging of NSCLC [17]. It is particularly well suited for sampling paratracheal (stations 4R, 4L), subcarinal (station 7), and hilar (stations 10R, 10L) lymph nodes. Conventional TBNA is however a procedure that is performed without direct visualization of the lymph node being aspirated, and because of this limitation, the reported yield for TBNA for hilar and mediastinal lymph nodes varies widely (14–91%) [18]. In a meta-analysis of 12 studies in 910 patients, the sensitivity rate of TBNA was 76%, while the specificity rate was 96% [18]. The high false-negative rate of conventional TBNA makes it a less attractive modality for staging of the mediastinum. Therefore, TBNA would probably be the preferred minimally invasive method for patients with radiographic evidence of enlarged mediastinal lymph nodes adjacent to the airways, as bronchoscopy is usually performed in lung cancer patients and assessment for endobronchial lesions can be performed during the same procedure [19]. The optimal diameter of the needle is between 19 G and 22 G although the 19 G needle is preferred as more clumps of tumor cells are sampled with the larger needle [14]. Rapid on-site cytological evaluation of the aspirates improves the yield, is cost-effective, and eliminates unnecessary passes during the procedure [20].

Endobronchial Ultrasound-Guided Transbronchial Aspiration

Endobronchial ultrasound-guided TBNA (EBUS-TBNA) has revolutionized the approach to the diagnosis and staging of NSCLC. EBUS-TBNA is minimally invasive; provides access to nearly all lymph node stations (upper and lower paratracheal, subcarinal, hilar, and interlobar); has the ability to combine diagnosis and staging in a single procedure; has resulted in higher diagnostic yields than typically associated with conventional TBNA; equivalent, if not better, diagnostic yield when compared with mediastinoscopy; and has the ability of providing adequate tissue for molecular analysis [21–27]. In a prospective cohort study of 108 patients, real-time EBUS-guided TBNA detected malignant lymph node involvement with a sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic

accuracy of 95%, 100%, 100%, 90%, and 96%, respectively [27]. In a recently published meta-analysis, EBUS-TBNA was reported to have a high-pooled sensitivity of 93% and specificity of 100% for the confirmation of malignancy [28]. Even in patients with lymph nodes under 1 cm (cN0 by CT criteria), with the use of EBUS-TBNA, a significant percentage could still be shown to have pN2/N3 disease (some despite also being negative on CT and PET–CT) [29, 30]. A recent randomized study evaluated a staging strategy combining endosonography and surgical staging compared with surgical staging alone [31]. Two hundred forty-one patients with potentially resectable NSCLC were randomized to surgical staging alone and to endosonography (EBUS and EUS) followed by surgical staging if negative. Nodal metastases were found in 41 patients (35%) by surgical staging vs. 56 patients (46%) by endosonography ($p=0.11$) and in 62 patients (50%) by endosonography followed by surgical staging ($p=0.02$). This corresponded to sensitivities of 79% vs. 85% ($p=0.47$) and 94% ($p=0.02$). Thoracotomy was unnecessary in 21 patients (18%) in the mediastinoscopy group vs. nine patients (7%) in the endosonography group ($p=0.02$). The complication rate was similar in both groups [31].

In addition to its role in the diagnostic and staging evaluation of the patient suspected of having lung cancer, EBUS-TBNA has been shown to be a useful diagnostic modality in patients suspected of having lymphoma, metastatic disease to the mediastinal nodes from an extrathoracic cancer, and benign diseases such as sarcoid. Steinfort et al. [32] evaluated ninety-eight patients who underwent EBUS-TBNA for evaluation of isolated mediastinal lymph nodes. Clinico-radiologic features suggested sarcoidosis as the likely diagnosis in 43 patients. In the remaining 55 patients, EBUS-TBNA achieved definitive diagnosis in 42 patients (76%; 95% confidence interval [CI] 55–90). Lymphoma was ultimately diagnosed in 21 of 55 patients (38%). EBUS-TBNA demonstrated lymphoma in 16 (76%) patients; however, four patients required further surgical biopsy to completely characterize lymphoma subtypes. Surgical biopsy was required to diagnose specific lymphoma subtypes not readily amenable to diagnosis with low-volume specimens. Sensitivity and specificity for definitive diagnosis of lymphoma were 57% (95% CI 37–76) and 100% (95% CI 91–100), respectively [32]. Kennedy et al. [33] demonstrated EBUS-TBNA sensitivity of 90.9%, specificity of 100%, PPV of 100%, and NPV of 92.9% for the diagnosis of lymphoma. In a study by Tournoy et al. [34], 92 patients with extrathoracic malignancies with suspicion of mediastinal or hilar metastases were evaluated with EBUS-TBNA. Mediastinal and/or hilar metastatic spread was detected in 52 patients (57%) with a sensitivity and negative predictive value of 85% and 76%, respectively [34]. Garwood et al. [35] demonstrated non-caseating granulomas on EBUS-TBNA in 41 of 48 patients (85%) suspected of having pulmonary sarcoid. Factors affecting the diagnostic yield of EBUS-TBNA include decreased lymph node size (<5 mm), paratracheal location, airway distortion, and nodal calcification [36].

Endoscopic Ultrasound-Guided Fine Needle Aspiration

The mediastinal lymph nodes that are accessible through EUS include the aortopulmonary (station 5), subcarinal (station 7), paraesophageal (station 8), and inferior pulmonary ligament (station 9) [37]. In a prospective cohort study of 104 patients, EUS-FNA detected malignant lymph node involvement with a sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of 92%, 100%, 100%, 94%, and 97%, respectively [38]. In addition to the mediastinal nodal stations, EUS-FNA is particularly well suited to FNA of the left adrenal gland and has been shown to frequently alter the staging and management of patients with NSCLC [39]. A major drawback of EUS-FNA is the high false-negative rate; therefore, EUS-FNA should be performed primarily on patients with radiological evidence of mediastinal lymphadenopathy [37]. Two studies report the combined use of EBUS and EUS to evaluate the mediastinum [40, 41]. For mediastinal staging, EUS provided additional

information to EBUS-TBNA in 20 lung cancer patients with enlarged mediastinal lymph nodes or mediastinal lesions [40]. In a larger study of 33 patients for the staging of lung cancer, a total of 119 lesions were sampled by EUS-FNA ($n=50$) and EBUS-TBNA ($n=60$) [41]. When EBUS-TBNA samples were compared with EUS-FNA samples, 11 additional cancer diagnoses and three samples with suspicious cells were obtained by EBUS-TBNA that had not been obtained by EUS-FNA. Conversely, EUS-FNA diagnosed 12 additional cancer diagnoses, one suspicious, and one specific benign diagnosis in addition to EBUS-TBNA. With a combined EBUS–EUS approach using a single bronchoscope, the sensitivity for cancer detection can be as high as 96% (EUS 89%, EBUS 91%), specificity 100%, and the negative predictive value 96% (EUS 82%, EBUS 92%) [42].

Electromagnetic Navigational Bronchoscopy

Electromagnetic navigational bronchoscopy (ENB) is a localization device that guides endoscopic tools (forceps, brush, and needle) to preselected locations within the periphery of the bronchial tree allowing the clinician to biopsy lesions beyond areas that are traditionally not accessible by bronchoscopy. It can also guide TBNA of peribronchial lymph nodes and placement of fiducial markers for stereotactic radiosurgery. Three companies currently make ENB systems: superDimension (Minneapolis, MN, USA), Veran Medical Technologies (St. Louis, MO, USA), and Broncus (Mountain view, CA, USA). In a study by Gildea et al. [43], 54 patients with peripheral lesions underwent ENB. The mean lesion size was 23 mm (range 8–78 mm), and 57% were <2 cm in diameter. A definitive diagnosis was made in 40/54 (74%) peripheral lesions and in 31/31 (100%) of the lymph nodes sampled. For all malignant lesions (total 43), 32 (74.4%) were successfully diagnosed by ENB. Pneumothorax occurred in two patients (3.5%). In another study, Eberhardt et al. [44] biopsied 92 peripheral lesions in 89 subjects. No fluoroscopy was used. Mean lesion size was 24 mm (range 10–58 mm). The overall diagnostic yield was 67% and appeared to be independent of size. The sensitivity for malignant disease was only 60%, and the negative predictive value for malignant disease was 44%. The incidence of pneumothorax was 2.3%. Lamprecht et al. [45] studied ENB sampling using rapid on-site cytological evaluation during the procedure, and it showed sensitivity and specificity of 84.6% and 100%, respectively. In a randomized trial using ENB, radial probe EBUS, and EBUS combined with ENB [46], the authors hypothesized that the use of electromagnetic navigation along with radial probe EBUS visualization of the peripheral lesion would increase the diagnostic yield. One hundred eighteen patients with peripheral nodules were randomized to EBUS, ENB, or EBUS combined with ENB. The diagnostic yield of 88% obtained by combined ENB and EBUS was superior to the diagnostic yield of either technique alone (59–69%). More importantly, the negative predictive value for malignant lesions increased from 44% to 75% with the combined use of ENB and a radial EBUS probe [46].

The success of ENB biopsies is determined largely by lesion size and location. Lesions typically need to be greater or equal to 8 mm in size. Above this size, the diagnostic yield depends most upon accessibility from the bronchial tree. Lesions in direct line with a bronchus that is visible on CT are more likely to be successfully biopsied. Lesions in the apical segments of the upper lobe and the superior segments of the lower lobes tend to be more challenging [43–46].

It must be emphasized that the false-negative rate of ENB (closely related to the negative predictive value) is significant. The false-negative rate of transthoracic needle aspiration is in the range of 0.20–0.30 [1], and it is probable that this is a similar finding with ENB done without radial EBUS [47]. Thus, in a patient with a suspicious nodule, a negative biopsy result on ENB cannot be used to rule out malignancy. While the study by Eberhardt et al. [46] combining radial EBUS with ENB is encouraging, it is yet to be confirmed by other institutions. Complications with ENB are rare. The pneumothorax rate is in the range of

3–8% [43–46]. Scant hemoptysis has been noted, with no cases of severe hemoptysis [44–46].

ENB has also been used to place fiducial markers for stereotactic radiosurgery. Anantham et al. [48] placed 39 fiducials via navigation bronchoscopy into nine patients. There was a 10% migration rate after placement, likely due to coughing. One patient suffered a chronic obstructive pulmonary disease exacerbation, and there were no instances of pneumothorax. In another study, a combination of ENB and radial EBUS was used to place fiducials in 43 patients [49]. Although 13 of the patients suffered displacement of fiducials (30%), all were able to undergo stereotactic radiosurgery. Only one pneumothorax was seen [49].

Radial Probe Endobronchial Ultrasound

Radial probe endobronchial ultrasound (R-EBUS) consists of a miniature ultrasound probe attached to a flexible catheter and contains a rotating crystal tip that provides a 360° image of the surrounding structure. The ultrasound probe is passed within a guide sheath through the working channel and advanced to the peripheral target lesion. A recent meta-analysis [48] of the published literature (16 studies with 1,420 patients) evaluating R-EBUS revealed a sensitivity rate of 0.73 (95% CI 0.70–0.76) and specificity of 1.00 (95% CI 0.99–1.00) for the detection of lung cancer, with a positive likelihood ratio of 26.8 and a negative likelihood ratio of 0.28. Significant interstudy variation was noted with the EBUS method used. In addition, significant interstudy heterogeneity for sensitivity of malignancy was noted, with prevalence of malignancy, lesion size, and reference standard reported as possible explanations. The rate of pneumothorax was only 1%. The authors concluded that R-EBUS is a safe and relatively accurate tool in the investigation of peripheral pulmonary nodules [50].

A recent meta-analysis [49] was conducted to determine the overall diagnostic yield of several guided bronchoscopic techniques developed to improve the yield of transbronchial biopsy (TBBx) for diagnosing pulmonary nodules (PN) (electromagnetic navigation (ENB), virtual bronchoscopy (VB), radial probe endobronchial ultrasound (R-EBUS), ultrathin bronchoscope, and guide sheath). A total of 3,052 lesions from 39 studies were included. The pooled diagnostic yield of guided bronchoscopic techniques was 70%, higher than the yield for traditional TBBx. The yield increased as the lesion size increased. The pneumothorax rate was only 1.6% which is significantly smaller than that reported for TTNA (15%). The meta-analysis showed that the diagnostic yield of guided bronchoscopic techniques is better than traditional TBBX and although the yield remains lower than TTNA (reported diagnostic yield is 90%), the procedural risk is lower. Guided bronchoscopy may be an alternative or be complementary to TTNA for tissue sampling of PN [51].

Adequacy of Samples Obtained During Bronchoscopic Procedures

When TBNA or EBUS-TBNA is used to sample mediastinal lymph nodes, at least a moderate number of lymphocytes must be present to ensure the adequacy of the specimen and avoid a false-negative result. Adequacy criteria are not well established and may vary among pathologists [52]. Baker et al. [53] reported a significant difference in the predictive values of negative TBNA's with and without lymphocytes (78% vs. 36%). Similarly Alsharif et al. [54] found that the presence and quantity of bronchial cells had no bearing on adequacy because these cells were found in the majority of the samples and did not correlate with the number of lymphocytes.

There is increasing awareness that the quality of the specimens has a profound influence on accurate histologic assessment and molecular diagnostic results. There have been numerous studies looking at the use of EBUS-TBNA for biomarkers and tumor genetics in lung cancer. A study by Mohamed et al. [55] investigated the feasibility of EBUS-TBNA for obtaining tissue samples from mediastinal lymph nodes for immunohistochemical (IHC) analysis and noted that

immunostaining was feasible in all studied specimens. In a study by Nakajima et al. [56], histologic cores of lymph node samples obtained from 30 patients with lymph node metastases diagnosed by EBUS underwent DNA extraction, bisulfate modification, and methylation status of a panel of six genes using methylation-specific polymerase chain reaction (PCR). Methylation status could be assessed in all of the samples obtained [56]. Schuurbiers et al. [57] concluded that molecular testing of EGFR and K-Ras on cytologic material obtained by EBUS-TBNA is feasible and could be performed on 77% of their specimens. Another study by Smouse et al. [58] showed that 67% of cytology specimens were adequate for molecular testing with some of the samples having as little as 25% tumor cellularity. Arcila et al. [59] noted that 79% of cytology specimens and 89% of small biopsy specimens submitted for molecular testing were sufficiently cellular. The rate of EGFR and K-Ras mutations detected in cytologic specimens in the study was comparable to the rate detected in surgical specimens [59].

In a study of 46 patients with metastatic NSCLC to mediastinal lymph nodes, samples obtained via EBUS-TBNA were analyzed for EGFR mutations using a loop-hybrid mobility shift assay, PCR, and direct sequencing [60]. EGFR mutations were found and confirmed in 25.6% of 43 cases eligible for analysis. In a recent published trial, EGFR gene analysis of EBUS-TBNA samples was technically feasible in 26 out of the 36 (72.2%) patients with lymph node metastasis [61]. DNA sequencing for EGFR and K-Ras mutations was performed on 209 cytologic specimens (99 EBUS, 67 TTNAs, 27 body fluids, and ten image-guided FNAs), from patients with lung cancer [62]. The overall specimen insufficiency was low (6.2%). EBUS (4%) and bodily fluid cases (3.7%) showed lower insufficiency rates than other cases. EGFR mutations were detected in 34 of 175 specimens (19.4%) of NSCLC with a significantly higher frequency in adenocarcinoma (29%). K-Ras mutations were detected in 23.6% of NSCLCs with no statistical differences between adenocarcinoma and non-adenocarcinoma. The results support clinical utilization of routinely prepared cytology specimens [62]. To determine the feasibility of detecting ALK fusion genes in samples obtained by EBUS-TBNA, 109 cases with hilar/mediastinal lymph node metastases detected by EBUS-TBNA were analyzed through IHC, fluorescence in situ hybridization (FISH), and PCR [63]. IHC revealed ALK positivity in seven cases (6.4%), all of which showed the fusion gene by FISH and PCR. Multigene mutation analysis can be performed in EBUS-TBNA samples of metastatic lymph nodes from NSCLC patients. In a recent study, genetic alterations (EGFR, K-Ras, p53) were analyzed in metastatic hilar or mediastinal lymph nodes sampled by EBUS-TBNA in 156 patients [64]. All samples could be evaluated for EGFR mutations, with 42 mutations found. Of the remaining samples, 4/113 and 47/113 had K-Ras and p53 mutations, respectively.

Rapid On-Site Evaluation of Specimens

Rapid on-site evaluation (ROSE) has been shown to increase the diagnostic yield of non-bronchoscopic and extrathoracic FNAs [65, 66], and its utility in increasing the diagnostic yield by 25–46% of TBNA for peripheral lung lesions has similarly been documented in non-randomized controlled trials [20, 67]. While showing a promising role, ROSE of TBNA has been controversial. In a study of 168 consecutive patients with enlarged mediastinal and or hilar lymph nodes randomized to undergo TBNA with or without ROSE, no significant difference was found between the TBNA alone group and the TBNA with ROSE group in terms of diagnostic yield (75.3% vs. 78.3%, respectively; $p=0.64$) and the percentage of adequate specimens (86.5% vs. 78.4%, respectively; $p=0.11$) [68]. The median number of biopsy sites was significantly lower in the TBNA with ROSE group. While the complication rate of bronchoscopy was lower in the TBNA with ROSE group, the complication rate of TBNA was similar between the two groups [68]. In this randomized study, the most important

benefit of ROSE was the possibility to avoid additional biopsies without loss of diagnostic yield, and this was associated with decreased risk of bronchoscopy. What is the best method for ROSE? In a study of 827 needle aspirates, Papanicolaou-based rapid stain prepared by a technician and read by a cytopathologist was compared to the Wright–Giemsa rapid stain prepared and read by a cytopathologist [69]. False-negative aspirates were more frequent in the Wright–Giemsa stain compared to the Papanicolaou stain (14.2% vs. 7.3%, respectively; $p=0.008$).

Because the volume of tumor cells in biopsies may be small resulting in insufficient material for molecular analysis, it is recommended that material obtained from needle aspirates or pleural fluid should be preserved as cell blocks, so that tumor is archived for immunohistochemical and molecular studies [12]. It is recommended that these materials should be used judiciously in making the diagnosis of lung cancer to preserve as much material as possible for potential molecular studies [70, 71].

Conclusion

Traditionally, lung cancer had been classified as small-cell lung cancer or NSCLC, and treatment decisions were based on this differentiation. In the past decade, we have learned that NSCLCs are heterogeneous tumors that respond to different therapeutic agents based on histologic phenotypes and molecular characteristics. As a result of enhanced understanding of the molecular heterogeneity of this disease, paradigm shifts in the treatment of advanced NSCLC have occurred, resulting in personalized therapy that has yielded improved response rates and survival in selected patients. Our job as clinicians trained to perform diagnostic procedures is to recognize the importance of accurate tissue acquisition so that distinct histologic diagnosis and molecular characterization is performed on every patient with lung cancer. We have at our hands an array of diagnostic tools, and we must make every effort to work in a multidisciplinary way to ensure that the right test and the right studies are performed. Our task is often difficult as we have newer, less invasive procedure such as EBUS-TBNA, which means that FNAs for cytologic specimens are usually the primary means of diagnosis. There is ample evidence however that even with needle aspirates of lung lesions or lymph nodes, accurate molecular and histologic subtyping can be achieved. As we move forward with research and expand our knowledge of lung cancer, multidisciplinary thoracic oncology teams will play an even more important role to ensure state-of-the-art care for the lung cancer patient.

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Part IV

Lung Cancer Staging

The New Lung Cancer TNM Classification: Review and Clinical Implications

19

Roberto F. Casal and Rodolfo C. Morice

Introduction

Lung cancer remains the number one cause of cancer-related mortality in the Western world, with more than 1,000,000 deaths each year [1]. Staging is vital in the approach to lung cancer since it offers both prognostic information and a guide for treatment decisions. A unified and universally accepted staging system is also essential to standardize nomenclature for international comparisons of clinical trials. The TNM system provides a detailed description of cancers based on the extent of the anatomic involvement, by defining the primary tumor (T), the regional lymph node involvement (N), and the presence of distant metastases (M) [2]. In this chapter, we will review the newly adopted 7th edition of the International Association for the Study of Lung Cancer (IASLC) TNM staging system, and we will discuss its clinical implications, strengths, and limitations.

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History

The tumor–node–metastases (TNM) staging system currently applied to almost all solid malignancies was coined by Dr. Pierre Denoix in the 1940s [3]. As chair of the Union Internationale Contre le Cancer (UICC) staging committee, he coordinated the standardization of TNM staging for 23 solid organ cancers [4]. The first proposal for lung cancer TNM staging was developed by Dr. Clifton Mountain and adopted by the American Joint Committee on Cancer (AJCC) and the UICC in 1973 and 1974, respectively [5]. This original system was based on outcome data from a single institution (M.D. Anderson Cancer Center, Houston, TX, USA) and a limited number of patients (2,155; 1,712 with non-small cell lung cancer (NSCLC)). Three subsequent revisions occurred in the following 25 years, all based on Dr. Mountain's database which continued to grow up to 5,319 cases by the time of the last revision in 1997 [6]. Some of the limitations of this system such as the small number of patients—particularly for subgroup analysis—the single institution origin, and lack of external validation prompted the IASLC to create the IASLC Staging Committee. This group composed of international members of all disciplines involved in lung cancer was set to develop and analyze a more powerful, current, and universal database of patients with lung cancer in order to review its staging. An unrestricted grant from Eli Lilly helped establish the database

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(the company had no role in data collection or analysis), which was created in collaboration with the CRAB (Cancer Research and Biostatistics Office, Seattle, Washington). Subcommittees were formed to retrieve and analyze data on T, N, and M descriptors, prognostic factors, nodal mapping, bronchopulmonary carcinoid tumor, and small-cell lung cancer (SCLC) [7]. The IASCL recommendations for the 7th TNM staging system were published in a series of articles in the *Journal of Thoracic Oncology* in 2007–2009 [8–18]. While the 6th Edition of the AJCC and UICC lung cancer TNM staging system published in 2002 was mainly a review of Dr. Mountain's work, the 7th edition, adopted in January 2010, was based on a truly international database of patients treated by all modalities, with rigorous analysis and validation [19].

Data Source and Methodology

Data on staging and outcome from 46 preestablished databases in 19 countries was utilized. Data belonged to patients who had been treated between the years 1990 and 2000 and from three major types of databases: series (40%), clinical trials (30%), and registries (30%). The origin of the data was from Europe (58%), North America (21%), Asia (14%), and Australia (7%) [8]. 100,869 cases were submitted, with 81,015 meeting inclusion criteria and accepted for analysis. The inclusion criteria were new lung cancer diagnosis (not recurrent cancer), adequate follow-up for survival analysis, histological subtyping, and complete clinical (cTNM) and/or pathological (pTNM) staging [20]. A total of 67,725 NSCLC and 13,290 SCLC were included, and all treatment modalities were represented (surgery, 36%; multimodality treatment, 23%; chemotherapy only, 21%; radiotherapy only, 11%; and best supportive care or no treatment, 9%) [7, 8, 20]. The NSCLC study population included 53,640 clinically staged cases (79.2%), 33,933 pathologically staged (50.1%), and 20,006 both clinically and pathologically staged (29.5%). Ninety-five percent of NSCLC cases were followed until death or at least 2 years and 88% until death or at least 5 years [8].

The major determinant for development of subgroups of T, N, and M descriptors as well as for stage grouping was overall survival. The latter was calculated by Kaplan–Meier method and measured from the date of entry for clinically staged patients (date of diagnosis for registries, date of registration for protocols) and date of surgery for pathologically staged patients to the date of death or last contact. Both internal and external validations were performed. For internal validation, results of interest among types of databases (surgical series vs. clinical trials vs. registries) and among different geographical regions were compared. For external validation, cases of NSCLC from the Surveillance, Epidemiology, and End Results Program (SEER) database from 1998 to 2000 were utilized [21]. Cox proportional hazards regression was used to calculate hazard ratios between adjacent groups and to assess the prognostic value of the proposed stage grouping in both the test set and the external validation data [8].

Modifications in T Descriptors

The analysis included 18,018 cases with no nodal or distant metastases and 180 cases whose disease was previously categorized as M1 due to ipsilateral nodule in a different lobe. 5,760 were clinically staged (c) and 15,234 were pathologically staged (p). Log-rank statistics were derived from hypothetical size cut points, and the highest log-rank statistic was used to select the optimum cut point. Tumor size, additional tumor nodules, and pleural dissemination were evaluated. Unfortunately, there was insufficient number of patients to investigate "non-size" T descriptors such as visceral pleura invasion, central location within lobar or main stem bronchi, partial or complete atelectasis, and direct invasion of particular structures. These traditional criteria were retained, but their true prognostic value deserves further study.

Tumor Size

Optimal survival differences were identified for patients whose disease was pathologically staged at cut points 2, 3, 5, and 7 cm—hence, the creation of new subgroups (see Table 19.1): T1a (≤2 cm; 77% 5-year survival rate), T1b (>2 cm to 3 cm; 71% 5-year survival rate), T2a (>3 cm to 5 cm; 58% 5-year survival rate), T2b (>5 cm to 7 cm; 49% 5-year survival rate), and T3 (>7 cm; 35% 5-year survival rate). As evidenced from above, the size cut point of 3 cm was confirmed and retained to differentiate T1 from T2 tumors, but these are now further subdivided into T1a/b and T2a/b. On the other hand, tumors greater than 7 cm in size (previously T2c by 6th TNM) are now upstaged to T3, since their survival was comparable to other T3 definitions (i.e., $T3_{Inv}$, invasion). Among clinically staged patients, survival differences between T1a, T1b, and T2a were not consistently statistically significant, probably due to the more limited number of patients with available data [7, 10].

Additional Ipsilateral Tumor Nodules

The prognosis of patients with additional tumor nodules in the same lobe of the primary tumor or in a different lobe of the ipsilateral lung was also investigated. These nodules were considered synchronous primaries only if they had different histology or if they were clearly defined as synchronous in the database. Patients with additional satellite nodules in the same lobe of the primary tumor had 28% 5-year survival rate, which was similar to that of other T3 tumors (i.e., $T3_{Inv}$, 31% 5-year survival) and better than that of T4 tumors (i.e., $T4_{Inv}$, 22% 5-year survival). Hence, they were downstaged from T4 (6th TNM) to $T3_{Satell}$. Patients with additional tumor nodules in a different lobe of the ipsilateral lung had a 22% 5-year survival rate, not different from that of patients with $T4_{Inv}$ (22% 5-year survival), and better than that of patients with pleural dissemination or distant metastases. Thus, these patients were downstaged from M1 (6th TNM) to $T4_{Ipsi\ Nod}$ (ipsilateral nodule) (see Table 19.1) [7, 10].

Pleural Dissemination

While pathological data did not show significant survival differences between $T4_{Inv}$ and T4 pleural dissemination (found at surgery), comparison of clinical staging for this descriptor seems more appropriate since the clinical finding of pleural disease contraindicates surgery. Additionally, using clinically staged patients also provided a much larger of cases for analysis. Clinically staged patients with pleural dissemination clearly have statistically significant worse survival than patients with $T4_{Inv}$ and than patients with $T4_{Ipsi\ Nod}$, but slightly better than patients with distant metastases (now referred to as M1b). Median survival times were 8 months for pleural dissemination, 13 months for $T4_{Inv}$, 18 months for $T4_{Ipsi\ Nod}$, and 6 months for distant metastases. Hence, pleural or pericardial dissemination (either present as malignant effusion or nodules) was upstaged from T4 (6th TNM) to M1a (see Table 19.1) [7, 10].

Summary of T Changes

- T1 is divided into T1a (≤2 cm) and T1b (>2–3 cm).
- T2 is divided into T2a (>3–5 cm) and T2b (>5–7 cm).
- Tumors >7 cm are upstaged from T2 to T3.
- Ipsilateral same lobe nodule is downstaged from T4 to $T3_{Satell.}$
- Ipsilateral different lobe nodule is downstaged from M1 to $T4_{Ipsi\ Nod.}$
- Pleural or pericardial dissemination is upstaged from T4 to M1a.

Modifications in N Descriptors

Of 67,725 patients with NSCLC who met the initial screening requirements, 38,265 were clinically free of distant metastases and had clinical N staging (cN) reported, and 28,371 were surgically managed and had pathologic N staging (pN) reported. cN staging included all imaging and tests done including data from mediastinoscopy,

Table 19.1 Definitions for descriptors of the 7th edition TNM classification for lung cancer

	Subgroup	Definition
T (tumor)		
T0		No primary tumor
T1		Tumor ≤3 cm, surrounded by lung or visceral pleura, not more central than the lobar bronchus
	T1a [a]	≤2 cm
	T1b [a]	>2 cm and ≤3 cm
T2		>3 cm and ≤7 cm or with any of the following: visceral pleura invasion, involvement of main bronchi but ≥2 cm distal to main carina, atelectasis/obstructive pneumonitis not involving the entire lung
	T2a [a]	>3 cm and ≤5 cm
	T2b [a]	>5 cm and ≤7 cm
T3		
	$T3_{>7}$ [a]	>7 cm
	$T3_{Inv}$	Tumor directly invading chest wall, diaphragm, phrenic nerve, mediastinal pleura, or parietal pericardium
	$T3_{Centr}$	Tumor in main bronchus <2 cm from main carina or complete lung atelectasis/obstructive pneumonitis
	$T3_{Satell}$ [a]	Separate tumor nodule/s in the same lobe as primary tumor
T4		
	$T4_{Inv}$	Tumor of any size with invasion of the heart, great vessels, trachea, carina, esophagus, vertebral body, or recurrent laryngeal nerve
	$T4_{Ipsi\ Nod}$ [a]	Separate tumor nodule/s in different lobe, ipsilateral to primary tumor
N (regional LN)		
N0		No regional metastases
N1		Metastases to ipsilateral peribronchial, perihilar, or intrapulmonary LN
N2		Metastases to subcarinal or ipsilateral mediastinal LN
N3		Metastases to contralateral hilar or mediastinal LN or involvement of any scalene or supraclavicular LN
M (metastases)		
M0		No distant metastases
M1		
	$M1a_{Contr\ Nod}$ [a]	Separate tumor nodule/s in contralateral lung
	$M1a_{Pl\ Dissem}$ [a]	Malignant pleural or pericardial effusion
	M1b [a]	Distant metastases
Special situations		
TX, NX		T or N status cannot be assessed
T_{is}		In situ tumor
$T1_{ss}$		Superficial spreading tumor of any size, confined to the wall of the trachea or main bronchi

LN lymph node, *Inv* invasion, *Centr* central, *Satell* satellite, *Ipsi Nod* ipsilateral nodule/s, *Contr Nod* contralateral nodule/s, *Pl Dissem* pleural dissemination

[a]New subgroups added in the 7th TNM

but not from thoracotomy. Positron emission tomography (PET) was not widely used during the study period, so PET data were not available. Survival analysis in relation to subsets of pN1 and pN2 stages was reported in 2,876 patients with R0 (microscopically complete) resections who had no induction chemotherapy. The committee explored whether subdivision by anatomical location within same N stage, by the presence of "skip metastases," or by the number of involved lymph node stations had any influence on survival. While analyzing the N descriptors, discrepancies

between the Naruke lymph node map adopted by the Japan Lung Cancer Society and the Mountain–Dressler modification of the American Thoracic Society (MD-ATS) map utilized by all other countries came to float [6, 22]. Since these discrepancies can hamper data analysis, the IASLC proposed a new nodal map [13].

Nodal Staging

Clear differences in overall survival were found for both clinically and pathologically staged cases, supporting the traditional classification of N0, N1, N2, and N3, without changes from the 6th TNM (5-year survival rates were 42%/56% for cN0/pN0, 29%/38% for cN1/pN1, 16%/22% for cN2/pN2, and 7%/6% for cN3/pN3). No differences in survival were found for patients with different anatomic location of their N1 lymph nodes (LN) (peribronchial [12–14] vs. interlobar [11] vs. hilar [10]) or in the number of LN stations involved. However, there was a trend towards worse survival as the number of positive stations increased. "Skip metastases" (N2 disease in the absence of N1 disease) were analyzed, particularly for upper lobe tumors (where these are more frequent), and improved survival was found for left upper lobe tumors and AP zone LN skip metastases, but not for right upper lobe tumors with 4R metastases. The analysis on the N descriptor was thought to be partly hampered by differences between the Naruke and the MD-ATS nodal maps, as described below [11, 13].

Nodal Map

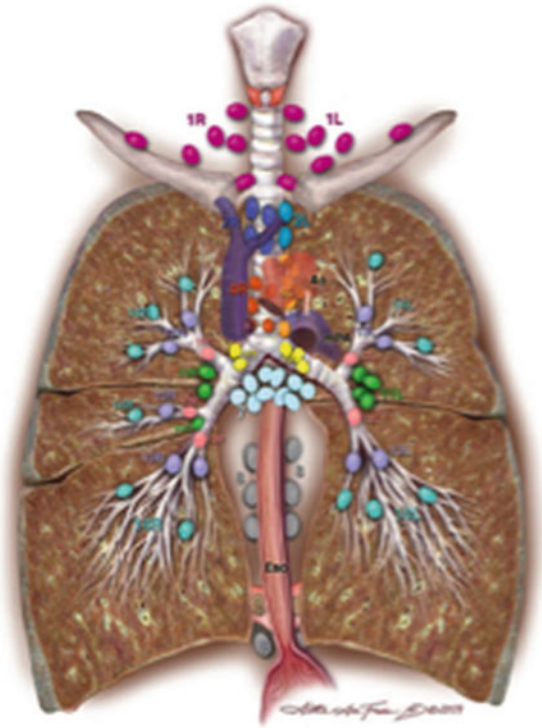
The discrepancy between the Naruke and the MD-ATS map that affects staging the most is one of the LNs in the subcarinal space along the inferior border of the right main stem bronchus, which are labeled station 10R (N1) by the Naruke map and station 7 (N2) by the MD-ATS map. Since data were analyzed retrospectively, there were no means to reconcile this significant difference. Smaller discrepancies between the two systems included station 1 in the Naruke map, corresponding to stations 1 and 2 in the MD-ATS map, and stations 2, 3, and 4R in the Naruke map, corresponding to 4R in the MD-ATS map. The IASLC Staging Project proposed a new nodal map to reconcile these differences (Fig. 19.1). The newly proposed map provides concise anatomic descriptions of upper and lower boundaries for all lymph node stations. The pleural reflection no longer serves as the border between stations 4 and 10, and this boundary is now defined by vascular landmarks which can be more readily identified during bronchoscopy or surgery (i.e., lower rim of the azygos vein on the right and the upper rim of the pulmonary artery on the left). The arbitrary division along the midline of the trachea created by the ATS was eliminated, and the new boundary between right- and left-sided stations 2 and 4 was moved to the left lateral wall of the trachea (following the lymphatic drainage system). Station 3 in the Naruke map (LN anterior to the trachea on the midline) which corresponded to stations 2R and 4R in the MD-ATS map was eliminated, and the MD-ATS prevascular (3a) and retrotracheal (3b) nomenclatures were retained. The subcarinal group defined as station 7 in the MD-ATS (but both 10R and 7 in the Naruke map) was retained, but with precise definition of its borders. Individual LN stations were grouped into "zones," not for nomenclature purposes, but for future exploratory analysis of overall survival (see Fig. 19.1) [11, 13].

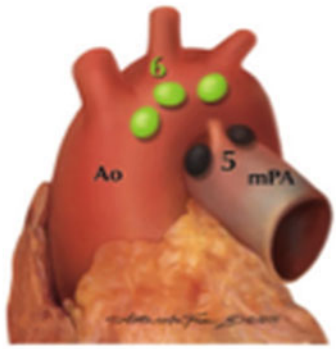
Summary of N Changes

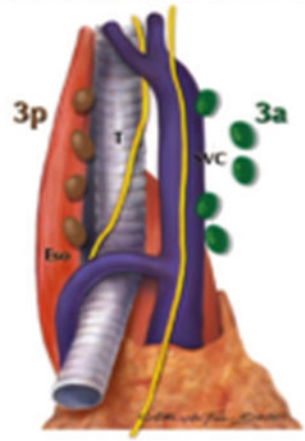
- No changes were made in N descriptors, retaining the traditional N0, N1, N2, and N3.
- A new nodal map was proposed to reconcile differences in nomenclature between the existing maps and to provide precise anatomic definitions for all LN stations.

Modifications in M Descriptors

The M descriptors committee analyzed not only patients with distant metastases (traditional M1 disease by 6th TNM) but also patients with







Supraclavicular zone
1 Low cervical, supraclavicular, and sternal notch nodes

SUPERIOR MEDIASTINAL NODES

Upper zone
2R Upper Paratracheal (right)
2L Upper Paratracheal (left)
3a Prevascular
3p Retrotracheal
4R Lower Paratracheal (right)
4L Lower Paratracheal (left)

AORTIC NODES

AP zone
5 Subaortic
6 Para-aortic (ascending aorta or phrenic)

INFERIOR MEDIASTINAL NODES

Subcarinal zone
7 Subcarinal

Lower zone
8 Paraesophageal (below carina)
9 Pulmonary ligament

N1 NODES

Hilar/Interlobar zone
10 Hilar
11 Interlobar

Peripheral zone
12 Lobar
13 Segmental
14 Subsegmental

Fig. 19.1 IASLC proposed lymph node map reproduced *with permission from* Rusch VW et al. The IASLC lung cancer staging project: a proposal for a new international lymph node map in the forthcoming 7th edition of the TNM classification for lung cancer. J Thorac Oncol 2009;4(5): 568–77

Table 19.2 Stage grouping of the 7th edition TNM classification for lung cancer

Descriptor	N0	N1	N2	N3
T1a	IA	IIA	IIIA	IIIB
T1b	IA	IIA	IIIA	IIIB
T2a	IB	▼ IIA (IIB)	IIIA	IIIB
T2b	▲ IIA (IB)	IIB	IIIA	IIIB
$T3_{>7}$	▲ IIB (IB)	▲ IIIA (IIB)	IIIA	IIIB
$T3_{Inv}$	IIB	IIIA	IIIA	IIIB
$T3_{Satell}$	▼ IIB (IIIB)	▼ IIIA (IIIB)	▼ IIIA (IIIB)	IIIB
$T4_{Inv}$	▼ IIIA (IIIB)	▼ IIIA (IIIB)	IIIB	IIIB
$T4_{Ipsi\ Nod}$	▼ IIIA (IV)	▼ IIIA (IV)	▼ IIIB (IV)	▼ IIIB (IV)
$M1a_{Contr\ Nod}$	IV	IV	IV	IV
$M1a_{Pl\ Dissem}$	▲ IV (IIIB)	▲ IV (IIIB)	▲ IV (IIIB)	▲ IV (IIIB)
M1b	IV	IV	IV	IV

▲ upstaged, ▼ downstaged, ( ) previous stage
Inv invasion, *Satell* satellite, *Ipsi Nod* ipsilateral nodule/s, *Contr Nod* contralateral nodule/s, *Pl Dissem* pleural dissemination

ipsilateral "different" lobe nodules and contralateral lung nodules, as well as patients with pleural dissemination as it was described above. 5,592 clinically staged T4 and M1 were included, followed by an additional 1,004 cases included in a secondary analysis of "best stage"—defined as pathological stage when available and clinical otherwise. Of a total of 6,596 patients included, 1,216 had been treated surgically and 5,380 non-surgically. In accordance to recommendations from the T committee, the analyses excluded from T4 category those patients with ipsilateral same lobe nodules (now referred to as $T3_{Satell}$).

As mentioned above, overall survival for pleural dissemination was shorter than that of other T4 and closer to that of metastatic disease, so pleural or pericardial disease was upstaged from T4 (6th TNM) to M1a. The median survival for patients with additional nodule/s in the contralateral lung was 10 months. It was not possible to differentiate between single or multiple contralateral nodules. Although there was a statistically significant difference in survival between patients with contralateral lung nodules and those with pleural dissemination ($P=0.0235$), the two groups were closer to each other than to the proposed T4 or to patients with distant metastasis ($P<0.0001$ for both comparisons). Accordingly, the 7th TNM subdivided the M stage into M1a for pleural/pericardial dissemination and contralateral lung nodules and M1b for distant metastases. The median survival for patients with distant metastases was 6 months, with 22% surviving at 1 year [9].

Summary of M Changes

- Pleural or pericardial dissemination is upstaged from T4 to M1a.
- Contralateral lung tumor nodule/s is reclassified as M1a.
- Distant metastases are reclassified as M1b.

Modifications in Stage Groupings

Despite the creation of new T and M descriptors, no new subcategories were added to the current stage groups. The staging grouping committee chose to allow descriptors to move to a new category with other descriptors with similar prognosis, sacrificing backward compatibility with 6th TNM. Different combinations of T, N, and M descriptors were analyzed with hazard rations (HR) calculated using T1a N0 as the reference. Groups with statistically similar HR were then assigned to the same stage. There were a total of 17 stage migrations, where ten subsets were downstaged and seven were upstaged (Table 19.2). Survival for the stage grouping

Table 19.3 Survival by clinical and pathologic stage for new stage grouping

	Clinical staging		Pathological staging	
Stage	MST (months)	5-year survival (%)	MST (months)	5-year survival (%)
IA	60	50	119	73
IB	43	43	81	58
IIA	34	36	49	46
IIB	18	25	31	36
IIIA	14	19	22	24
IIIB	10	7	13	9
IV	6	2	17	13

MST median survival time. Source: [17]

based on clinical and pathological staging is summarized in Table 19.3. The new stage grouping provided a better delineation of median and 5-year survival between stages IB and IIA, and IIA and IIB, compared with 6th TNM. Of note, survival in stage IV was paradoxically better than that of stage IIIB [17].

Small-Cell Lung Cancer (SCLC) and Bronchopulmonary Carcinoid Tumors

SCLC represents approximately 15% of all lung cancers. Since SCLC is rarely amenable for surgery, the use of TNM staging for SCLC is seldom utilized, and for simplicity, disease is either referred to as "limited" (LD) or "extensive" (ED). The former corresponds to disease confined to one hemithorax with or without ipsilateral LN or pleural effusion and the latter to all other cases. This broad classification can potentially hide patients who would benefit from more aggressive therapies [20]. The IASLC evaluated the applicability of the new TNM descriptors to SCLC. 8,088 patients had complete cTNM descriptors (3,430 cM0 and 4,530 cM1), and 349 had full pTNM staging. There was a poor agreement (58%) between clinical and pathological staging (when both were performed), particularly at the nodal stage, which emphasizes the need for mediastinal sampling in early cases amenable for surgery (keeping in mind that PET was uncommon when the data was retrieved). The results of the analyses performed by this IASLC subcommittee confirmed that TNM staging closely correlates with survival of SCLC by stage, identifies patients with different prognosis, and can be applied to surgically managed patients [16, 18].

Bronchopulmonary carcinoid tumors were not encompassed by the 6th TNM. The IASLC analyzed their database with 513 completely staged carcinoids as well as the SEER database (utilized for external validation as explained above) with 1,619 cases. Stage I (7th TNM) was the most common in both databases (IASLC 82%, SEER 78%). Data on typical vs. atypical histology was rarely available. Both T and N status were a statistical significant predictor of survival in both databases, and M status was only analyzed and significant in SEER database, since most IASLC patients were M0. Patients with multiple same lobe nodules had a 5-year survival of 100%, which should prompt reevaluation of stage status (IIB) in future analyses. The IASLC recommends applying the TNM staging to bronchopulmonary carcinoid tumors [15].

Discussion

The 7th TNM staging system represents a major step forward in lung cancer care with a clear progression from previous versions of the staging system. It is the result of an enormous effort in the creation and extensive analysis of a large truly international database, with internal and external results validation. The 7th TNM may be considered to have successfully addressed the needs of the UICC and AJCC of establishing a TNM system that more accurately reflects the survival and

prognosis of patients with different stages of lung cancer. In addition, it has met the purpose of creating a prominent common nomenclature needed for the comparison of international trials. Of course, with the development of new descriptors, the new TNM system has inevitably gained higher complexity. We will briefly discuss some limitations and clinical implications of the methodology and different descriptors.

Methodology

One of the major limitations was the retrospective collection of data from sources which were not actually designed to collect data for the development of a staging system. Hence, data on certain descriptors was abundant, while on others (such as non-size T descriptors) it was scant and insufficient for analysis. Due to the international nature of the study, and the constraints in personnel and funding, the IASLC could not perform its own data audit and had to rely on the integrity of the data as supplied [20].

Of note, although the database was international in nature, patients from Africa and South America or from countries like China or Russia Central were not included or largely underrepresented.

As we mentioned before, the migration of descriptors and stages has sacrificed the backward compatibility with previous TNM staging. This was, unfortunately, inevitable, since the only alternative was to create new descriptors and stages, which would have made the system of limited clinical applicability. This backward incompatibility makes it difficult to extrapolate established treatment algorithms to the new stage groupings. For example, in a patient with $T4_{\text{Ipsi Nod}}$ N0-1M0, which was previously considered stage IV (M1) and is now considered IIIA, it would be tempting to assume that he/she would benefit from surgery. However, a new treatment algorithm should be studied based on the new stages in a clinical trial [23].

Although many people might expect a staging system to be able to allocate patients to different treatment strategies, this would only be an oversimplification of lung cancer management. The TNM staging system has a limited capacity to define prognosis with a particular treatment and it was not intended to do so. Optimal treatment can only be defined with clinical trials. Suitability for a particular therapy is based on the interaction of different factors: patient-related (i.e., performance status), tumor-related, and therapy-related [7].

T Descriptors

The 7th TNM has clearly reinforced the crucial impact that tumor size has on prognosis, with well-defined and validated new cut points. However, no specific guideline is offered for the measurement of tumors with computed tomography (CT). Whether lung or mediastinal windows should be used is not clear, and it might be relevant for semisolid, cavitary, infiltrative lesions or ground-glass opacities (GGO). Since in pathology specimens the solid component of a tumor (and not the peripheral lepidic one) is more strongly linked with prognosis, we might extrapolate that to our imaging techniques [24]. The longest dimension of the tumor should be used, making multiplanar CT reconstruction a potentially more accurate way of measuring. Difficulties in tumor measuring may also arise in cases of atelectasis, post-obstructive pneumonia, or with central masses invading the hilum or lymph node stations. The IASLC did not count with enough data to address any of these issues. For pathologic measurement, the unfixed specimen should be used, since fixation is known to shrink the specimen size by about 20% [25].

Certain aspects of the invasion of the mediastinum may also require further clarification in the future. For instance, while direct invasion of mediastinal pleura and invasion of parietal pericardium are both considered T3, invasion of mediastinal fat is considered T4. However, there is normally fat between the pleura and pericardium, making this distinction confusing.

Data on "non-size" T descriptors such as the distance from the carina or the presence of partial or complete lung atelectasis was scant. Although these descriptors were not evaluated

by the IASLC, they were still retained into the 7th TNM, which might be debatable. Of note, there is significant data on retrospective studies that did not support these descriptors as relevant prognostic factors [26].

Visceral pleural invasion (VPI) increases the T factor from T1 to T2, upstaging a tumor from IA to IB, even if it is <3 cm in diameter. This becomes relevant since adjuvant chemotherapy is sometimes considered after resection of stages IB NSCLC, but not IA [27]. The IASLC has proposed a new histological classification to describe the extent of pleural invasion: PL0 (T1), as lack of pleural invasion beyond the elastic layer; PL1 (T2), as invasion beyond the elastic layer; PL2 (T2), invasion to the surface of the visceral pleura; and PL3 (T3), invasion of the parietal pleura. However, they were not able to define prognosis associated to the different extents of pleural involvement due to insufficient data [14].

Descriptors for additional lung nodules underwent major modifications, but many clinicians are still unclear of when to apply them. The IASLC was not very strict with their inclusion criteria in this category. Synchronous primary lung cancers (SPLC) were meant to be excluded, but its definition was not quite rigorous and, instead, it was left to the "judgment" of the data sources. Proposing histology as major factor to define SPLC brings is also debatable. First of all, most SPLC will have the same histology type (which would be logical since the etiology of both tumors is likely the same) [28]. Additionally, identification of histologic subtype is erroneous in about 30% of the cases, and final pathologic diagnosis requires resection. Hence, a preoperative definition should be sought since it is essential for clinical management [24]. Tumors studied by the IASLC in the analysis of additional nodules likely included various types (SPLC, solid nodules, GGO), which were also subject to different therapies, leading to selection bias. The difference in survival between $T3_{Satell}$, $T4_{Ipsi\ Nod}$, and contralateral nodules (M1a) could be in part explained by the fact that the first two underwent surgery in 88% and 96% of the cases, respectively, and cases with contralateral nodules were almost never resected. Also, the IASLC database was not able to differentiate between one or multiple additional nodules [9, 10].

N Descriptors

No major changes resulted from the analyses of the N descriptors. Among patients undergoing resection without induction therapy, three distinct prognostic groups were identified by the IASLC: single-zone N1, multiple-zone N1 or single-zone N2, and multiple-zone N2 disease. Unfortunately, the number of patients available in each subset was too small to yield statistically valid analyses and modify the N descriptors. Ruffini et al. independently analyzed this proposed stratification of the N descriptors in their own single institution database with excellent results [29]. Their population consisted of 1,150 patients with N0 disease, 289 patients with single N1 nodes, 200 patients with either multiple N1 or single N2, and 67 patients with multiple N2 disease. The 5-year survival rates were 55%, 35%, 25%, and 8%, respectively. In view of these results, and those of the IASLC, prospective evaluation of the impact of the number of LN involved in addition to their anatomic location seems only fair.

The IASLC staging manual requires that three mediastinal and three N1 lymph nodes or stations be sampled. What remains unclear is whether they refer to the number of individual nodes or stations, which can create a significant difference in staging. Unfortunately, to date, there is no validated data to support a specific number of LN or stations to be sampled, and systematic intraoperative node assessment is recommended by clinical guidelines [24, 30, 31].

M Descriptors

Patients with extrathoracic metastases rarely undergo surgery and they are typically staged clinically. The type of tests used to stage these patients differed considerably from different sources, and observations such as the prognostic implications of single vs. multiple distant metastases could not be reliably obtained [9].

The period examined by the IASLC was prior to the widespread use of PET and PET–CT, when CT was the predominant modality used for staging. PET has since then adopted a key role in staging of NSCLC in surgical candidates, with pooled sensitivity and specificity of 74% and 85%, respectively [23, 32]. In fact, it has shown to prevent unnecessary thoracotomies in 20% of patients by detecting intra- or extrathoracic metastases [33, 34]. Unfortunately, its role in staging could not be evaluated by the IASLC due to the chosen study period as mentioned above.

Summary

The UICC 7th edition of the TNM classification system is undoubtedly a major improvement in our scientific basis for the staging of lung cancer, supported by a large international database and subject to thorough internal and external validation process. Some limitations are deeply related to the retrospective nature of the data collection and will hopefully be overcome with the new prospective data set developed by the IASLC to inform changes to the 8th TNM. Although a valuable prognostic tool, a TNM system relies only on anatomic extent, leaving aside prognostic factors related to the patients, to the tumor behavior, and to the environment, which can influence prognosis. As we place it in practice, more ambiguities will come up to light, and it is paramount to gather, scrutinize, and share this data to better comprehend the limitations of this TNM system and to rise above them.

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Mediastinoscopy and Its Variants

20

Ramón Rami-Porta and Sergi Call

Introduction and Definition of the Procedure

Mediastinoscopy is a surgical procedure that allows the inspection and the palpation of the upper mediastinum as well as the taking of biopsies of lymph nodes, tumours or any other tissue within the range of the exploration. For lung cancer staging, the range of exploration includes the cervical lymph nodes of the sternal notch, the lymph nodes along the trachea and both main bronchi, that is, the superior and inferior, left and right, paratracheal lymph nodes, the subcarinal nodes and the right and left hilar lymph nodes, according to the International Association for the Study of Lung Cancer (IASLC) lymph node map [1]. Inspection and palpation of the upper mediastinum are essential to identify the lymph nodes, see their aspect and feel their consistency and degree of attachment to mediastinal structures, as well as to differentiate between mere contact and tumour invasion of the mediastinum. The removal or the taking of biopsies of lymph nodes are performed under direct vision, and these specimens allow the pathologist to examine the status of the nodal capsule and the involvement of the extranodal tissues that are criteria of incomplete resection [2].

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History and Historical Perspective

When Eric Carlens described the technical details of mediastinoscopy and reported six exemplary cases in 1959, he had already performed more than 100 procedures without complications [3]. Mediastinoscopy was quickly spread in Europe as the books by Tauno Palva [4] and Otto Jepsen [5] show. The main advantage of mediastinoscopy was that it allowed the diagnosis of intrathoracic diseases with no need to open the chest cavity. For lung cancer, diagnosis and staging was simultaneous in many cases. Tuberculosis, sarcoidosis, silicosis, vascular anomalies, mediastinal tumours and inflammation could also be diagnosed via this transcervical approach. Its systematic indication in the clinical staging before lung resection showed that those lung cancers with involved mediastinal lymph nodes identified at mediastinoscopy had worse prognosis than those with nodal disease identified at thoracotomy [6]. This gave a prognostic perspective to the procedure in addition to diagnosis and staging. With the introduction of computed tomography (CT) in clinical practice, the most common trend was to indicate mediastinoscopy when there were abnormal lymph nodes [7]. However, its systematic use, regardless of the size of the lymph

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nodes on CT scan, was favoured by some authors even for early stages [8]. The design of the video-mediastinoscope by Lerut in 1989 and of the two-bladed video-mediastinoscope by Linder and Dahan in 1992 increased the possibilities of the exploration for staging and therapeutic indications, leading to mediastinal lymphadenectomy and complex therapeutic procedures, such as closure of bronchopleural fistula and lobectomy through the transcervical approach [9–15].

Indications and Contraindications

For lung cancer staging, the present guidelines of the American College of Chest Physicians (ACCP) and of the European Society of Thoracic Surgeons (ESTS) recommend to pathologically confirm any mediastinal abnormality seen on the chest CT and positron emission tomography (PET) scans. This confirmation may be done either by endoscopic techniques, such as transbronchial needle aspiration (TBNA), endobronchial ultrasound-guided fine needle aspiration (EBUS-FNA) or oesophageal ultrasound-guided FNA (EUS-FNA). If these explorations are positive for cancer, the information may be adequate to start a multidisciplinary treatment protocol. However, if they are unavailable or are negative, a surgical technique is recommended to confirm their negative results, because their negative predictive value is too low to make further therapeutic decisions [16, 17]. The most common surgical technique is mediastinoscopy, but for staging purposes, mediastinotomy or thoracoscopy could be performed if the target lesion is within the range of these explorations. When CT and PET scans are negative, the ESTS still recommends mediastinoscopy in tumours with a clinical stage higher than T1N0M0, when the tumours are centrally located, when there are lymph nodes on the CT scan with a diameter greater than 1.6 cm and when the primary tumour has a low maximum standardised uptake value. In these circumstances, mediastinal nodal involvement may be present but be unapparent on radiographic or metabolic imaging [17].

The ESTS guidelines also recommend to pathologically confirm tumour response after induction therapy. As at initial staging, this can be done by endoscopic techniques, but if their results are negative, then a surgical procedure is recommended. Over the years, remediastinoscopy has proved to be a safe and reliable restaging method [18–23]. It is important to confirm or rule out persistent nodal disease after induction therapy because their persistence is an unfavourable prognostic factor and lung resection should be avoided because it does not add any survival benefit [21, 24, 25].

There are very few contraindications. Severe neck rigidity and large goitres are anatomic abnormalities that can prevent the correct insertion of the mediastinoscope, but they are extremely rare in lung cancer patients. Aortic aneurism is a contraindication, because the aortic arch is compressed by the mediastinoscope when it is inserted in front of the trachea and may be injured. Abnormal coagulation tests are a relative contraindication. As in any other intervention, they should be corrected before the operation and the operation rescheduled when they are normalised. In the past, superior vena cava obstruction, a previous mediastinoscopy or a previous mediastinal operation by median sternotomy, tracheostomy or total laryngectomy were considered contraindications, but experience has proved that mediastinoscopy can be performed safely when other less invasive procedures have not established a diagnosis [26–29].

Description of the Equipment Needed

General

For the incision and initial dissection, the following instruments are needed: standard surgical knife, dissection forceps, Mayo and Metzenbaum scissors and a right-angle dissector. Silk 2–0 sutures may be necessary to ligate small veins. Absorbable 2–0 and 3–0 sutures are used to close the incision in two layers.

Specific

There are two types of scopes: the conventional ones and the video-mediastinoscopes that, since the late 1980s, are progressively replacing the former. Mediastinoscopes are in the right-angle shape, with the vertical arm as handle and the horizontal arm, in the shape of a truncated cone, as the scope proper. The conventional mediastinoscopes are in a single piece, and the video-mediastinoscopes are made either in a single piece or in two spreadable blades to widen the operative field. Video-mediastinoscopes are connected to a camera, and the exploration is seen on a television monitor. The equipment is completed with a light source and a recorder to register the operations.

The dissection–suction–coagulation device is fundamental to dissect and identify the lymph nodes from the peritracheal fatty tissue. Suction keeps the operative field clean at all times and coagulation controls bleeding from small veins, lymph nodes or fatty tissue.

A glass tube connected to a needle on one side and to suction on the other is used for puncture test when the nature of the structure to be biopsied is not clear. This is more useful when the conventional mediastinoscope is used. Mediastinal structures are much better seen with the video-mediastinoscope, and this makes the puncture test rarely necessary.

There are several types of biopsy forceps. Some are spherical and others, oval, and they come in different sizes.

There also are several types of graspers and ring forceps that allow the surgeon to hold the tissue with one hand and dissect with the other, while the assistant holds the mediastinoscope in place.

Endoscopic clips should be available in case clipping of the bronchial arteries is necessary. Although not strictly necessary, the new haemostatic/cutting devices based on ultrasound technology, such as the harmonic scalpel, may reduce the risk of bleeding and are easy to use especially with the two-bladed video-mediastinoscope that allows a larger operative field for the insertion of these devices.

Figure 20.1 shows the basic instruments for mediastinoscopy and Fig. 20.2, the endoscopy tower and the general view of the operative field.

Application of the Technique

The surgical technique is essentially the same Carlens described in 1959, but several variants have been developed to widen the range of the exploration and to increase its sensitivity.

Preoperative Care

Patients planned to undergo mediastinoscopy should have a complete history and physical examination. It is important to know if the patient had previous interventions in the neck and in the mediastinum, i.e. cervicotomy for goitre or neck tumours and tracheostomy, laryngectomy or median sternotomy for mediastinal or heart diseases. These rarely contraindicate mediastinoscopy, but the surgeon should be aware of them. Neck flexibility should be checked, too, because it is important to properly insert the mediastinoscope. Complete blood count and biochemistry, as well as coagulation tests, should be available before the operation. For those patients with high or moderate risk for thromboembolism (patients with a mechanical heart valve, atrial fibrillation or venous thrombosis), bridging anticoagulation is recommended with therapeutic doses of subcutaneous low-molecular-weight heparin 5 days before the operation. Regarding the perioperative antiplatelet therapy, it is recommended to stop aspirin and clopidogrel 5–7 days prior to surgery and restart within 24 h after surgery, except for doses of 100 mg of aspirin that do not need to be stopped [30].

Chest X-rays, CT of the chest and PET scans are necessary to identify the target areas in the mediastinum and should be available at the time of the operation. Although mediastinoscopy should be as complete as possible in all cases, if the surgeon knows the location of the abnormal lymph nodes or the site where the tumour contacts

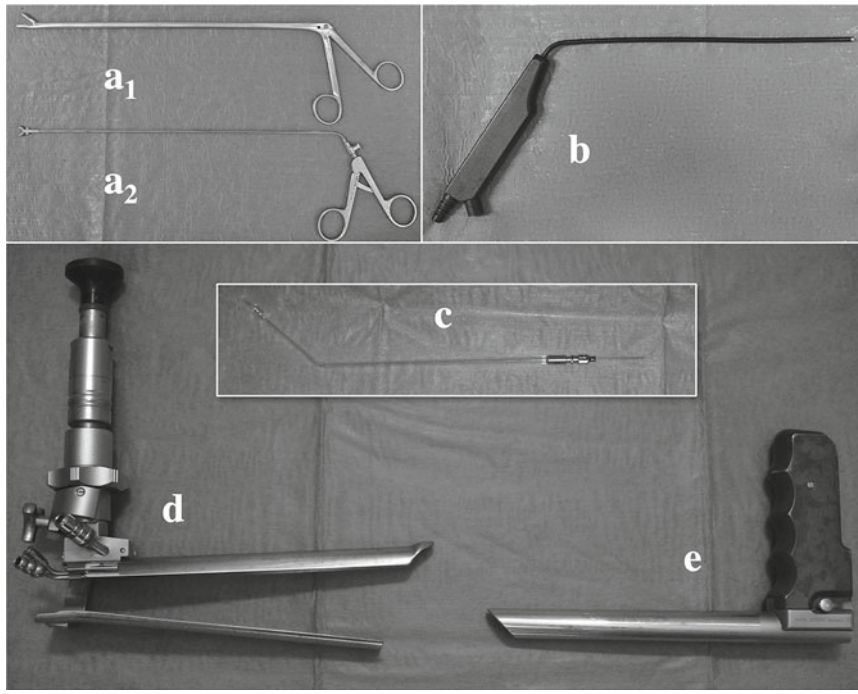

Fig. 20.1 Basic instruments set ($\mathbf{a}_1$) biopsy forceps with oval jaws, size 8 mm×16 mm. ($\mathbf{a}_2$) Biopsy forceps with spherical jaws, size 5 mm. (**b**) Dissection–suction–coagulation cannula. (**c**) Glass tube connected to a needle for puncture test. (**d**) Linder-Dahan two-bladed spreadable video-mediastinoscope. (**e**) Lerut video-mediastinoscope

the mediastinum, these areas are not likely to be missed. The patient should be seen by an anaesthesiologist to assess the risk associated with general anaesthesia and should be informed of the most frequent complications (left recurrent laryngeal nerve palsy, pneumothorax) and of the rare but potentially fatal ones (bleeding, tracheobronchial and oesophageal perforation), as well as of the potential need for blood transfusion. The patient is required to sign an informed consent form.

Patient's Position and Operative Field

Under general anaesthesia and oro-tracheal intubation, the patient is positioned in the supine decubitus. A double-lumen oro-tracheo-bronchial tube may be necessary if additional procedures are planned. For standard intercostal thoracoscopy or for mediastino-thoracoscopy, for which opening of the mediastinal pleura to reach the pleural space is required during mediastinoscopy, selective single-lung ventilation is needed to inspect the pleural space properly. The patient's shoulders are raised with a long sand cushion. This allows some hyperextension of the neck and exposure of a long segment of the intrathoracic trachea, especially in young patients. The patient's head is allowed to rest on a circular rubber pillow to prevent displacement during the operation. In addition to the EKG leads and the blood pressure cuff, a pulse metre is fixed in one right-hand finger to control the occlusion of the innominate artery that may occur during mediastinoscopy, when excessive pressure is exercised on the artery with the mediastinoscope against the anterior chest wall. Pressure is easily relieved by repositioning the mediastinoscope (Fig. 20.3).

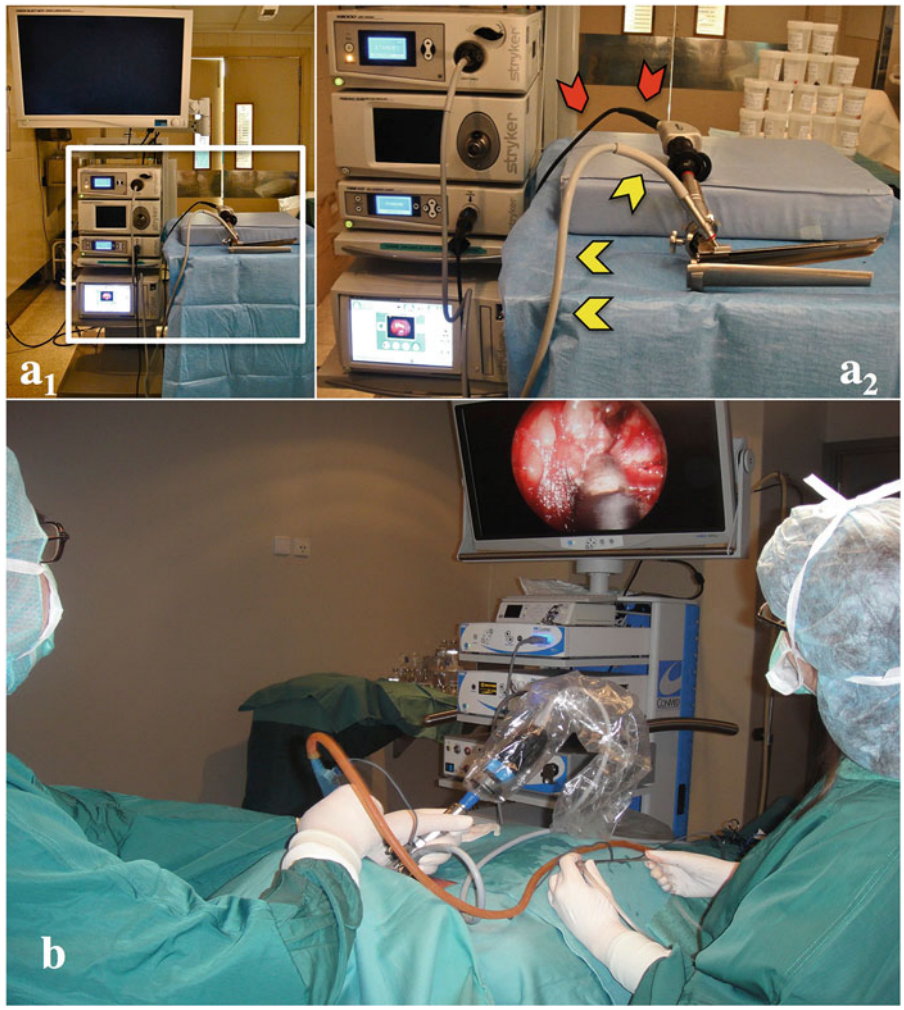

Fig. 20.2 Endoscopy tower: (**a**$_1$) components of the video-mediastinoscopy tower: monitor, image processor system, light source and recording device. The main components of the video image detection (*white box*) are expanded in (**a**$_2$): video-endoscope cable (*red arrows*) is connected to the image processor device. Fiberoptic cable (*yellow arrows*) is connected to the light source. (**b**) Operating room view. The monitor is located in front of the surgeon at the patient's feet and on the left. The surgeon sits comfortably on a chair at the patient's head

An operative field is prepared and draped from the mandible, cranially, to the xiphoid, caudally, and from nipple to nipple, laterally. An extra drape is positioned caudal to the sternal notch to cover the sternum. In case median sternotomy is needed during mediastinoscopy, this drape can be quickly removed.

The surgeon either stands or sits at the head of the patient, depending on the moment of the operation. The assistant and the scrub nurse stand on the right. The television monitor, if the procedure is performed with a video-mediastinoscope, is positioned at the patient's feet, slightly on the left.

Incision and Initial Dissection

A 5-cm collar incision is performed as close to the sternal notch as possible. After incising the skin, subcutaneous tissue and platysma, the avascular midline is incised and the paratracheal muscles are dissected and separated

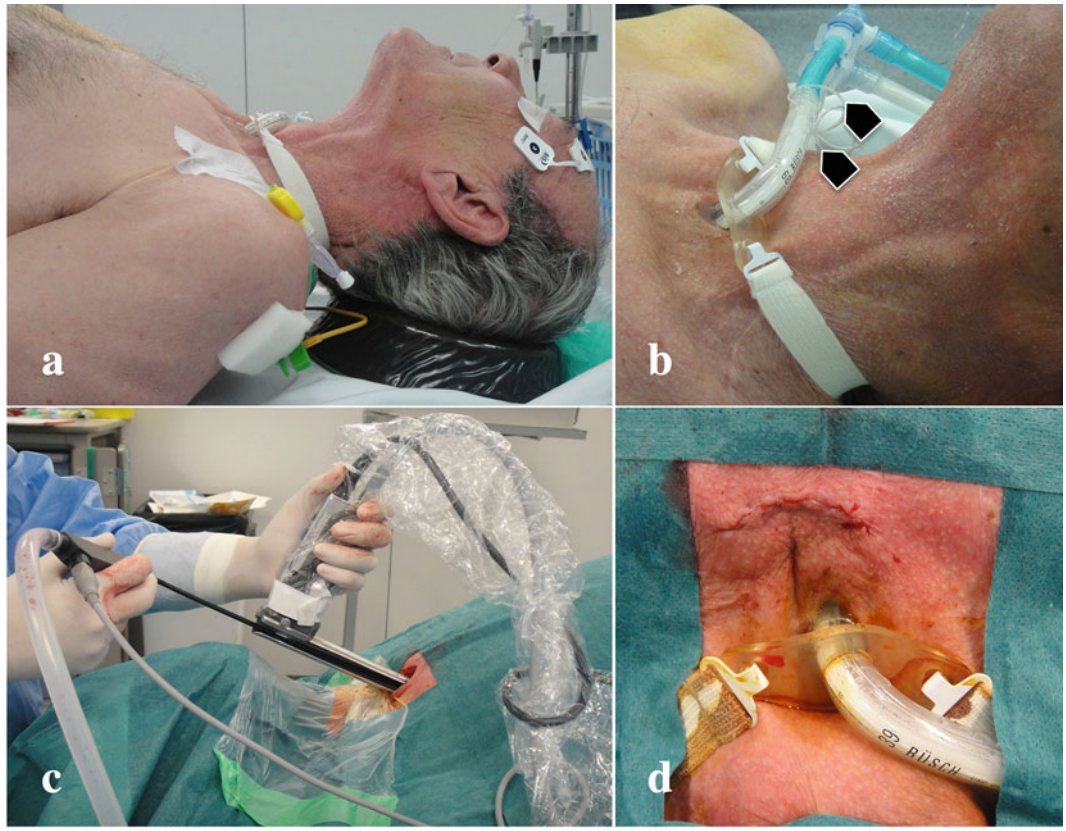

Fig. 20.3 Patient with tracheostomy, a classic contraindication of mediastinoscopy. The patient had a centrally located tumour, and mediastinoscopy was indicated to rule out mediastinal nodal disease. (**a**) Position of the patient for videomediastinoscopy. The neck is hyperextended, and the head rests on a circular pillow. (**b**) A double-lumen oro-tracheo-bronchial tube (*black arrows*) is inserted because a pleural inspection was planned. (**c**) Insertion of the videomediastinoscope. (**d**) View of the wound after closing the incision with absorbable intradermal suture

laterally. Although this is a low-neck incision, sometimes the thyroid gland can be found covering the trachea. By blunt dissection and finger retraction, the thyroid gland can be pulled cranially to allow the insertion of the mediastinoscope. The pretracheal fascia is intimately attached to the trachea. It is held with dissection forceps and incised with scissors. The fascia is further separated from the trachea by finger dissection: the index finger is inserted into the fascial opening and the finger is carried caudally tearing most of the length of the pretracheal fascia.

Palpation

Contrary to other endoscopies performed in virtual cavities, i.e. the pleural cavity (pleuroscopy), the peritoneum (laparoscopy) or a joint (arthroscopy), there is no mediastinal space as such. A space must be created in the upper mediastium by finger dissection. In addition to creating an adequate mediastinal space, palpation allows the surgeon to feel the size, consistency and degree of attachment of mediastinal lymph nodes, mediastinal tumours or bronchogenic carcinomas with direct mediastinal contact or invasion.

Palpation must be systematic, and the anatomical landmarks must be recognised. In the typical case, after inserting the distal phalange of the index finger, the pulsation of the innominate artery can be felt. In young patients, when the neck is hyperextended, the innominate artery may become cervical and may be seen after completing the cervical incision. Care must be taken not to injure it in these initial manoeuvres. In older patients, the innominate artery may be located more caudally. Following the course of the innominate artery on the left, the aortic arch can be felt. Then, the finger is passed more distally behind the aortic arch. By palpation, the tracheal cartilages can be felt. Close to the carina, they are disrupted, as the trachea separates into the two main bronchi.

Insertion of the Mediastinoscope and Mediastinal Inspection

After creating a peritracheal space by finger palpation, the mediastinoscope is inserted into the upper mediastinum. At this point, the exploration is performed more comfortably if the surgeon sits on a chair. The height of the operating table and of the chair have to be regulated to relieve tension at the surgeon's shoulders and elbows.

From top to bottom, the pulsation of the innominate artery is seen first. The pulsation of the ascending aorta is seen on the left. More caudally, at the level of the right tracheo-bronchial angle, the azygos vein can be identified. The fatty tissue of the right paratracheal space has to be dissected to find the azygos vein. This landmark is important because, according to the new regional lymph node map, nodes caudal to the inferior rim of the azygos vein are coded as right hilar nodes, or 10R, although they are anatomically located in the mediastinum [1]. If the dissection is carried out more distally on the right, the whole length of the right main bronchus can be seen and, in some patients, even the origin of the right upper lobe bronchus. Over the right main bronchus, the right pulmonary artery is found, usually the distal end of the exploration on the right. Over the subcarinal space, the prolongation of the pretracheal fascia has to be torn to reach the subcarinal nodes. The right pulmonary artery crosses in front of them and the oesophagus is behind. Care must be taken not to injure these structures. If the integrity of the oesophagus is questionable, a naso-oesophageal tube can be inserted and air injected into it. With the subcarinal space flooded with saline, air will be evident if there is an oesophageal perforation. In more than two thousand mediastinoscopies, we have inserted a naso-oeasophageal tube once, only, to rule out oesophageal perforation. On the left, it is important not to injure the recurrent laryngeal nerve that runs along the left paratracheal margin. The left tracheo-bronchial angle can be identified and, distal to it, the left pulmonary artery, marking the end of the exploration on the left. Nodes caudal to its upper rim are now coded as left hilar nodes, or 10 L [1].

Biopsy

Lymph node biopsies for lung cancer staging must be systematically taken to obtain the maximal benefit from the exploration. Ideally, the taking of biopsies should start on the contralateral side to the tumour to rule out N3 disease. Macroscopically abnormal nodes should be sent for frozen section examination, and if nodal involvement is identified, mediastinoscopy may be terminated unless the patient is in a protocol that requires more information on the extent of nodal disease. Then, the subcarinal and the ipsilateral paratracheal nodes are biopsied. If the nodes are not removed entirely, the initial biopsies of each lymph node are ideal to examine the involvement of the nodal capsule and the extranodal tumour invasion. Each complete node or all the biopsies from one node are kept in a different container and properly labelled according to the present nodal nomenclature [1]. This makes the counting of the removed and involved nodes much easier and reliable. Whenever possible, it is better to remove the entire nodes to avoid missing micrometastases and increase the sensitivity of

the exploration. Mediastinal lymph nodes are embedded in the peritracheal fatty tissue. Exploration of this fatty tissue with the dissection–suction–coagulation device allows the surgeon to identify them and free them from their surrounding. Sometimes, fragments of lymph nodes or whole small lymph nodes are suctioned during dissection. In this case, it is recommendable to filter the contents of the suction container to retrieve the suctioned lymph nodes or their fragments for pathological examination.

Mediastinoscopy allows the surgeon to reach the cervical nodes at the sternal notch, the superior and inferior paratracheal nodes on both sides, the subcarinal nodes and the right and left hilar nodes. However, the superior paratracheal nodes are hidden by the mediastinoscope when it is inserted and are not easy to identify. They are better explored and biopsied in the open fashion at the time of cervicotomy. The European Society of Thoracic Surgeons (ESTS) guidelines require biopsies from, at least, one right and one left inferior paratracheal nodes and one subcarinal node for an acceptable mediastinoscopy in clinical practice. For cancers of the left lung, exploration of the subaortic and para-aortic nodes is also required, either by left parasternal mediastinotomy, extended cervical mediastinoscopy or left thoracoscopy [17] (Fig. 20.4).

Control of Haemostasis and Closure

The use of the dissection–suction–coagulation cannula minimises bleeding during dissection of peritracheal tissue. Mediastinal lymph nodes usually are dark blue or black because of their anthracotic content. The azygos vein or a partially visualised superior vena cava may resemble lymph nodes. In case of doubt, especially if the standard mediastinoscope is used, a puncture test should be performed. If blood is seen along the glass suction tube, the needle should be removed and the bleeding site gently pressed with gauze for haemostasis. During this manoeuvre, care must be taken not to puncture through the trachea, because perforation of the endotracheal cuff is possible and already has been described [31]. All biopsy sites should be checked before closure. Coagulation of biopsied lymph nodes or peritracheal fatty tissue is enough to control bleeding. Control of bleeding from the bronchial arteries in the subcarinal space, especially those running in front of the left main bronchus, should be tried first with gauze packing and coagulation. If bleeding persists, clipping of the bronchial artery may be necessary. The gauze used for packing must be removed through the mediastinoscope to minimise tumour seeding in the cervical incision. Major bleeding is an uncommon complication that may occur in 0.4% of procedures and may come from the azygos vein, the pulmonary arteries, the innominate artery—the most common sites of serious bleeding—, the superior vena cava and the aorta. Packing and median sternotomy is the usual procedure for haemorrhage control [32]. The glass cannula for puncture test may be connected to a syringe to puncture and aspirate lymph nodes. This is especially useful when the nodes are fixed to vessels. In this case, pulling or taking biopsies from the nodes may injure the attached vessel. The aspirate is then sent for cytological examination.

The paratracheal muscles are not sutured to the midline. This facilitates remediastinoscopy, if it is needed. The incision is closed in two layers: platysma and subcutaneous tissue together with 2–0 continuous absorbable suture and skin with 3–0 absorbable intradermal suture. Drainage is not necessary. The wound is dressed with gauze that can be removed in 24 h.

Postoperative Care

The patient is awakened and extubated in the operating room and sent to recovery room till he/she is fully conscious and the vital constants are normal and stable. Then, the patient is transferred to the normal ward or to the outpatient surgery room. Oral intake is started 6 h after the operation. The patient can be discharged on the same day, if an outpatient surgery programme is active in the hospital, or next day. The admission rate after outpatient mediastinoscopy for all indications ranges from 1% to 4%, and the

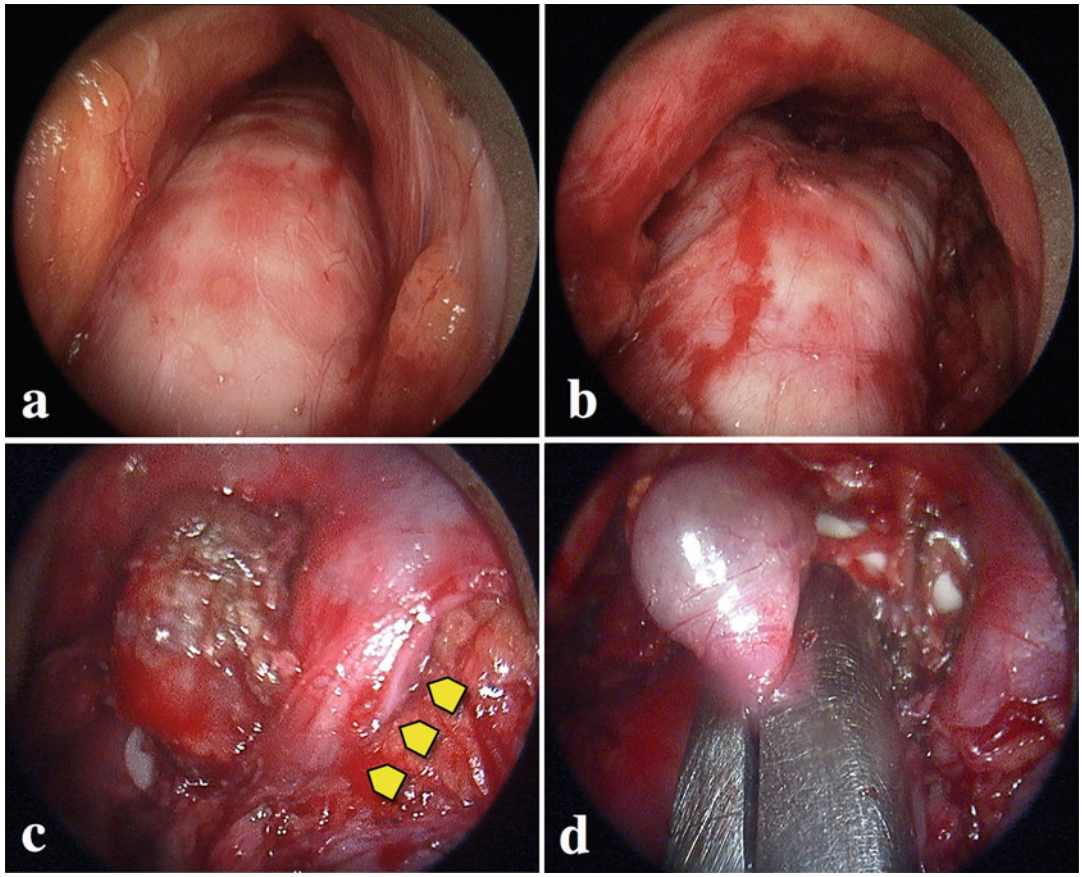

Fig. 20.4 Endoscopic images of video-mediastinoscopy. (**a**) Proximal trachea. (**b**) Distal trachea, right and left main bronchi. (**c**) Right hilar lymph node. This lymph node is located caudal to the inferior rim of the azygos vein (*yellow arrows*). (**d**) Hilar lymph node biopsy

main reasons are supraventricular arrhythmias, pneumothorax, bleeding from bronchial artery or late end of the operation [33–36]. Postoperative chest X-rays are not necessary unless something unusual has occurred during (opening of the mediastinal pleura or bleeding) or after surgery (fever, dyspnoea or chest pain).

Complications

Intraoperative complications are infrequent, ranging from 0.6% to 3.7% [37, 38]. The occlusion of the innominate artery and bleeding from the most common sites have been described above. Other complications are wound infection, pneumothorax, mediastinitis, left recurrent laryngeal nerve palsy, oesophageal perforation, bronchial injury, chylomediastinum, haemothorax and incisional metastasis [39–46]. Mortality is below 0.5% [4, 47, 48].

Technical Variants

Technical variants of mediastinoscopy have been devised over the years to reach mediastinal locations beyond the reach of the standard exploration and to expand the possibilities of this transcervical approach.

Extended Cervical Mediastinoscopy

Subaortic and para-aortic nodal stations cannot be reached with mediastinoscopy. Left parasternal mediastinotomy, performed over the second or third intercostal space, facilitates the exploration of this area but requires an additional incision and very often the removal of a costal cartilage [49, 50]. In 1987, Ginsberg et al. [51] reported their experience in extended cervical mediastinoscopy as a staging procedure for cancers of the left upper lobe, using the approach first described by Specht in 1965 [52]. To stage cancers of the left lung, after mediastinoscopy has been completed and from the same cervical incision, a passage is created by finger dissection over the aortic arch, between the innominate artery and the left carotid artery, either in front or behind the left innominate vein. Once the fascia between these two vessels is torn with the finger, the finger can be advanced easily over the aortic arch. Then, the mediastinoscope is inserted and the lymph nodes in the subaortic station can be explored and biopsied. By moving the mediastinoscope medially, the para-aortic nodes also can be explored, although differentiating between subaortic and para-aortic nodes is not easy because mobilisation of the mediastinoscope is limited by the bony structures of the chest wall. Extended cervical mediastinoscopy does not allow the surgeon to palpate the subaortic space well. If palpation is needed to differentiate between mere contact and tumour invasion in this area, then parasternal mediastinotomy is a much better approach. The parasternal incision allows the surgeon to inspect the subaortic space directly, but the mediastinoscope can also be used to facilitate the exploration. Additionally, a small rib spreader can be inserted to widen the operative field. Bimanual palpation from the collar incision and from the parasternal incision is useful to explore the integrity of the aortic arch. Access to the pericardium, pleural space and lung is also possible from this incision. Right parasternal mediastinoscopy is useful to assess the superior vena cava, the azygos vein, the right pulmonary artery, the right superior pulmonary vein and the right anterior mediastinal nodes [53].

Mediastinoscopic Biopsy of Scalene Lymph Nodes

From the cervical incision of mediastinoscopy, the mediastinoscope can be passed under the insertions of the sternocleidomastoid muscle on one or both sides of the neck to reach the scalene lymph nodes. There is one publication on this technique, only, but the reported results are clinically relevant: 15% of patients with N2 disease and 63% of those with mediastinal N3 diagnosed at mediastinoscopy had subclinical N3 disease in the scalene lymph nodes [54]. These results have to be taken into account when selecting patients for clinical trials on N2 disease.

Inferior Mediastinoscopy

The mediastinoscope is inserted into the anteroinferior mediastinum from a subxiphoid approach. Although this is rarely needed, inferior mediastinoscopy is useful to explore mediastinal lesions beyond the reach of mediastinoscopy [55, 56].

Mediastino-Thoracoscopy

From the superior mediastinum, at the time of mediastinoscopy, the mediastinal pleura can be opened and the pleural space, explored. On the right side, this can be performed either between the trachea and the superior vena cava or between the superior vena cava and the anterior chest wall. On the left, the supra-aortic approach is the most direct one, as used for extended cervical mediastinoscopy [51, 52]. Single-lung ventilation facilitates the exploration of the pleural space in patients with pleural effusion, lung nodules, parietal pleura nodules and diaphragmatic and pericardial lesions. If the target lesions cannot be reached with the mediastinoscope, a thoracoscope can be passed through it; by doing so, even the diaphragm can be reached. Pleurodesis also can be performed through this approach [57, 58]. The two-bladed video-mediastinoscopes also allow the insertion of endoscopic staplers to

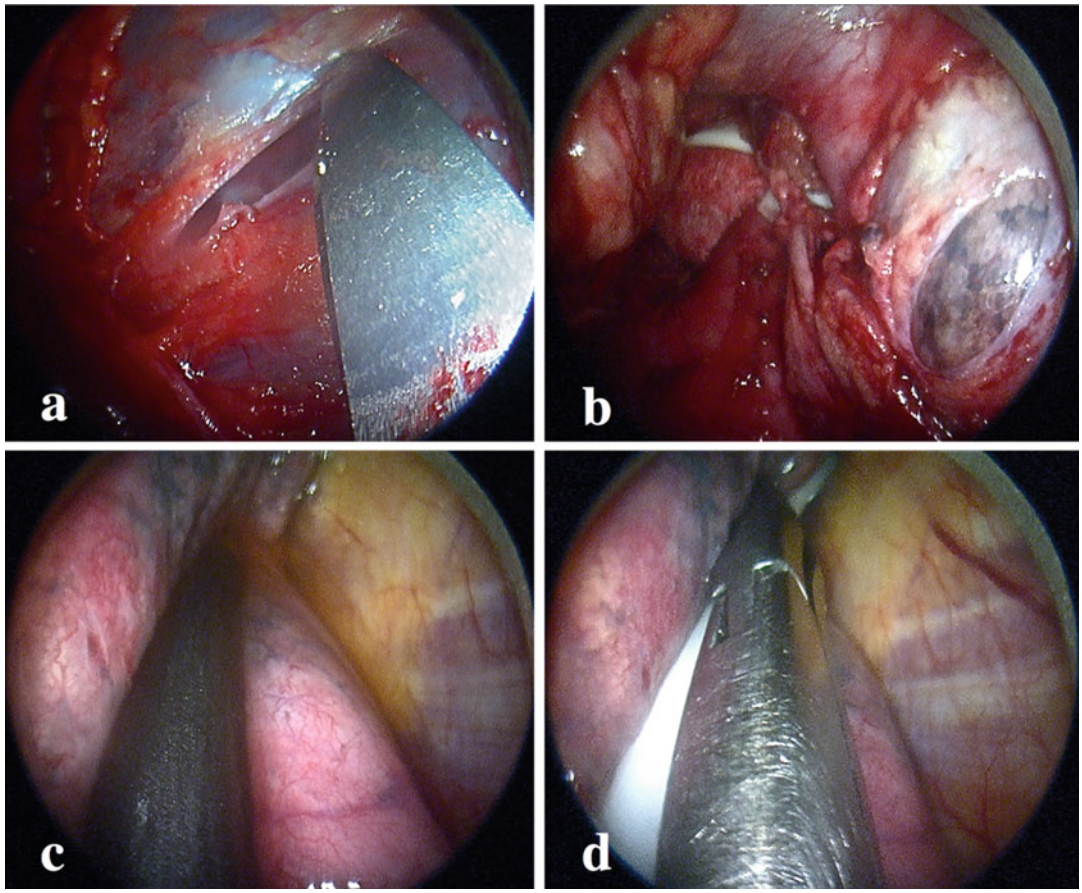

Fig. 20.5 Mediastino-thoracoscopy. (**a**) The mediastinal pleura are opened by endoscopic scissors. (**b**) View of the right lung through the incision of the mediastinal pleura. (**c**) Exploration of the pleural space with single-lung ventilation. Pleural effusion of clear fluid is identified, and it is suctioned by suction cannula. (**d**) Small bore chest tube is inserted by endoscopic forceps

perform wedge resection of the lung in case of lung cancer and additional peripheral lung nodules (Fig. 20.5).

Video-Assisted Mediastinoscopic Lymphadenectomy

Video-assisted mediastinoscopic lymphadenectomy (VAMLA) is a very thorough mediastinoscopy with the objective to remove the upper mediastinal lymph nodes. It is performed with the two-bladed video-mediastinoscope through a standard collar incision for mediastinoscopy. A holder can be used to fix the video-mediastinoscope so that the surgeon can work with two hands, holding the specimen with a forceps with one hand and the dissector with the other. The subcarinal and the right inferior paratracheal lymph nodes are removed en bloc with the mediastinal fatty tissue. Those located in the left inferior paratracheal station are removed one by one not to injure the left recurrent laryngeal nerve [10, 11]. VAMLA can be combined with video-thoracoscopy to improve the radicality of lymphadenectomy [59] (Fig. 20.6).

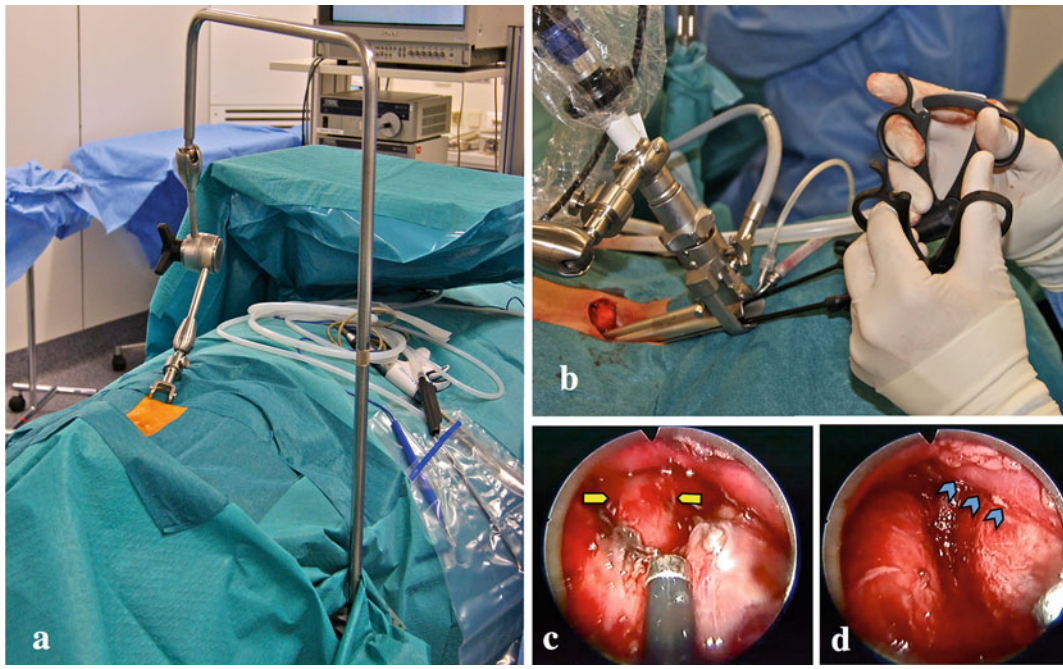

Fig. 20.6 Video-assisted mediastinoscopic lymphadenectomy (VAMLA). (**a**, **b**) The surgeon can work with two hands because the video-mediastinoscope is fixed by an articulated holder. (**c**) View of the subcarinal space after removing all subcarinal lymph nodes. The tip of the dissection–suction–coagulation device is located at the carina, between the two main bronchi. *Yellow arrows* show the oesophagus completely dissected. (**d**) View of the right mediastinal pleura after removing right inferior paratracheal lymph nodes en bloc with the mediastinal fatty tissue. *Blue arrows* show the superior vena cava

Transcervical Extended Mediastinal Lymphadenectomy

In comparison with VAMLA, transcervical extended mediastinal lymphadenectomy (TEMLA) is a more extensive procedure. The objective of TEMLA is to remove all the mediastinal nodes from the cervical station to the para-oesophageal station. A cervical incision slightly longer than that for mediastinoscopy is performed, but the sternum is elevated with a hook fixed to a metal frame mounted on the operating table. The procedure is almost exclusively performed in an open fashion, but a two-bladed mediastinoscope is used to dissect the subcarinal and the para-oesophageal lymph nodes, and a videothoracoscope is inserted to have a better vision at the time of dissection of the subaortic space [12].

Evidence-Based Review

Conventional Mediastinoscopy Versus Video-Mediastinoscopy

There are evident advantages of video-mediastinoscopy over conventional mediastinoscopy. The view of the operative field is much larger and can be seen simultaneously by all personnel in the operating theatre. The whole procedure or parts of it can be recorded for future use in clinical sessions, medical meetings and educational materials. However, because there are no prospective randomised trials comparing both procedures, there is no clear evidence indicating that video-mediastinosocopy is safer or more effective than conventional mediastinoscopy. However, video-mediastinoscopy seems to be a more thorough exploration, because of an

Table 20.1 Staging values of mediastinoscopy

Author, year and reference	Type of mediastinoscopy	*N*	Sensitivity	NPV	Diagnostic accuracy
Rami-Porta & Mateu-Navarro, 2002 [61]	CM	148	0.78	0.85	0.90
	VM	137	0.86	0.90	0.94
Venissac et al., 2003 [64]	VM	240	0.91	NA	0.98
Lardinois et al., 2003 [65]	VM	195	0.87	NA	0.95
Leschber et al., 2008 [62]	CM	52	NA	0.81	0.84
	VM	119	NA	0.83	0.88
Karfis et al., 2008 [67]	VM	87	0.8	0.59	0.85
Anraku et al., 2010 [63]	CM	505	0.92	0.95	0.97
	VM	140	0.95	0.98	0.98
Call S et al., 2011 [66]	Routine CM and VM	655	0.85	0.90	0.94
	Selective VM	625	0.81	0.90	0.95

CM conventional mediastinoscopy, *N* number of patients, *NA* not available, *NPV* negative predictive value, *VM* videomediastinoscopy

increased number of biopsied lymph nodes and explored lymph node stations compared with conventional mediastinoscopy, as well as a better tool for training [60].

Staging Values of the Different Techniques

For conventional mediastinoscopy, recent reports show that sensitivity ranges from 0.78 to 0.92; negative predictive value, from 0.85 to 0.95; and diagnostic accuracy, from 0.84 to 0.97 [61–63]. For videomediastinoscopy, sensitivity ranges from 0.86 to 0.95; negative predictive value, from 0.83 to 0.98; and diagnostic accuracy, from 0.88 to 0.98 [61–67]. The results tend to be slightly better for videomediastinoscopy, but the differences are not statistically significant (Table 20.1).

There are six published reports, including 528 patients, on extended cervical mediastinoscopy, and two of them are from the same institution [68, 69]. Sensitivity ranges from 0.69 to 0.83; negative predictive value, from 0.89 to 0.95; and diagnostic accuracy, from 0.91 to 0.98 [51, 69–72]. Although the publications are scarce, the reported experiences show that the results are reproducible in different countries and that the technique has a high negative predictive value, which is very clinically relevant to indicate lung resection (Table 20.2).

The initial reports from the two groups who developed VAMLA in 2002 and 2003, describing their results with 40 and 25 patients, respectively, showed sensitivities, negative predictive values and diagnostic accuracies of 1 [10, 11]. An updated publication from one of the groups, with 144 patients, reported a sensitivity of 0.88 and a negative predictive value of 0.98 [73].

Sensitivity and negative predictive value of TEMLA are high: 0.9 and 0.95, respectively, in the first reports including 83 patients [12], and 0.94 and 0.97, respectively, in an updated reports with 256 patients [74]. In addition, TEMLA has proved to be highly reliable as a restaging method in those patients with lung cancer initially staged by endoscopic techniques and fine needle aspiration. In these cases, sensitivity, negative predictive value and accuracy were 0.95, 0.97 and 0.98, respectively [75].

Summary and Recommendations

Mediastinoscopy explores the upper mediastinum and is useful in the assessment of nodal disease and direct tumour invasion. To expand the range of the exploration, procedures such as parasternal mediastinotomy, extended cervical mediastinoscopy, mediastino-thoracoscopy and inferior mediastinoscopy have been devised during the past decades. Other related procedures have the objective to perform a mediastinal lymphadenectomy

Table 20.2 Staging values of extended cervical mediastinoscopy

Author, year and reference	*N*	Sensitivity	NPV	Diagnostic accuracy
Ginsberg et al., 1987 [51]	100	0.69	0.89	0.91
López et al., 1994 [70]	46	0.83	0.97	0.98
Freixinet et al., 2000 [71]	106	0.81	0.91	0.95
Metin et al., 2011 [72]	55	0.69	0.89	0.91
Obiols et al., 2012 [69]	221	0.67	0.95	0.94

N number of patients, *NPV* negative predictive value

as thorough as that performed by thoracotomy. They are indicated when the mediastinum is normal on CT and PET scans, and their sensitivity and negative predictive values are higher than those for mediastinoscopy. At the present time, the ESTS guidelines are valuable, have been prospectively validated, with sensitivity and negative predictive values of 0.84 and 0.94, respectively, [76] and, therefore, should be applied in the management of patients with lung cancer.

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Endobronchial Ultrasound: Basic Principles

21

Antoni Rosell Gratacos and Noelia Cubero

Introduction and Definition of the Procedure

Endobronchial ultrasound (EBUS) is a diagnostic technique that takes advantage or the physical properties of ultrasound waves. It has revolutionized diagnostic bronchoscopy because it allows the physician to see beyond the bronchial wall. There are currently two imaging modalities: radial EBUS and linear EBUS. Linear EBUS is performed with a specially designed flexible bronchoscope that incorporates a transducer at the distal end allowing real-time guided needle aspiration. It can visualize and sample mediastinal and parabronchial structures. To detect solitary pulmonary lesions, a radial ultrasound probe has to be passed through the working channel of a standard bronchoscope. Sampling of these lesions is performed under fluoroscopy [1–4].

The sound is a mechanical energy that travels through a medium as a wave with a frequency between 20 Hz and 20 kHz. Higher frequencies are called ultrasound (20 kHz–200 MHz). The frequency used for the miniature probes such as those in EBUS ranges between 1 and 30 MHz. Images are generated when ultrasound waves are emitted by a transducer, reflected on a tissue interface (conformed by anatomical structures), and then received back by the same transducer. The so reflected echoes are then transformed into electrical signals. According to the wave equation [speed = wavelength (λ) × frequency (F)], the higher the frequency is, the lower the wavelength. More frequency means better resolution of the images but lower depth penetration, so the main disadvantage of high frequency transducers is poor tissue penetration (Table 21.1). The challenge of the ultrasonography of the lungs is related to the acoustic properties of air, as ultrasound waves are not well transmitted through air. By miniaturizing transducers, these limitations are overcome because mediastinal and peribronchial structures can be well visualized without having alveolar air obscuring the view [5, 6].

The Doppler effect, named after the Austrian physicist Christian Doppler, who presented it in Prague in 1842, is the change in a wave frequency for an observer that is moving relative to its source. It is very evident when a vehicle sounding a siren or horn approaches, passes, and recedes from an observer. The Doppler effect refers to the frequency shift that is observed when sound is reflected from a moving target like red blood cell aggregates:

$$\text{Frequency (fd)} = \frac{2\text{fV cosine}\,\Theta}{\text{C}}$$

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Table 21.1 Resolution vs. penetration depth

Frequency		
Low ····· ►		High
Penetration depth	High	Low
Resolution	Low	High

$F(fd)$ = Doppler shift frequency (the difference between the transmitted and received frequencies)
f = Frequency of the incident US beam (emitted from transducer)
C = Speed of sound in the body (assumed to be 1,540 m/s)
V = RBC velocity
Θ = angle of US beam to flow direction

From the Doppler equation above, we see that the Doppler effect is influenced by the following factors:

1. The frequency of the ultrasound beam (f) used
2. The angle of the ultrasound beam to the flow direction (Θ)
3. The velocity of flowing red blood cells (V)

A Doppler ultrasound makes use of the Doppler effect in measuring and visualizing the blood flow through the blood vessels. The flow moving to the transducer reflects ultrasound waves at a higher frequency.

The ultrasound images reflected have three characteristics that define them: amplitude, frequency, and phase. Color Doppler is a mode where the phase and frequency information of the ultrasound is presented as a color-coded overlay on top of the image. The colors red and blue are used to represent flow direction toward or away from the ultrasound transducer. When the amplitude is integrated to the traditional phase/frequency (color Doppler) images, it reflects the energy of the autocorrelation signal. This type of color flow imaging has been given the name of power Doppler. The power Doppler has improved flow sensitivity up to five times. The disadvantages of power Doppler are that it provides no information regarding flow velocity or flow direction [7].

History and Historical Perspective

The application of ultrasound within the lungs was first described in 1992. Up until now, to obtain diagnostic samples from lymph nodes in the central regions of the lungs, a surgical mediastinoscopy was needed. This procedure is performed by making an incision in the chest and inserting an instrument to extract samples. Surgical techniques, while considered as the gold standard to stage lung cancer, have the downside of being invasive, expensive, requiring general anesthesia, and having a potential risk of complications. Prior to EBUS, the non-surgical technique commonly used was transbronchial needle aspiration (TBNA). This procedure is performed without real-time imaging as the lymph nodes are located only by the knowledge of anatomy and images previously obtained through computerized tomography scan. This procedure is highly operator dependent and has a low diagnostic accuracy and difficulty accessing lymph nodes [8–10].

Gastrointestinal endoscopy has used the ultrasound for staging esophageal carcinoma, carcinoma of the cardia and rectum, in the diagnosis of primary tumors and lymph node metastasis, as well as involvement of the neighboring structures. Prior to the availability of endobronchial ultrasound, endoesophageal ultrasound (EUS) was initially used to assess the lymph nodes in the chest, but the pretracheal and lower paratracheal regions and the perihilar structures remained inaccessible to ultrasound assessment due to limited contact and interposition of the airways. Due to that limitation, the application of ultrasound endobronchially was investigated and developed from 1989 onward [11, 12].

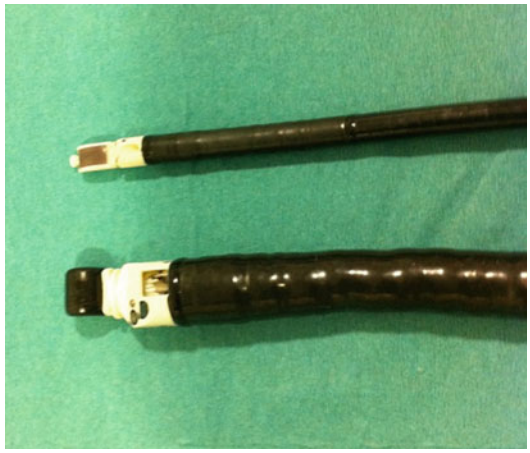


Fig. 21.1 Difference in the diameter of EBUS and EUS

Due to the smaller size of the airway, lumen instruments that are used for gastrointestinal applications could not be applied inside of the airways (Fig. 21.1). The use of miniaturized endovascular sonographic probes did not improve significantly the TBNA procedure [13, 14]. Flexible catheters were developed to be applied inside the central airways with a saline-filled balloon at the tip in order to improve contact of the ultrasound with the airways.

The probes have been in the market since 1999 and can be applied with regular flexible bronchoscopes that have a biopsy channel of at least 2.8 mm. Finally, dedicated bronchoscopes with an integrated curvilinear electronic transducer at the tip were developed [15].

In a near future, technical and image reconstruction improvements will expand our capacity to diagnose. Multimodal vision bronchoscopes with different diameters and intelligent software to recognize ultrasonographic malignant features are expected.

Indications, Contraindications, and Limitations

Indications

EBUS is a minimally invasive procedure that has proven highly effective to evaluate the regional extension of lymph node involvement in bronchogenic carcinoma (staging and restaging); to identify and localize mediastinal structures adjacent to the airways (mediastinal tumors, heart, and esophagus and great vessels) before diagnostic or therapeutic interventions; to localize solid structures in the lung tissue for biopsy procedures; to stage the depth of bronchial wall invasion and in the diagnosis of infections or inflammatory diseases that affect the lungs such as sarcoidosis or other cancers like lymphoma causing enlarged lymph nodes in the chest [16, 17].

EBUS-TBNA is indicated for the assessment of mediastinal and hilar lymph nodes. It can be used to sample the upper paratracheal (station 2R, 2L), the lower paratracheal (station 4R, 4L), the subcarinal (station 7), the hilar (station 10), and the interlobar (station 11) lymph nodes. The prevascular (station 3a), retrotracheal (station 3p), aortopulmonary window or subaortic (station 5), para-aortic (station 6), paraesophageal (station 8), and pulmonary ligament (station 9) lymph node stations are usually not accessible by this technique (Fig. 21.2).

Nodal stations are defined by anatomical limits (Table 21.2).

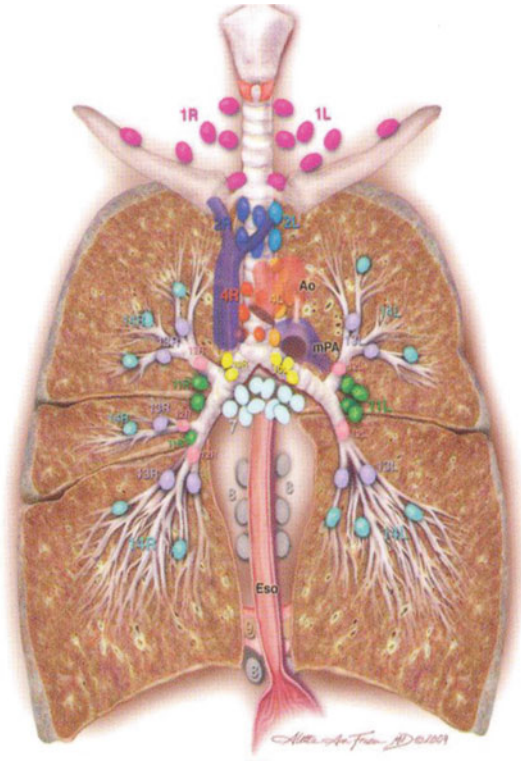
Radial EBUS is indicated for the study of peripheral lung nodules, and it has also been used to study the mediastinal lymph nodes; however, linear EBUS is preferred for this indication.

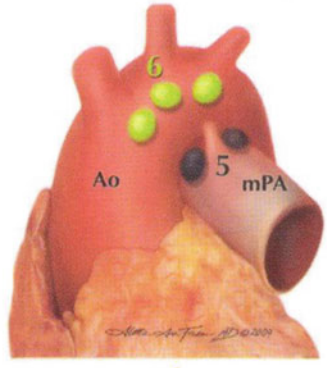
Contraindications

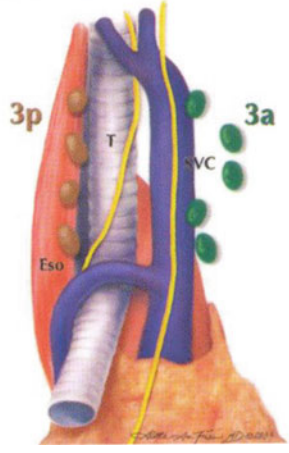
There are no contraindications for EBUS others than those for flexible bronchoscopy when performing blind TBNA or transbronchial biopsy. The complications are rare and usually related to the underlying biopsy procedure rather than the use of ultrasound [1].

A case of acute mediastinitis after linear EBUS-TBNA of necrotic lymph nodes was reported in 2011 [18].

When performing radial EBUS, the pneumothorax rate reported was 1.6% which is significantly smaller than that reported for the study of the peripheral pulmonary lesions by transthoracic needle aspiration [19].







Supraclavicular zone

1 Low cervical, supraclavicular, and sternal notch nodes

SUPERIOR MEDIASTINAL NODES

Upper zone

- 2R Upper Paratracheal (right)
- 2L Upper Paratracheal (left)
- 3a Prevascular
- 3p Retrotracheal
- 4R Lower Paratracheal (right)
- 4L Lower Paratracheal (left)

AORTIC NODES

AP zone

- 5 Subaortic
- 6 Para-aortic (ascending aorta or phrenic)

INFERIOR MEDIASTINAL NODES

Subcarinal zone

- 7 Subcarinal

Lower zone

- 8 Paraesophageal (below carina)
- 9 Pulmonary ligament

N1 NODES

Hilar/Interlobar zone

- 10 Hilar
- 11 Interlobar

Peripheral zone

- 12 Lobar
- 13 Segmental
- 14 Subsegmental

Fig. 21.2 Mediastinal and hilar lymph nodes map. Reproduced with permission from Rusch VW et al. The IASLC lung cancer staging project: a proposal for a new international lymph node map in the forthcoming seventh edition of the TNM classification for lung cancer. J Thorac Oncol 2009;4(5):568–77

Table 21.2 Nodal definitions (IASLC)

Nodal stations	Upper border	Lower border
1: Low cervical, supraclavicular, and sternal notch nodes (the limit between L and R * is in the midline of the trachea)	Lower margin of cricoid cartilage	Clavicles bilaterally and, in the midline, the upper border of the manubrium
2: Upper paratracheal nodes (the midline is along the left lateral border of the trachea)	Apex of the lung and pleural space and in the midline, the upper border of the manubrium	R: Intersection of caudal margin of innominate vein with the trachea; L: superior border of the aortic arch
3 :Prevascular and retrotracheal nodes *3a: Prevascular* R: the anterior border is posterior aspect of the sternum, and the posterior border is the anterior border of superior vena cava L: the anterior border is the same, but the posterior border is the left carotid artery *3p: Retrotracheal*	Apex of the chest	Level of carina
4: Lower paratracheal nodes 4R: Includes right paratracheal nodes and pretracheal nodes extending to the left lateral border of trachea	Intersection of caudal margin of innominate vein with the trachea	Lower border of azygos vein
4L: Includes nodes to the left of the left lateral border of the trachea, medial to the ligamentum arteriosum	Upper margin of the aortic arch	Upper rim of the left main pulmonary artery
5: Subaortic (aortopulmonary window) Subaortic lymph nodes lateral to the ligamentum arteriosum	The lower border of the aortic arch	Upper rim of the left main pulmonary artery
6: Para-aortic nodes ascending aorta or phrenic Lymph nodes anterior and lateral to the ascending aorta and aortic arch	A line tangential to upper border of aortic arch	The lower border of the aortic arch
7: Subcarinal nodes	The carina of the trachea	**L**: The upper border of the lower lobe bronchus; **R**: the lower border of bronchus intermedius
8: Paraesophageal nodes (below carina) Nodes lying adjacent to the wall of the esophagus and to the right or left of the midline, excluding subcarinal nodes	L: The upper border of the lower lobe bronchus; R: the lower border of the bronchus intermedius	The diaphragm
9: Pulmonary ligament nodes Nodes lying within the pulmonary ligament	The inferior pulmonary vein	The diaphragm
10: Hilar nodes Includes nodes immediately adjacent to the main stem bronchus and hilar vessels including the proximal portions of the pulmonary veins and main pulmonary artery	R: The lower rim of the azygos vein; L: upper rim of the pulmonary artery	Interlobar region bilaterally
11: Interlobar nodes: Between the origin of the lobar bronchi 11S*: Between the upper lobe bronchus and bronchus intermedius on the right 11I:Between the middle and lower lobe bronchi on the right		
12: Lobar nodes: Adjacent to the lobar bronchi		
13: Segmental nodes: Adjacent to segmental bronchi		
14: Subsegmental nodes: Adjacent to the subsegmental bronchi		

**R* designates right-sided nodes and *L* left-sided nodes
**S* designates superior and *I* inferior

Limitations

1. For linear EBUS: Structures that are farther than 2–3 cm from the tracheal wall or very distant from the main airway are difficult to reach. Patients who are diagnosed with tracheal pathologies such as amyloidosis or osteo-chondroplastic tracheopathy do not benefit from linear EBUS diagnosis. Very small lymph nodes (<5 mm) can not be accessed with this method either.
2. For radial EBUS: Peripheral lesions with no contact to the airway or not visible by fluoroscopy are not accessible to radial EBUS. Costly damage to the bronchoscope can occur by inadverted needle penetration of its inner sheath.
3. For both: The learning process required to interpret the ultrasound images and perform the procedure is long. Equipment and ancillary instruments such as needles and miniprobes are expensive and so are repairs. Possible false-negative results, either for not reaching the planned target or samples, are small or insufficient.

Description of the Equipment Needed

EBUS is an ultrasound probe combined with endoscopy. There are two types of ultrasound probes:

1. Radial EBUS: Balloon-tipped miniaturized probes of 2.8–3.2 mm, with 12 and 20 MHz transducers that can be inserted through the working channel of conventional flexible or rigid bronchoscopes. Driving units to rotate the miniaturized probes are also needed.
2. Linear EBUS: Sectorial transducers of 7.5 MHz incorporated at the tip of specially designed 7 mm flexible bronchoscopes as well as an ultrasound processor, which produces ultrasonic waves and creates the images.

Radial EBUS

Radial probe EBUS utilizes a rotating transducer at the end of a probe, which produces a 360° image, relative to the long axis of the bronchoscope. A 20 MHz frequency radial probe is commonly used, although 12 MHz and 30 MHz probes are also available. These frequencies penetrate tissue approximately 4–5 cm with a resolution of less than 1 mm, which enables the airway layers to be identified allowing the diagnosis of tumor invasion into the bronchial wall, with an overall sensitivity of 66.7%, specificity of 100%, and accuracy of 93–95% in identifying malignant tracheal wall invasion [14]. This radial probe is built in a catheter that has a water-inflatable balloon at the tip and is used to evaluate central airways (trachea and main bronchus). It can be inserted through a 2.8 mm working channel and rotates 360°, perpendicular to the insertion axis of the probe, to obtain detailed images of the surrounding structures including the bronchial wall structure.

There is a second kind of probe, the ultraminiature 20 MHz radial probe with an external diameter of 1.4 mm, used for the detection of peripheral lung nodules.

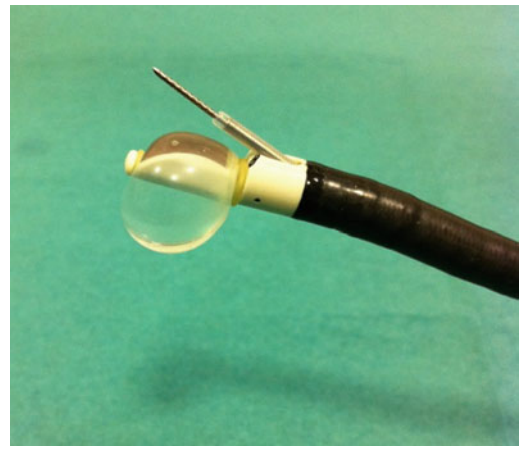


Fig. 21.3 Image of a linear ecobronchoscope

Linear EBUS

The linear EBUS (Fig. 21.3), also known as convex probe EBUS, incorporates a convex transducer with a frequency of 7.5 MHz at the tip of a flexible bronchoscope that scans parallel to the insertion direction of the bronchoscope,

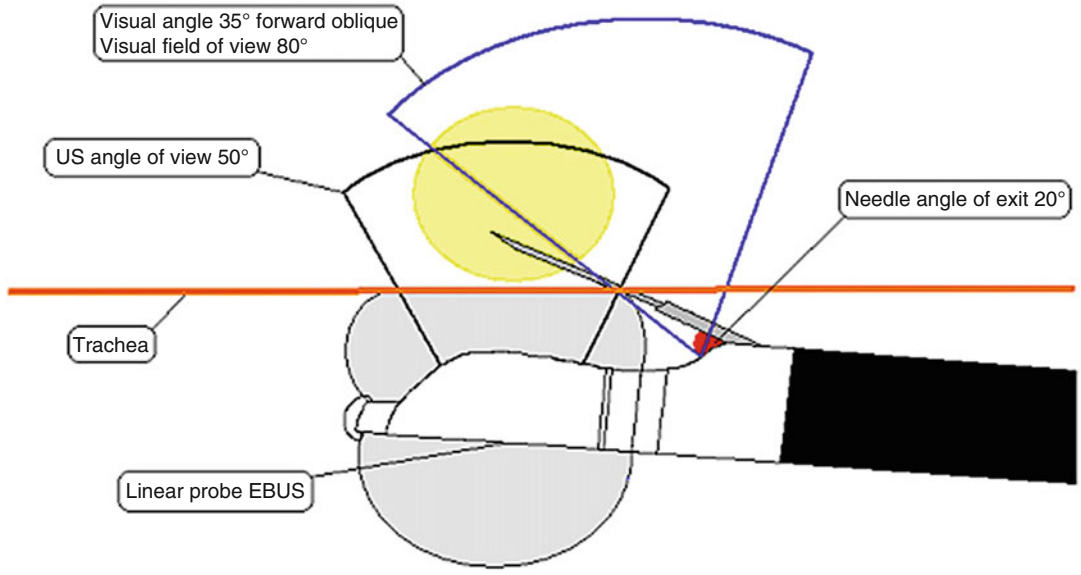


Fig. 21.4 Schema of the linear probe EBUS system (*Mario Gomez and Gerard A. Silvestri)*

generating a 50° image. The outer diameter of the insertion tube of the EBUS flexible bronchoscope is 6.7 mm and that of the tip is 6.9 mm, making this scope bigger than a standard therapeutic bronchoscope. For this reason, intubation using the oral route for insertion is mandatory. The angle of view is 80°, and the direction of view is 35° forward oblique (Fig. 21.4). Ultrasound images can be obtained by placing the probe in direct contact to the trachea or bronchial wall or after inflating the balloon on the tip of the bronchoscope with saline. Using the water-filled balloon can improve the image quality. In addition, the ultrasound images can be frozen, allowing for measurement of the lesion or lymph node in two dimensions. Ultrasound and white-light bronchoscopic images can be viewed simultaneously. The Doppler mode allows differentiation of tissue from vascular structures. Due to the diameter of the linear EBUS scope, complete inspection of the airways may require performing standard flexible bronchoscopy.

This scope allows for a needle to be inserted through the bronchoscope channel to biopsy lymph nodes or a suspicious lesion through the bronchial wall. The needle can be seen in real time on the video monitor, along with lymph nodes or region of interest (external to the airway) under ultrasound, enabling physicians to more accurately guide the procedure and obtain pathology samples (Fig. 21.5). This modality of EBUS offers the advantage of simultaneously obtaining the diagnosis and stage of lung cancer in a single procedure in the outpatient setting [2–5].

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) has typically been performed using the 22 gauge (G) dedicated TBNA needle (Fig. 21.6), but a new 21 G TBNA needle has been introduced in the market. A long-standing question has always been the optimum size of the biopsy needle. Previous comparative studies suggested that for conventional TBNA, larger needles might provide more biopsy material and thus an increased chance of improved diagnostic yield. The evaluation of 45 lesions by Nakajima et al. revealed no differences in the diagnostic yield between the 21 G and 22 G needles during EBUS-TBNA although histological structure was better preserved in the lesions collected by the 21 G needle; more blood contamination was present with the 21 G needle [20].

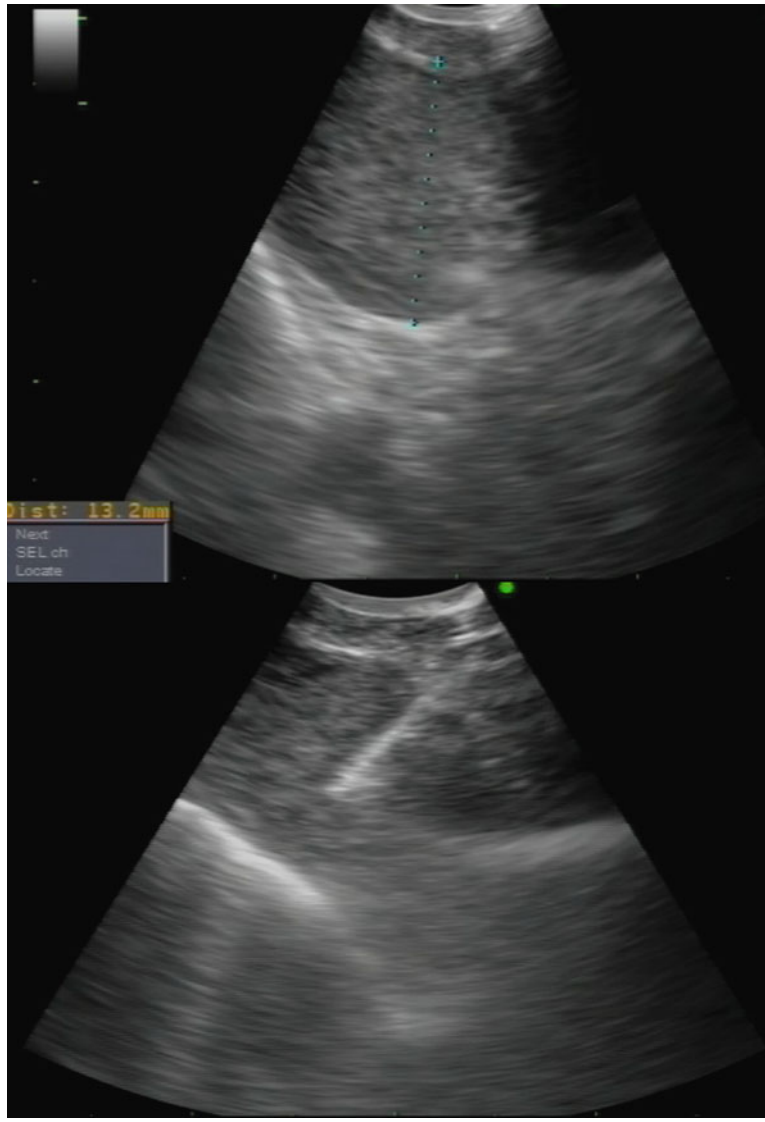


Fig. 21.5 Ultrasound image of a TBNA in a lymph node

Application of the Technique

The procedure can be done under general anesthesia and laryngeal mask or under moderate sedation in an outpatient setting. General anesthesia achieves a stable respiratory and cardiac motion that allows a better technique (visualization and puncturing) [21].

Radial EBUS

The probe is placed into a guide and inserted through a 2.8 mm or a 2.0 mm working channel of a flexible bronchoscope, depending on the probe size. A probe handled with meticulous care lasts for approximately 50–75 examinations. Then, the guide with the probe is advanced to the

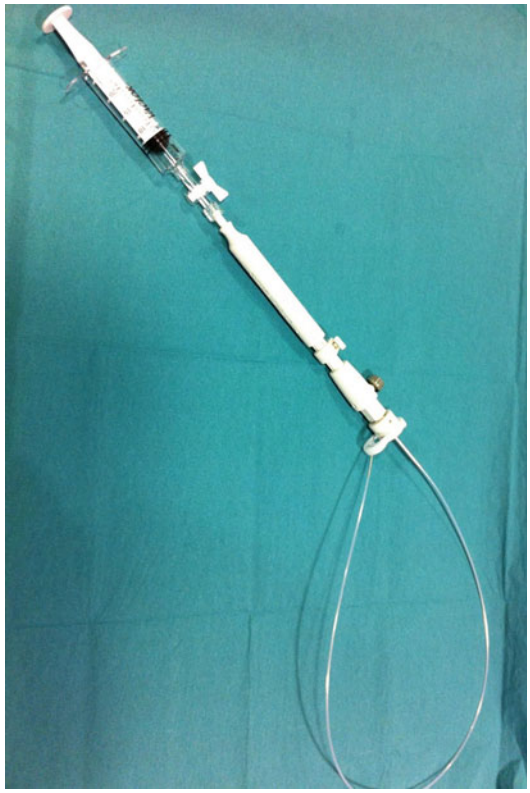


Fig. 21.6 Image of a 22 G TBNA dedicated needle

peripheral lesion (usually with the aid of fluoroscopy) to obtain a 360° image of the airway wall and surrounding structures external to the airway, perpendicular to the axis of the bronchoscope. After localizing the lesion, the physician moves the probe forward and backward throughout the airway to obtain images of the surrounding tissue, so to assess the internal structure of the lesion, determining its size, location, and depth of penetration. Then the probe is removed, leaving the guide in place. A biopsy instrument (forceps, needle, bronchial brush) is inserted through the guide sheath to obtain pathologic and cytological specimens. A chest radiography should be performed after the procedure to evaluate for pneumothorax. EBUS-guided transbronchial lung biopsy has a higher diagnostic yield than fluoroscopically guided transbronchial lung biopsy (80%, compared with 76%), in the evaluation of peripheral lung masses and solitary pulmonary nodules. It can even be used to identify fluoroscopically invisible peripheral lesions less than 3 cm in diameter but previously identified by chest CT.

The downside to using a radial probe is that the device must be removed from the bronchoscope channel before other sampling tools can be inserted; therefore, the physician loses the ability to view both the endoscopic and ultrasound images simultaneously while performing the biopsy, which can increase the chance of missing the target site or can reduce diagnostic yield [2–5].

Linear EBUS

Linear EBUS provides real-time imaging of the surface of the airways, blood vessels, lungs, and lymph nodes, allowing performing a transbronchial needle aspiration (TBNA) to obtain tissue or fluid samples from the lymph nodes without the need of surgery (Fig. 21.7).

The EBUS bronchoscope is placed orally and advanced to the trachea until the target tissue is located. The ultrasound probe is gently pressed to the bronchial wall and passed along the structures to be investigated. At the target site, the balloon is inflated with distilled water until close contact is achieved and the wall and surrounding structures become visible. The ultrasound images are processed using a dedicated ultrasound scanner and are stored on video and photographic prints. The trachea can be examined for a short time if the patient is sedated or placed under general anesthesia and if preoxygenation is sufficient, since it needs a short apnea time. The probe can be passed to all regions of interest [1].

Once the structure that needs to be studied has been identified, a dedicated 22 G or 21 G needle can be used to perform TBNA. After penetration into the lymph node, the internal stylet is used to clean out the internal lumen, which may become clogged with bronchial membrane. The internal stylet is then removed. Negative pressure can be applied with a syringe on demand. The needle is usually moved back and forth inside the lesion of interest 10–15 times over 30–60 s. The needle is then withdrawn into the catheter and removed

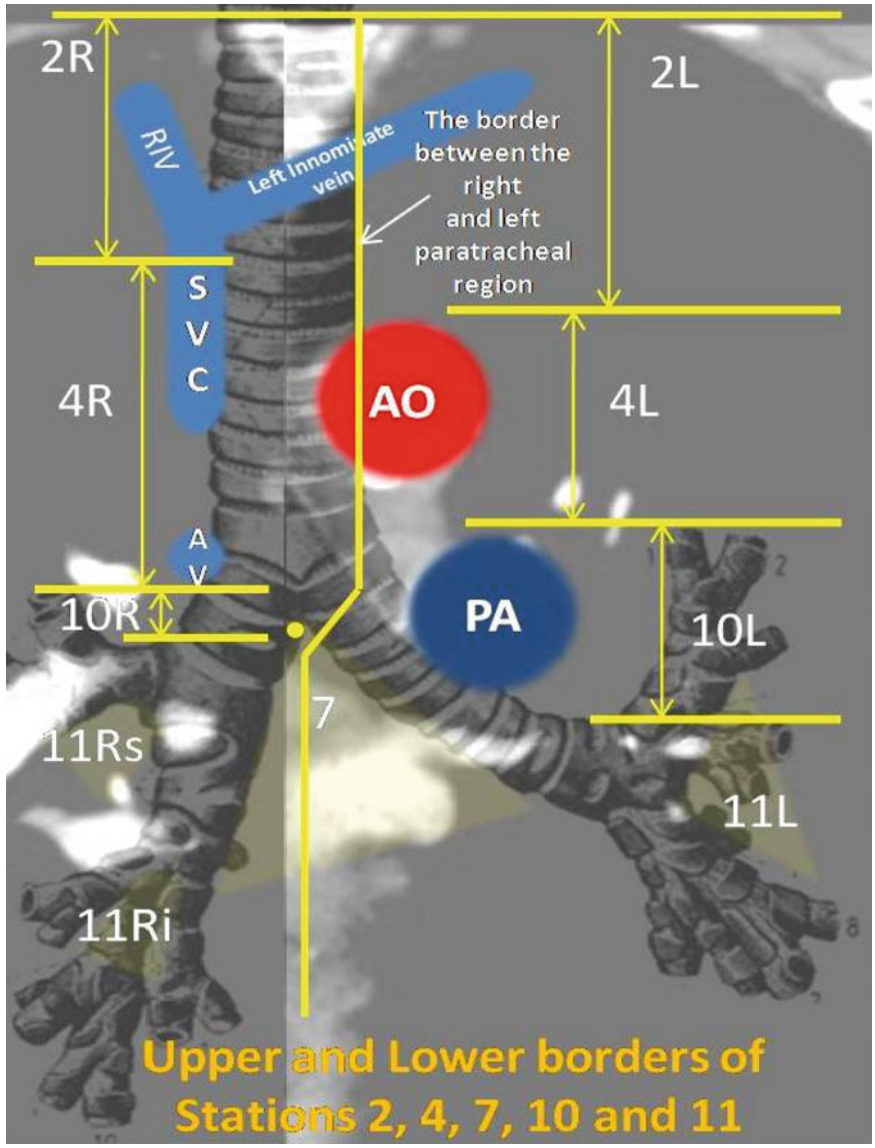


Fig. 21.7 CT–WLB–EBUS correlations for regional lymph nodes by IASLC system (*Bronchoscopy International 2010. Septimiu Murgu, MD & Henri Colt, M.D.*)

from the bronchoscope, and the internal stylet is used once again to push out the aspirated material. With a cytologist available for rapid on-site cytological evaluation (ROSE) of the aspirates, TBNA is continued until adequate sampling is confirmed (Fig. 21.8). Once the aspirated material is pushed out on to the slide glass [22], pathologists in the operating room can process and examine biopsy samples as they are obtained and can request additional samples to be taken immediately if needed. Without rapid on-site cytology, it has been reported that three aspirations per lymph node station or two aspirations with one tissue core are recommended (Fig. 21.9).

Mediastinal staging with EBUS is executed with a strategy of sampling: first N3, then N2, and last N1 nodes. This strategy is designed to eliminate the risk of upstaging patients as a result of contamination of specimens with tumor cells from a positive lower-stage lymph node. In addition,

Fig. 21.8 ROSE

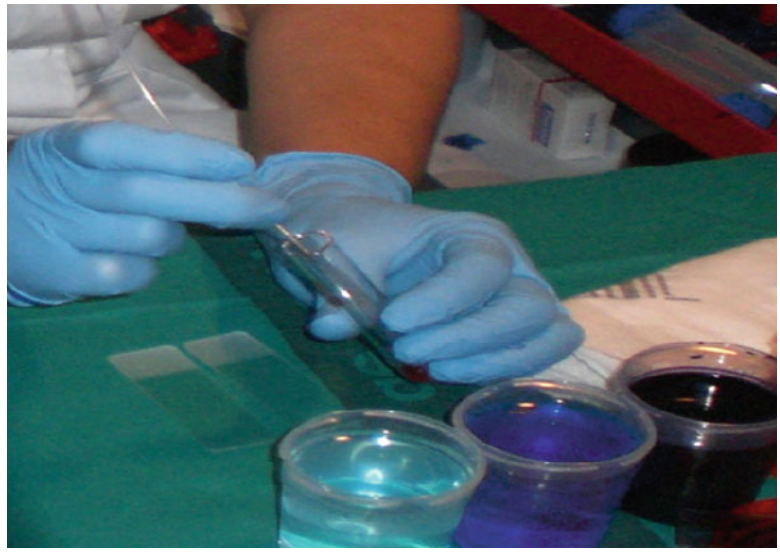


Fig. 21.9 Cell block

rapid on-site cytological evaluation (ROSE) of needle aspirates is used to assess sample adequacy and to detect a positive biopsy [23].

No guidelines exist regarding the number of mediastinal lymph node stations that should be sampled to ensure adequate preoperative staging of lung cancer patients. Inadequate sampling can lead to either understaging (missing N3 or N2 disease) or incomplete assessment of the extent of the disease (missing multi-station disease), both of which have the potential to alter recommended initial therapy. Recent studies of EBUS for lung cancer staging report an average of fewer than two lymph nodes sampled per patient, suggesting that only one lymph node station is sampled in many of the patients. The European Society of Thoracic Surgery recently published guidelines on preoperative lymph node staging

for non-small cell lung cancer (NSCLC). They concluded that although there are no data to indicate that a more systematic nodal sampling should be done, more is better than less. Extrapolation from the surgical data supports that approach. Recommendations from the American Thoracic Society are sampling bilateral upper and lower paratracheal lymph nodes and subcarinal nodes (five stations) [1, 3].

Although routine systematic sampling of multiple mediastinal lymph node stations is a logical goal, it is difficult to determine whether it yields any benefit to patients compared with targeted sampling of fewer but more clinically suspicious nodes. The theoretical benefits of a more systematic sampling are greater sensitivity for detection of mediastinal disease in general and N3 and multi-station disease in particular. The necessity of a systematic nodal sampling assumes greater importance, and development of guidelines seems appropriate [24, 25].

There is little literature to guide the cytologist in determining the adequacy of the on-site specimen. It is clinically imperative for the EBUS-TBNA operator to be certain of the adequacy of the specimen as the procedure will continue or stop based upon an accurate analysis of nodal tissue. At present, there is a lack of uniformly accepted on-site adequacy criteria for EBUS-TBNA procedure. A recent study proposes these adequacy criteria and an algorithmic approach to the EBUS-TBNA diagnosis: any smear with more than five low-power fields (10× objective, ×100 magnification) of at least 100 lymphocytes each and containing less than two groups of bronchial cells/low-power field (10× objective; ×100 magnification) can be considered adequate for evaluation. These criteria pretend to avoid misinterpretation of chronically inflamed lung parenchyma as an adequate lymph node sample and to limit the possibility of not recognizing underlying pathology obscured by excessive bronchial contamination. The presence of germinal center fragments means that a smear is adequate for evaluation, independent of the above-mentioned criteria. Germinal centers are a common feature of lymph nodes but infrequent in inflamed lung parenchyma. These adequacy criteria are to be applied only to the smears not showing any identifiable pathology such as malignancy or granuloma, since these entities can entirely replace the lymph nodes [26].

It is commonly accepted that lymph nodes with short-axis diameter of 1 cm or more and round or oval shape are considered to be suspicious of malignancy. Other factors to take into account are echogenicity, border contour, calcification, and vascularization of the lymph node [27].

The procedure is short enough to be carried out in an outpatient setting and can be performed under moderate sedation so patients recover quickly and can generally go home the same day [8].

Training Requirements

This procedure requires a combination of skills. EBUS should be reserved for experienced bronchoscopists, and it has a long learning curve. The trainee should become familiar with ultrasonic imaging. The American College of Chest Physicians guidelines for interventional pulmonary procedures states that trainees should be supervised for 50 EBUS procedures and a physician should perform 5–10 procedures per year to maintain competency. The European Respiratory Society/American Thoracic Society joint statement on interventional pulmonology recommends that the initial training consists of 40 supervised procedures and that 25 procedures should be done per year to maintain competency [1, 3].

The EBUS Bronchoscopy Education Project (http//:www.bronchology.com) provides bronchoscopy educators and training program directors with competency-oriented tools and materials to train student bronchoscopists and assess progress along the learning curve. This course addresses endobronchial ultrasound physics, equipment (processors, bronchoscopes, needles, radial, and linear array transducers), techniques, mediastinal anatomy, lung cancer staging according to universally accepted IASLC guidelines, and EBUS–CT–white-light bronchoscopy correlations. This project provides standardized schedules, contents,

checklists, assessment tools, training models, and train-the-trainers instructions, but there is no officially accepted method of assessing EBUS technical skills or competency. In a recent study, significant differences between groups with different degrees of experience in EBUS procedures were noted for total procedure time, percentage of lymph nodes identified, and percentage of successful biopsies. In the same study, the use of an EBUS simulator in the assessment of EBUS skill level was validated, as it can accurately discriminate between operators with different levels of clinical EBUS experience. [28]

A recent study provides a potential model for evaluating competence in both trainees and consultants as it can monitor ongoing practice. This report suggests that the learning curve for EBUS is greater than previously reported using different methods and that even experienced bronchoscopists vary in their speed of learning [29].

Summary and Recommendations

The use of ultrasonography in respiratory endoscopy represents one of the most relevant and significant technical advances of the last decade. Compared to standard bronchoscopy with fluoroscopy, radial EBUS improves the diagnostic yield for peripheral nodules smaller than 2 cm; in case of mediastinal or hilar adenopathy and peritracheal lung tumors, radial or linear EBUS improves the yield, eliminating the need for additional procedures. Linear EBUS has become part of the study protocols and recommendations of different scientific societies for the staging of mediastinal and hilar lymph nodes in patients with suspected or known bronchopulmonary neoplasm. Combined EUS and EBUS can reach almost all nodal stations with a reported sensitivity of 93%. Current lung cancer staging guidelines acknowledge endosonography as a minimally invasive alternative to mediastinoscopy to detect nodal disease, reducing the need for surgical staging in up to two thirds of the patients [24, 25].

One of the main question is how reliable are the endobronchial ultrasound features to predict lymph node metastasis. Memoli et al. evaluated 227 lymph nodes in 100 patients, being 22.5% of the nodes positive for malignancy. According to their results, lymph node size on both CT scan and ultrasound and ultrasonographic shape (round and oval), are predictors of malignancy (*P*: 0.0002). Echogenicity, border contour, and site of biopsy were not significantly associated with cancer. Hypermetabolic lymph nodes on PET scan did not predict malignancy once adjusted for CT scan size. They also concluded that the number of samples taken is unlikely to significantly improve sensitivity; as in 94.8% of lymph nodes with a clear diagnosis, the ROSE of the first pass correlated with subsequent passes [27].

EBUS-TBNA is usually performed using de 22 G dedicated TBNA needle. There are no differences in the diagnostic yield between the 21 G and 22 G needles during EBUS-TBNA although it has been found that histological structure was better preserved in the lesions collected by the 21 G needle. Routinely using a new needle for each station may be a significant expense without any clear benefit. The use of a new needle only after a positive biopsy with ROSE would be one way to efficiently target the additional expense to only those patients likely to benefit.

In a recent study, it has been demonstrated that the sensitivity of endosonography is similar to that of mediastinoscopy (85% vs. 79%, respectively) and that endosonography is associated with a lower complication rate (1% vs. 6% for mediastinoscopy), so it is proposed that endosonography should be the first step for mediastinal nodal staging. According to this group, up to 11 patients need to undergo mediastinoscopy to identify one single patient with mediastinal nodal metastasis [25].

To improve the yield of EBUS-TBNA, it is important to optimize the methodology of specimen handling during the procedure. Molecular testing is an emerging tool for the management of patients with lung cancer, especially in directing targeted therapy with *EGFR* (epidermal growth factor receptor) tyrosine-kinase inhibitors, and *EGFR* gene mutation assessment, and other molecular markers such as *ALK* (anaplastic lymphoma kinase) fusion gene alteration and V-Ki-ras2 Kirsten rat sarcoma viral oncogene

homologue (*KRAS*) mutations are of importance for current management decisions. Furthermore, there is a possibility of genetic difference between the primary tumor and metastatic sites because of the tumor heterogeneity. Molecular assessment of the lymph nodes by EBUS-TBNA may lead to optimal treatment of patients with advanced lung cancer [22].

Current evidence on the safety and efficacy of the EBUS procedure appears adequate to support the use of this procedure.

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Endobronchial Ultrasound: Clinical Applications

22

Donald Ray Lazarus, Carlos A. Jimenez, and George A. Eapen

Introduction

Ultrasound has long been used to image thoracic structures, and the use of an ultrasound endoscope allowing visualization of structures surrounding the esophagus was first described in 1980 [1]. It was not until the early 1990s that endobronchial ultrasound (EBUS) was developed, but since then EBUS has dramatically changed the practice of bronchoscopy [2, 3]. Before the advent of EBUS, the bronchoscopist's view was limited to those structures he or she could visualize within the airways or with fluoroscopy. With EBUS the bronchoscopist can now visualize the structures in and adjacent to the airway wall using ultrasound. EBUS can be performed using a radial probe (RP-EBUS) or a convex probe (CP-EBUS) [4]. This chapter will review the clinical applications of EBUS. A more detailed discussion of the technical aspects of EBUS will be undertaken elsewhere in this text.

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Basic Equipment and Technique

EBUS using the radial probe offers a 360° view of the airway wall as well as the structures surrounding it [2]. In RP-EBUS the flexible bronchoscope is advanced to the area of interest. Then a flexible ultrasound probe connected to an ultrasound unit and screen is inserted into the airway via the working channel of the bronchoscope [5]. The probe is surrounded by a balloon sheath which is filled with water. Once the probe is in the airway, the balloon sheath is inflated with water, optimizing ultrasound contact with the airway wall [6]. RP-EBUS using the standard 20 MHz probe allows a depth of penetration of up to 5 cm with a resolution of less than 1 mm [2].

EBUS using the convex probe, in contrast, is performed using a specialized bronchoscope which has an integrated 7.5 MHz convex ultrasound transducer at its tip. The direction of view is 30° forward oblique with an angle of view of 90°. While the CP-EBUS does not provide as good an image resolution as RP-EBUS, it does offer greater depth of penetration. Perhaps the greatest advantage of CP-EBUS is that the bronchoscope also has a separate working channel which allows transbronchial needle aspiration to be performed under real-time ultrasound guidance [7]. A special echogenic 21 or 22 gauge needle with an internal stylet is used to obtain the samples [6]. Miniature forceps have also been developed that allow forceps biopsies to be taken

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Table 22.1 Indications for radial probe EBUS

Diagnostic evaluation of endobronchial lesions
Guiding therapy of endobronchial lesions or lesions adjacent to the bronchi
Diagnostic evaluation of pulmonary parenchymal nodules
Staging of non-small cell lung cancer
Diagnosis of mediastinal lesions
Guiding placement of fiducial markers

under real-time ultrasound guidance using the CP-EBUS bronchoscope [8].

Clinical Applications of Radial Probe EBUS

Although the clinical applications of radial probe and convex probe EBUS do overlap somewhat, they are largely complementary. The indications for RP-EBUS are summarized in Table 22.1.

RP-EBUS for the Evaluation of Endobronchial Lesions

Most lung cancer is detected after it has reached late stage when treatment outcomes are poor. Detection of lung cancer early in its course while the disease is still preinvasive or minimally invasive may allow more effective early treatment. Patients who are at high risk for lung cancer may have central early lung cancers: radiographically occult central lesions detected at an early stage by bronchoscopy or sputum cytology. Diagnosis and treatment of these lesions can be challenging. The addition of autofluorescence bronchoscopy to standard white-light bronchoscopy has greatly improved the sensitivity of bronchoscopy for detecting such lesions, but its low specificity means that it is often unable to distinguish early neoplastic lesions from inflammation, scarring, or other nonneoplastic localized changes [9, 10]. This can lead to unnecessary biopsies with increased cost and more risk to the individual patient [10]. Autofluorescence bronchoscopy is also less helpful for determining the depth of invasion of such early endobronchial lesions. The depth of invasion, along with the location of the lesion and the performance status of the patient, plays a major role in determining the most appropriate and effective type of therapy [9]. The standard 20 MHz radial probe is able to clearly distinguish the five normal layers of the bronchial wall of the trachea and cartilaginous bronchi (Fig. 22.1). The excellent resolution provided by RP-EBUS makes it an ideal tool for evaluating such endobronchial lesions [5, 11].

Herth et al. prospectively evaluated all patients undergoing autofluorescence bronchoscopy at two institutions. Those patients who had lesions with nonspecific changes ($n=32$) or findings suspicious for malignant changes ($n=42$) were also evaluated with RP-EBUS. The patients were classified by RP-EBUS into those of benign (having a preserved layered bronchial wall structure) or malignant (having thickened wall, destroyed layer structure, or parabronchial infiltration). Then endobronchial biopsies were obtained and the histology was correlated with the findings by RP-EBUS. RP-EBUS gave the correct diagnosis in 92% of benign lesions vs. 55% for autofluorescence bronchoscopy and in 97% of malignant ones vs. 69% for autofluorescence. This suggests that RP-EBUS significantly improves the diagnostic specificity and negative predictive value of autofluorescence bronchoscopy for such central early lung cancers and should be used in conjunction with autofluorescence bronchoscopy to evaluate them when available [10].

Several studies have shown RP-EBUS to be useful in assessing the depth of invasion of endobronchial tumors, which can be an important factor in determining therapy for such lesions. Kurimoto and colleagues compared RP-EBUS determination of depth of tumor invasion in 24 lung lobes resected for known lung cancer with histologic findings and found a 95.8% correlation between their conclusions [5]. Tanaka and colleagues used RP-EBUS to evaluate 35 patients with intrathoracic malignancies in vivo in order to assess the bronchial walls for depth of tumor invasion. Fifteen of these patients went on to have surgery, and there was a 93% correlation between the histologic determination of the depth of wall invasion and the assessment

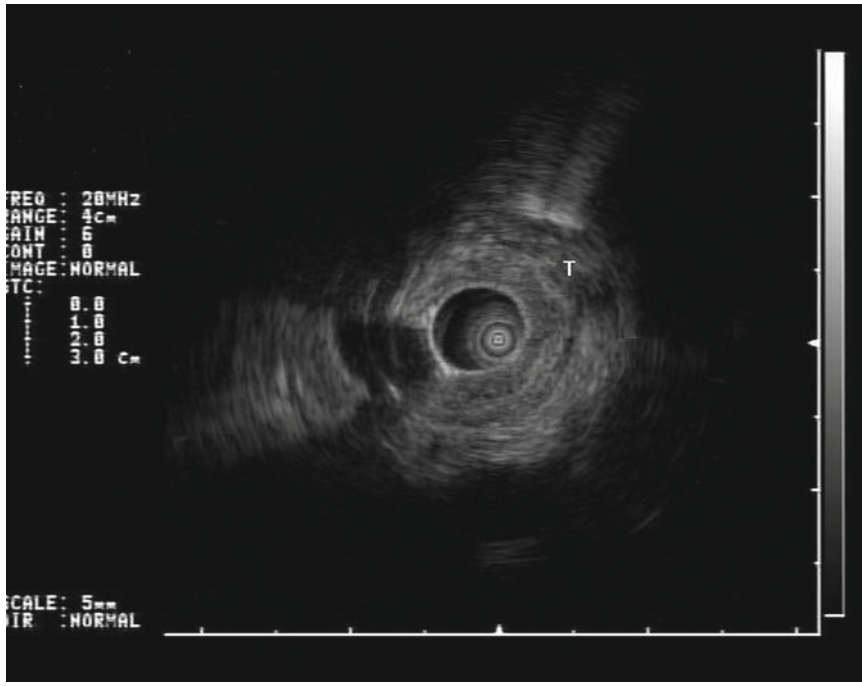

Fig. 22.1 Left main-stem tumor with cartilage disruption

made previously using RP-EBUS [12]. Miyazu et al. have also demonstrated the utility of RP-EBUS in helping clinicians choose the most appropriate therapy for central early lung cancers. Their group first evaluated six patients with central early lung cancer detected by autofluorescence bronchoscopy using RP-EBUS and used the information provided about depth of invasion to determine the suitability of each patient for photodynamic therapy (PDT). The two patients who had no cartilaginous involvement were deemed candidates for PDT and were treated with that modality with good outcome [13]. In another study their group used RP-EBUS to evaluate 12 patients with 18 biopsy-proven central squamous cell carcinomas who were thought to be good candidates for PDT based on standard bronchoscopy and high-resolution CT scan. Nine of 18 lesions assessed by RP-EBUS were found to be intracartilaginous and therefore candidates for PDT. All nine underwent PDT and had sustained complete remission at 32 months. The other nine lesions were determined to be extracartilaginous by EBUS. Of these six were resected, and histology confirmed the EBUS estimate of the depth of invasion in all six cases. RP-EBUS successfully identified the nine lesions not amenable to PDT so they could receive more appropriate treatment [14].

Herth et al. prospectively assessed the utility of RP-EBUS in therapeutic bronchoscopy more generally. They evaluated 1,174 patients who underwent therapeutic bronchoscopy and EBUS over a 3-year period. EBUS was used in conjunction with tumor debridement (mechanical, laser, APC), in airway stent placement, with endobronchial brachytherapy, in endobronchial foreign body removal, and in endobronchial abscess drainage. The authors report that EBUS changed the therapy or guided the intervention in 43% of the cases in which it was used. Examples include longer stent length for undetected parabronchial tumor spread, aiding decisions about when to stop ablative treatments due to proximity to vital structures, and changes to staging in brachytherapy [15].

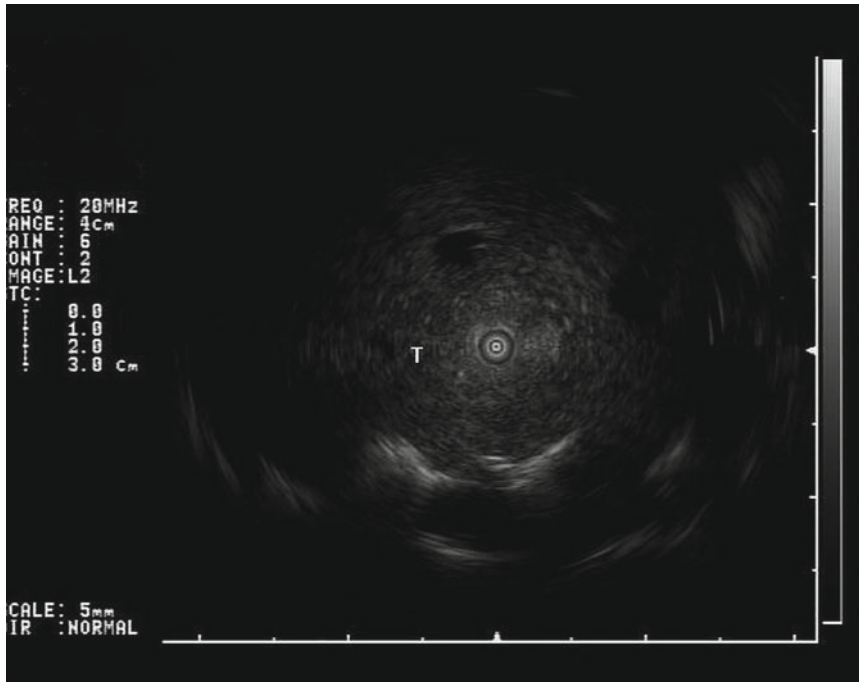

Fig. 22.2 Radial probe image of right upper lobe lung cancer

RP-EBUS for the Diagnostic Evaluation of Peripheral Pulmonary Lesions

Radial probe EBUS is also a useful tool in the diagnostic evaluation of peripheral pulmonary lesions (Fig. 22.2). Ultrasound characteristics of the peripheral pulmonary lesion seen with RP-EBUS may provide helpful information in addition to clinical and radiographic features commonly used to determine the probability that a nodule is malignant [4]. Kurimoto et al. analyzed 124 patients with peripheral pulmonary lesions who had both a confirmed histologic diagnosis and a preoperative RP-EBUS to attempt to identify ultrasound characteristics that could predict tumor type. They identified three patterns with six subpatterns. Type I lesions demonstrated a homogeneous pattern, and 23 of 25 lesions were benign (92%). Type II lesions (hyperechoic dots and linear arcs) and type III lesions (heterogeneous pattern) were almost all malignant: 98 of 99 lesions [16]. Chao's group subsequently attempted to develop a simpler predictive model. Peripheral lung lesions of an initial group of 20 patients with known histologic diagnosis were used to identify four ultrasound image patterns: a continuous hyperechoic margin, homogeneous or heterogeneous internal echoes, hyperechoic dots in the lesion, and concentric circles along the echo probe. They then enrolled 131 additional patients to assess these patterns prospectively. Five were excluded because the investigators could not agree on the pattern. Of the remaining 126 patients, 93 had a definitive diagnosis and were included in their analysis. After multivariate analysis only one of the characteristics—the presence of concentric circles—retained a statistically significant predictor of the nature of the lesion. Eighteen of nineteen lesions with concentric circles were benign [17]. Kuo et al. assessed 224 patients with peripheral lung lesions who underwent RP-EBUS and were eventually given a definitive diagnosis. RP-EBUS images were reviewed and three ultrasound characteristics were selected for analysis: continuous or noncontinuous margin between the lesions and the adjacent lung, presence or absence of an air bronchogram within

the lesion, and homogenous or heterogeneous echogenicity of the lesion. The presence of a continuous lung margin, absence of a discrete air bronchogram within the lesion, and a heterogeneous echogenicity of the lesion were all found to be predictors of malignancy. A lesion with none of the three features has a negative predictive value of 93.7% for malignancy, and a lesion with two of the three features has a positive predictive value for malignancy of 89.2% [18].

RP-EBUS is also frequently used to aid in obtaining tissue diagnosis of peripheral pulmonary lesions. Conventional flexible bronchoscopy with transbronchial lung biopsy (TBLB), usually with fluoroscopic guidance, has often been used to diagnose such lesions. Complications are rare, but the diagnostic yield varies widely and is affected by the size of the lesion and its location [19]. A systematic review published before EBUS or navigational bronchoscopy was commonly available found that while the sensitivity of bronchoscopy for central endobronchial disease was 88%, it decreased to 69% for peripheral lung nodules beyond the level of the segmental bronchi. The size of such peripheral lesions also affected diagnostic yield with traditional bronchoscopy, which had a pooled sensitivity for lesions >2 cm of 62% and for those of <2 cm in size of only 33%. By comparison, transthoracic needle aspiration with CT guidance (TTNA) had a pooled sensitivity of 92% for all lesions, although there was a trend toward lower accuracy for smaller lesions [20]. However, the superior sensitivity of TTNA for diagnosing malignant peripheral lung lesions is not without complications. TTNA carries a risk of pneumothorax as high as 20%, with 7% of patients requiring chest tube drainage. That risk is increased for those patients whose nodules are further from the pleura, who have emphysema, and who have smaller nodules. Diagnostic accuracy also decreases with a longer distance from the pleura and is less reliable for diagnosing nonmalignant lesions than malignant ones. Therefore, improved bronchoscopic approaches to peripheral lung lesions are desirable, and RP-EBUS is one of those approaches [21].

The first report of the use of RP-EBUS to aid in sampling peripheral pulmonary lesions was by Herth et al. in 2002. They evaluated 50 consecutive patients with peripheral pulmonary lesions in a crossover study. The patients were randomized to either receive TBLB with RP-EBUS followed by TBLB with fluoroscopy or vice versa. For the RP-EBUS biopsies, the EBUS probe was placed into the bronchi suspected to be the location of the lesion until it was seen with ultrasound. The probe was then removed and the forceps placed into the same bronchus and biopsies taken. The fluoroscopic biopsies were taken in the usual fashion. No significant differences in diagnostic yield were seen between the two methods. Diagnostic accuracy using RP-EBUS TBLB was around 80% [19]. In a randomized controlled trial of 221 patients, Paone and colleagues were able to show improved sensitivity (79% vs. 55%) and diagnostic accuracy (85% vs. 69%) with TBLB using RP-EBUS vs. TBLB without RP-EBUS [22]. Soon thereafter a guide sheath was introduced to improve the yield of RP-EBUS guided TBLB for peripheral lung lesions. This technique involves advancing the radial probe through a guide sheath to the lesion then withdrawing the probe once it has been localized while leaving the guide sheath in place. The biopsy tools are then advanced through the guide sheath to the lesion [23, 24]. In some reports, using RP-EBUS with guide sheath to sample peripheral pulmonary nodules has demonstrated impressive diagnostic yield, with Kurimoto and colleagues achieving a yield of 76% in lesions 10 mm or less in size [24]. Several factors seem to increase the yield when using RP-EBUS with guide sheath for peripheral pulmonary lesions. These include having the probe within the lesion rather than adjacent to it and taking at least five biopsy specimens [24, 25]. Another factor that may improve yield when diagnosing peripheral pulmonary lesions is the use of transbronchial needle aspiration (TBNA) for parenchymal lesions. Traditionally TBNA has been employed to sample mediastinal and hilar lymph nodes rather than peripheral pulmonary nodules. However, Chao et al. recently examined this in a randomized trial of 182 patients. They used

RP-EBUS without guide sheath or fluoroscopy to locate peripheral lung lesions. The patients were randomized to sampling with conventional techniques (including TBLB and bronchial washings) or conventional techniques with the addition of TBNA. The addition of TBNA to conventional techniques increased overall diagnostic yield from 60% to 78%. TBLB and bronchial wash demonstrated lower yield when the EBUS probe was located adjacent to the lesion rather than within it, but TBNA did not suffer a decrease in diagnostic yield [26].

There continues to be much interest in combining several bronchoscopic modalities to attempt to further improve diagnostic yield for peripheral pulmonary nodules. Asahina and colleagues combined virtual bronchoscopy with RP-EBUS and guide sheath in 29 patients with small peripheral pulmonary lesions. Their sensitivity was 92% for lesions between 20 and 30 mm in size, but only 44% for those less than 20 mm in size [27]. Combining a technique that improves maneuverability and navigation (such as electromagnetic navigational bronchoscopy) with one that confirms the destination (such as RP-EBUS) is a particularly attractive option [21]. Eberhardt et al. conducted a prospective randomized trial to precisely this approach. They randomized 120 patients and included 118 who had a definitive diagnosis in their final analysis. They were randomized to electromagnetic navigational bronchoscopy (ENB), EBUS, or a combination of both techniques. Diagnostic yield was higher with combined EBUS/ENB (88%) than with EBUS or ENB alone (69% and 59%, respectively). The yield of EBUS and that of ENB did not differ significantly [28]. Ishida's group showed similar results in a trial of 199 patients with small peripheral lung lesions who were randomized to EBUS with virtual bronchoscopic navigation vs. bronchoscopy with RP-EBUS but no virtual bronchoscopic navigation. They reported a diagnostic yield of 80% in the combined modality group against 67% in the group with EBUS alone [29]. The preponderance of the evidence suggests that using RP-EBUS in conjunction with multiple other modalities—such as a guide sheath, peripheral TBNA, and navigational bronchoscopy—may significantly improve diagnostic yield for small peripheral lung lesions.

Other Clinical Applications of RP-EBUS

Other clinical applications of RP-EBUS in both malignant and benign disease have been reported. RP-EBUS is still used in staging non-small cell lung cancer (NSCLC). For nodal staging with TBNA of mediastinal and hilar lymph nodes, CP-EBUS with real-time TBNA has largely supplanted RP-EBUS. However, the superiority of RP-EBUS for visualizing the airway wall has left it with a significant role in the staging of the primary tumor. RP-EBUS can be used to accurately assess the distance of the primary portion of the tumor from the carina, which is an important element of tumor staging [4]. RP-EBUS can also be used to differentiate external compression of a bronchus by tumor from direct tumor invasion of the airway wall, affecting the tumor stage. Herth et al. examined this prospectively in 105 patients who presented with central airway lesions. CT scan was first performed, followed by bronchoscopy with EBUS. The 105 patients who were analyzed went on to surgical procedures for treatment or staging which also involved sampling the airway so histologic confirmation of the bronchoscopic findings was available. EBUS was far superior to CT scan in predicting tumor invasion of the airway wall, with sensitivity, specificity, and diagnostic accuracy of 89%, 100%, and 94% for EBUS and 75%, 28%, and 51% for CT scan [30]. RP-EBUS, with and without navigational bronchoscopy as an adjunct, has also been used to aid in placing fiducial markers in order to guide stereotactic radiosurgery for lung tumors [31].

Applications of RP-EBUS in other benign disease have also been reported, although their general use has not yet been adopted. One group performed 20 RP-EBUS examinations in 10 lung transplant recipients to assess the airway layers. Good resolution of the five-layer airway structure was seen in these transplant recipients. Interestingly, the second layer consisting of hypoechoic submucosal tissue in the autologous

Table 22.2 Indications for convex probe EBUS

Staging of non-small cell lung cancer
Diagnosis of mediastinal lesions
Guiding transbronchial biopsy/aspiration of central pulmonary parenchymal nodules
Guiding placement of fiducial markers

portion of the airway was significantly smaller in patients with acute graft rejection than in those without acute graft rejection. The same layer was also found to be significantly larger in the autologous portion of the airway of patients with acute graft infection as opposed to those without acute graft infection. The significance of these findings in such a small study is unknown, but may be amenable to future investigation [32]. Another group compared high-resolution CT and RP-EBUS measurements of bronchial wall thickness and total wall area as a surrogate for bronchial remodeling in 35 asthmatics and 23 controls. There was no difference between the thickness or wall area as measured by CT vs. EBUS, and thicker bronchial walls were associated with more severe asthma. This has also not attained widespread clinical use, but may have some research applicability in the future [33].

Clinical Applications of Convex Probe EBUS

The indications for CP-EBUS are summarized in Table 22.2.

CP-EBUS for Diagnosing Mediastinal or Hilar Lesions or Adenopathy

Mediastinal abnormalities, especially lymphadenopathy, are common incidental imaging findings. Diagnosis of these lesions using conventional TBNA has been reported to have a widely variable diagnostic yield. Herth's group first reported a controlled trial of TBNA vs. TBNA with guidance by RP-EBUS to sample mediastinal lymphadenopathy. While there was no difference between TBNA and RP-EBUS-TBNA for those patients with subcarinal lymphadenopathy, the diagnostic yield was higher in the EBUS group for those patients with lymphadenopathy at any of the other mediastinal lymph node locations (84% for EBUS vs. 58% for conventional TBNA) [34]. The disadvantage of RP-EBUS guidance for TBNA of mediastinal lymph nodes is the inability to perform the needle aspiration under direct, real-time guidance. It was for this purpose that the specialized bronchoscope with an integrated convex probe and a working channel for needle aspiration was developed [7]. Since the introduction of CP-EBUS, many reports have been published detailing its utility in diagnosing mediastinal and hilar lesions.

The largest prospective study to date remains the one published by Herth et al. in 2006. They evaluated 502 consecutive patients referred for diagnosis of mediastinal or hilar lymphadenopathy greater than 1 cm in size. The referrals were either to diagnose adenopathies of unknown origin or to assist in staging lung cancer. The reference standard was cytology in positive cases and surgery or clinical follow-up in negative ones. An adequate sample was obtained in 93% of aspirated lymph nodes, with 94% being diagnostic and a specificity of 100%. The mean size of the LN sampled was 1.6 cm, and the prevalence of malignancy within the sampled nodes was very high (98%) [35].

CP-EBUS has also been useful for populations with a lower prevalence of lung cancer. The most common clinical entities for which attempts at diagnosis using CP-EBUS with TBNA has been reported are sarcoidosis and lymphoma. Boujaoude et al. reported a retrospective analysis of 78 consecutive patients with bilateral hilar and/or mediastinal lymphadenopathy. The overall yield was 92%. The most common diagnosis was sarcoidosis (73%), followed by lymphoma and reactive lymphadenopathy (both 10%), other conditions including infections and pneumoconiosis (6%), and non-lymphoma malignancy in one patient. Diagnostic yield of TBNA varied somewhat for different conditions, ranging from 67% for Hodgkin's lymphoma to 100% for reactive lymphadenopathy [36].

Wong et al. assessed 65 patients with suspected sarcoidosis and enlarged hilar or mediastinal lymph nodes by CT imaging, excluding those with known or suspected diagnosis of cancer and confirmed diagnosis of sarcoidosis. Tissue findings considered diagnostic of sarcoidosis were non-caseating granulomas without necrosis and negative culture results. Of the 65 patients, 61 (94%) had a final diagnosis of sarcoidosis. Most of these (56/65, or 87%) were confirmed by EBUS-TBNA, with the remaining five confirmed by mediastinoscopy. Of note, 51 patients also had transbronchial lung biopsy (TBLB). Only two patients who had negative EBUS-TBNA had TBLB suggesting sarcoidosis, but 11 patients who had negative TBLB had sarcoidosis confirmed on EBUS-TBNA. An adequate sample was obtained from 95% of the patients. Of the remaining three patients, one had mediastinoscopy confirming sarcoidosis, one had video-assisted thorascopic surgery (VATS) and was diagnosed with Wegener's granulomatosis, and one had no further diagnostic procedures. Two patients had adequate samples which were nondiagnostic and showed indefinite reactive changes. Both were followed for over 18 months with no further clinical or radiologic deterioration. In this population with a high pretest probability for sarcoidosis, EBUS-TBNA had a sensitivity of 91.8% with a positive predictive value of 87.5% [37].

Garwood et al. also assessed the utility of EBUS-TBNA for 50 consecutive patients with a high pretest probability for sarcoidosis who had a clinical suspicion of infection or malignancy. All the patients underwent EBUS-TBNA with rapid on-site cytologic evaluation (ROSE) to confirm adequacy of sampling. Lymph node aspirates that showed epithelioid non-caseating granulomas without necrosis without identified malignancy, lymphoma, or infection were considered diagnostic of sarcoidosis. Definitive diagnosis was obtained in 49 of the patients—48 had sarcoidosis and one had reactive lymphadenopathy. One patient was lost to follow-up after nondiagnostic TBNA. The diagnosis was reached with EBUS-TBNA in 41 of the patients. The remainder had nondiagnostic EBUS-TBNA and were diagnosed via standard TBNA after EBUS targeting, transbronchial lung biopsy, supraclavicular lymph node biopsy, or gallium scan. The sensitivity of EBUS-TBNA for the primary diagnosis of sarcoidosis in this group was 85% [38]. Tremblay et al. subsequently evaluated EBUS-TBNA vs. standard TBNA for the diagnosis of sarcoidosis. They randomized 50 patients with mediastinal or hilar lymphadenopathy to undergo bronchoscopy with either EBUS-TBNA or standard TBNA. No on-site evaluation was performed. Samples were reviewed by both the assigned clinical pathologist and a research pathologist. The diagnosis was assigned by an expert clinician who reviewed each patient's medical records at least 6 months after the bronchoscopy was performed. The diagnosis of sarcoidosis was confirmed in 47 of the 50 patients. The remaining three did not have a confirmed diagnosis, but had a benign subsequent clinical course and declined further invasive diagnostic testing. Granulomatous inflammation was found in 21 of 26 patients (80.8%) in the standard TBNA group and 22 of 24 patients (92%) in the EBUS-TBNA group. TBNA diagnostic yield was 54% in the standard TBNA group vs. 83% in the EBUS-TBNA group, a significant difference [39].

Because of prior reported discordance between cytologic and histologic samples in lymphoma, there has been some concern about using EBUS-TBNA to diagnose, subtype, and grade lymphomas presenting as mediastinal or hilar lymphadenopathy [40]. Kennedy et al. first assessed the diagnostic accuracy of EBUS-TBNA using the standard 22 gauge cytology needle with on-site cytology support. They retrospectively reviewed 25 patients with mediastinal lymphadenopathy in whom lymphoma was suspected with a reference standard of pathological tissue diagnosis or a composite of 6 months clinical follow-up including imaging. They attained adequate lymph node sampling in 24/25 patients, and EBUS-TBNA samples identified lymphoma in ten patients and benign disease in 14. One patient had a false-negative result from EBUS-TBNA. In their cohort EBUS-TBNA had a sensitivity of 91%, a specificity of 100%, and a negative predictive value of 93% for the diagnosis of

lymphoma [41]. Steinfort et al. retrospectively reviewed a prospectively collected database to assess the utility of EBUS-TBNA in diagnosing lymphoma. They evaluated patients referred for assessment of isolated hilar or mediastinal lymphadenopathy while excluding those with clinical and radiologic features strongly suggestive of sarcoidosis. Fifty-five patients were included. Those in whom EBUS-TBNA was nondiagnostic either underwent subsequent surgical biopsy or at least 6 months of clinical and radiographic surveillance. EBUS-TBNA provided adequate tissue for evaluation in 48/55 (87%) of cases and achieved diagnosis in 42/55 (76%) of cases. Lymphoma was ultimately found in 21/55 patients (38%), and EBUS-TBNA was diagnostic in 16 of these for a diagnostic sensitivity for lymphoma of 76%. Of the 16 patients with lymphoma diagnosed by EBUS, four needed additional surgical procedures to guide management. If the four patients who needed additional diagnostic procedures are considered to have had inadequate diagnostic tissue, a more accurate sensitivity for the definitive diagnosis of lymphoma may actually be 57%. The authors report a specificity of 100% and a negative predictive value of 87% for EBUS-TBNA in the diagnosis of lymphoma [40]. More recently Ko et al. reviewed 224 EBUS-TBNA specimens taken from 120 patients after excluding those which were taken from primary lung lesions or in which metastatic carcinoma was found. An on-site cytopathologist assessed each specimen for adequacy as aspirations were taken. In addition, the cytopathologist on-site triaged the specimens to appropriate ancillary studies based on their initial morphologic characteristics. The ancillary studies were performed on the cell suspensions obtained from rinsing the needles after each aspiration, and those used include microbiologic testing if granulomas were seen and immunophenotyping for those samples suggesting either lymphoma or reactive lymphadenopathy. When lymphoma was confirmed by immunophenotyping, subsequent immunohistochemistry and FISH analysis were also performed. Adequate lymphoid tissue was obtained in 95/120 patients. In 54 cases the initial impression was of benign lymphoid tissue. Ancillary studies were performed in the other 41 cases. Only ten cases of lymphoma were diagnosed, seven non-Hodgkin lymphomas and three Hodgkin lymphomas. Of the non-Hodgkin lymphomas, 6/7 were able to be fully classified using immunohistochemistry and FISH analysis. The seventh case had insufficient cellularity for immunophenotyping. Of the three cases of Hodgkin lymphoma, only one had sufficient tissue for immunohistochemistry in Reed–Sternberg cells. Two of three underwent subsequent excisional biopsies to confirm nodular sclerosis type by histology. The third was diagnosed with recurrent disease, so no histologic assessment was deemed necessary. The authors suggest that EBUS-TBNA is an acceptable alternative to excisional biopsy for diagnosing and classifying most non-Hodgkin lymphomas presenting as mediastinal or hilar lymphadenopathy if on-site cytopathologic evaluation is used to triage samples for additional testing [42]. The small number and size of studies looking at this particular application of EBUS-TBNA necessarily limit generalizable conclusions. While the yield of EBUS-TBNA for lymphoma presenting as mediastinal lymphadenopathy appears to be less than it is for sarcoidosis, it still seems to be fair and may spare many patients with lymphoma more invasive diagnostic procedures.

EBUS-TBNA has also been used to diagnose and occasionally treat a wide variety of other conditions presenting as mediastinal abnormalities. Similarly to conventional bronchoscopy, EBUS-TBNA has been used to diagnose numerous types of infectious diseases presenting with mediastinal masses or lymphadenopathies. These include bacterial, fungal, and mycobacterial infections [40, 43, 44]. Published case reports have shown EBUS-TBNA to be useful in the evaluation and treatment of bronchogenic cysts located in the mediastinum. While most bronchogenic cysts can be diagnosed by CT imaging alone, some with more mucoid contents mimic the attenuation of soft tissue on CT. In these cases EBUS-TBNA can be used to make the diagnosis, and needle aspiration with or without antibiotics has been used to treat patients with bronchogenic cysts who were not willing to undergo surgery

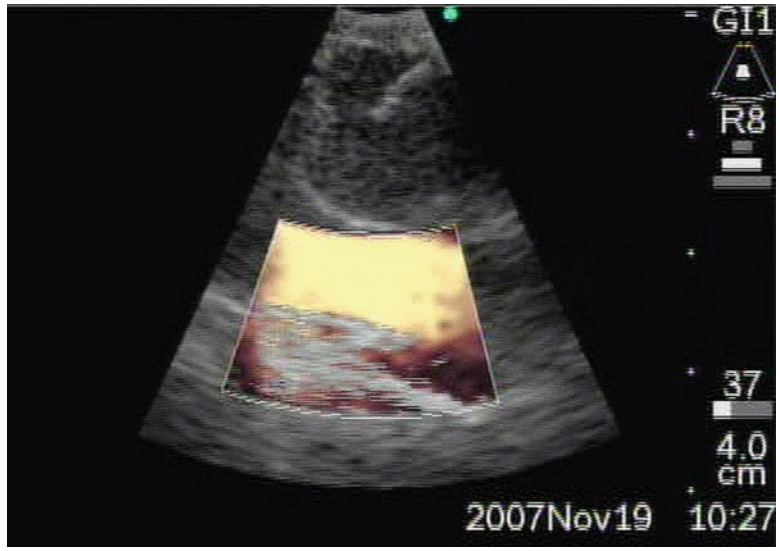

Fig. 22.3 EBUS-TBNA station 4R

[40, 45, 46]. EBUS-TBNA has also been used to sample thyroid nodules in patients with small cell lung cancer and intrathoracic goiters and parathyroid adenomas as well [47] (Casal R. personal communication, 1 May 2012).

CP-EBUS for the Staging of Non-Small Cell Lung Cancer

EBUS, particularly CP-EBUS, has found its most widespread use in the lymph node staging of non-small cell lung cancer. There has been great interest in this application of EBUS because the nodal stage has great impact on whether or not a patient will benefit from surgery. Imaging modalities have been unsatisfactory for determining nodal stage. Pooled analysis of CT scan and positron emission scanning (PET) for the noninvasive staging of the mediastinal and hilar lymph yields a sensitivity for CT of only 51% and for PET of only 74% [48]. Many patients with NSCLC therefore require invasive staging of the mediastinal lymph nodes. The most recent edition of the American College of Chest Physicians' evidence-based clinical practice guideline on the staging of non-small cell lung cancer recommends invasive staging of the mediastinal lymph nodes in the absence of known distant metastasis when there is discrete enlargement of mediastinal or hilar lymph nodes, when there is a central tumor, and when mediastinal lymph nodes demonstrate increased uptake on PET scan [48, 49].

EBUS-TBNA (Fig. 22.3) is one of the most common methods used to accomplish invasive mediastinal staging of NSCLC (Fig. 22.4). The ability of CP-EBUS to guide real-time TBNA of mediastinal lymph nodes has led to its largely replacing RP-EBUS for this purpose. The use of CP-EBUS for staging the mediastinal lymph nodes of patients with NSCLC was first described by Yasufuku et al. in 2005. They performed TBNA with CP-EBUS on 163 lymph nodes of 108 patients who had confirmed or suspected non-small cell lung cancer with mediastinal lymph nodes that were suspicious for metastasis in N2 or N3 position (An overview of Definitions for Descriptors of the 7th Edition TNM Classification for Lung Cancer is provided in Table 22.3). EBUS-TBNA yielded results positive for cancer in 64 patients. Of the remaining 44, seven were followed clinically for 12 months with a benign course. The other 37 patients with negative EBUS-TBNA underwent thoracotomy, with 33/37 having no evidence of N2/N3 lymph node metastasis. This yielded a

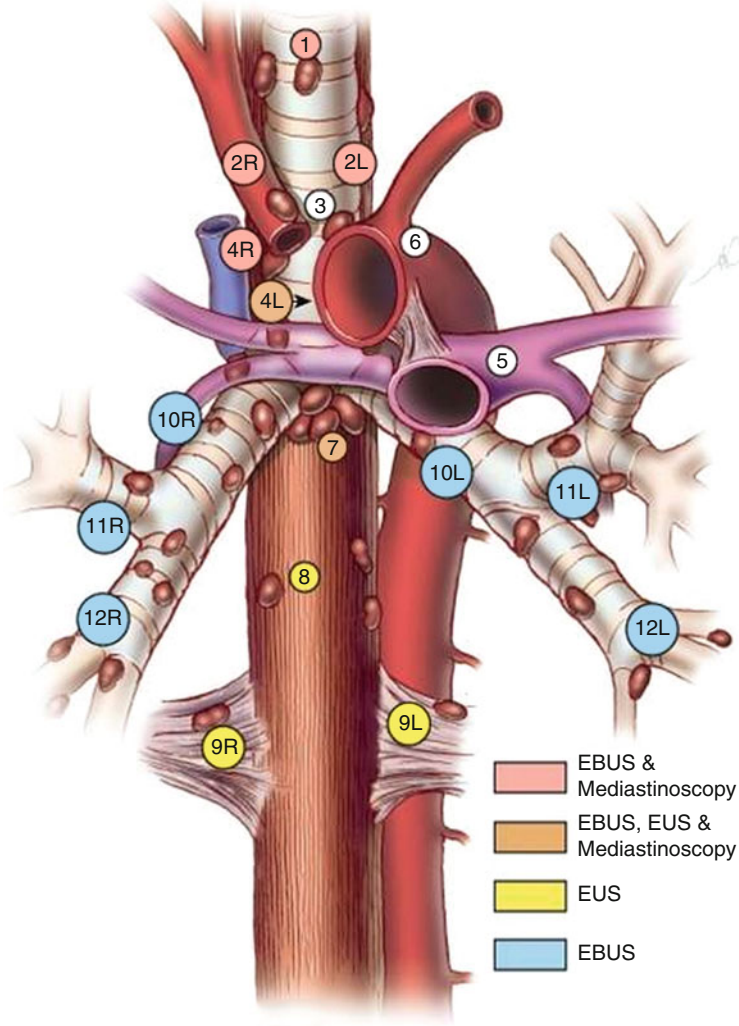

Fig. 22.4 Nodal stations (From Visual Art @ 2007, M.D. Anderson Cancer Center, The University of Texas.)

diagnostic accuracy of 96%, a sensitivity of 94.6%, and a negative predictive value of 89%. Specificity and positive predictive value were 100% [50]. Since then many other studies of EBUS-TBNA in staging of NSCLC have been published, often comparing this technique to other staging techniques.

Yasufuku et al. prospectively compared the performance of EBUS-TBNA for mediastinal staging to that of CT and PET scanning in 102 patients with proven or suspected lung cancer who were thought to be candidates for surgical resection. All patients received CT with contrast and full-body PET prior to undergoing EBUS-TBNA prior to planned surgery. Patients with proven or suspected lung cancer who were staged I, II, or IIIA with only a single positive N2 lymph node by EBUS-TBNA were considered operable and underwent resection with thoracic lymphadenectomy and comparison to staging by imaging and EBUS. Those patients who were not deemed operable had their staging results compared to the clinical course of their disease. EBUS correctly staged 24 of 26 patients who were ultimately proven to have mediastinal lymph node metastasis. Comparison of the three

Table 22.3 Definitions for descriptors of the 7th edition TNM classification for lung cancer

	Subgroup	Definition
T (tumor)		
T0		No primary tumor
T1		Tumor ≤3 cm, surrounded by lung or visceral pleura, not more central than the lobar bronchus
	T1a [a]	≤2 cm
	T1b [a]	>2 cm and ≤3 cm
T2		>3 cm and ≤7 cm, or with any of the following: visceral pleura invasion, involvement of main bronchi but ≥2 cm distal to main carina, atelectasis/obstructive pneumonitis not involving the entire lung
	T2a [a]	>3 cm and ≤5 cm
	T2b [a]	>5 cm and ≤7 cm
T3		
	$T3_{>7}$ [a]	>7 cm
	$T3_{Inv}$	Tumor directly invading chest wall, diaphragm, phrenic nerve, mediastinal pleura, or parietal pericardium
	$T3_{Centr}$	Tumor in main bronchus <2 cm from main carina, or complete lung atelectasis/obstructive pneumonitis
	$T3_{Satell}$ [a]	Separate tumor nodule/s in the same lobe as primary tumor
T4		
	$T4_{Inv}$	Tumor of any size with invasion of the heart, great vessels, trachea, carina, esophagus, vertebral body, or recurrent laryngeal nerve
	$T4_{Ipsi\ Nod}$ [a]	Separate tumor nodule/s in different lobe, ipsilateral to primary tumor
N (regional LN)		
N0		No regional metastases
N1		Metastases to ipsilateral peribronchial, perihilar, or intrapulmonary LN
N2		Metastases to subcarinal or ipsilateral mediastinal LN
N3		Metastases to contralateral hilar or mediastinal LN, or involvement of any scalene or supraclavicular LN
M (metastases)		
M0		No distant metastases
M1		
	$M1a_{Contr\ Nod}$ [a]	Separate tumor nodule/s in contralateral lung
	$M1a_{Pl\ Dissem}$ [a]	Malignant pleural or pericardial effusion
	M1b [a]	Distant metastases
Special situations		
TX, NX		T or N status cannot be assessed
T_{is}		In situ tumor
$T1_{ss}$		Superficial spreading tumor of any size, confined to the wall of the trachea or main bronchi

LN lymph node, *Inv* invasion, *Centr* central, *Satell* satellite, *Ipsi Nod* ipsilateral nodule/s, *Contr Nod* contralateral nodule/s, *Pl Dissem* pleural dissemination

[a]New subgroups added in the 7th TNM

modalities showed that EBUS-TBNA had a sensitivity of 92%, specificity of 100%, negative predictive value of 97%, and overall diagnostic accuracy of 98%. This was superior to both CT (sensitivity 77%, specificity 55%, NPV 88%, diagnostic accuracy 61%) and PET (sensitivity 80%, specificity 70%, NPV 92%, diagnostic accuracy 73%) [51]. Herth et al. subsequently prospectively evaluated 100 patients with suspected NSCLC who had CT scans without evidence of enlarged mediastinal lymph nodes and PET scans which were negative for significant

mediastinal uptake. After the imaging tests were completed, all patients underwent bronchoscopy with EBUS evaluation of the mediastinal and hilar lymph nodes. All nodes greater than 5 mm in short-axis diameter were sampled, and all patients had at least one node of that size. All 100 patients subsequently underwent either thoracotomy or mediastinoscopy, and the results of surgical pathology were used as the standard of reference. Eight patients with CT and PET scans negative for mediastinal involvement had EBUS-TBNA positive for lung cancer. Only one patient with negative EBUS-TBNA had additional lymph node metastasis (N1) detected at the time of surgery. In this group of patients EBUS-TBNA had a sensitivity of 89%, specificity of 100%, and negative predictive value of 99% for detecting mediastinal lymph node metastasis missed by CT and PET [52]. EBUS-TBNA was also compared to integrated PET-CT by Hwangbo et al. They enrolled 129 patients with histologically confirmed or suspected operable NSCLC. All patients underwent integrated PET/CT prior to bronchoscopy. They then underwent bronchoscopy with EBUS-TBNA of all identified target lymph node stations without on-site cytopathological support. Ultimately 117 patients were evaluated after excluding those with alternative diagnoses, with unexpected pleural metastases at the time of surgery, and who refused recommended surgery. Twenty-seven patients had mediastinal lymph nodes positive for malignancy with EBUS-TBNA. Of the 90 patients without malignancy on EBUS-TBNA, only three patients had malignancy found in mediastinal or hilar nodes at the time of surgery. EBUS-TBNA had sensitivity of 90%, specificity of 100%, negative predictive value of 97%, and diagnostic accuracy of 97% as compared to sensitivity of 70%, specificity of 60%, negative predictive value of 85%, and diagnostic accuracy of 62% for PET/CT. All the differences were significant except for sensitivity, which was nearly significant [53].

Mediastinoscopy has traditionally been considered the gold standard for invasive staging of the mediastinal lymph nodes in lung cancer with reported sensitivity ranging from 40% to 92%. Despite its longstanding status as the gold standard, mediastinoscopy is limited to accessing the paratracheal and subcarinal nodal stations, without the ability to sample the hilar nodes. Ernst et al. enrolled 66 patients who had lesions suspicious for NSCLC, were surgical candidates otherwise, and whose enlarged mediastinal lymph nodes (if present) were confined to paratracheal and subcarinal lymph node stations in a prospective crossover study. All patients underwent mediastinoscopy with EBUS-TBNA incorporated into the preoperative bronchoscopy of each patient—all performed within a week of the mediastinoscopy. Patients with negative mediastinal evaluation and those with limited IIIA disease (single positive N2 lymph node) were offered surgical resection. A definitive diagnosis was established by either mediastinal procedure in 49/66 patients (74%), and 61 patients went on to have surgery. In the per-patient analysis, EBUS-TBNA and mediastinoscopy did not differ in diagnostic yield (89% vs. 79%; $p=0.1$). In the per-lymph node analysis, EBUS-TBNA had a higher diagnostic yield than mediastinoscopy (91% vs. 78%; $p=0.007$) with the entire difference coming from better yield for EBUS for the subcarinal lymph node station [54]. Annema et al. randomized 241 patients with potentially resectable NSCLC to compare surgical mediastinal staging (mediastinoscopy with left parasternal mediastinotomy if needed) with endosonographic staging (consisting of endoscopic ultrasound-FNA and EBUS-TBNA). All patients who underwent endosonographic staging also underwent surgical staging afterward if no nodal metastases were found by endosonography. Endosonography plus surgical staging showed greater sensitivity than surgical staging alone (94% vs. 79%; $p=0.02$). There was not a significant difference in negative predictive value between the groups. One secondary outcome was also significantly less in the endosonography group: 7% underwent unnecessary thoracotomies vs. 18% in the surgical staging group [55]. Yasufuku et al. analyzed 153 patients with NSCLC who required mediastinoscopy as part of the staging evaluation of their cancer. All patients who were analyzed underwent EBUS-TBNA

followed immediately by standard cervical mediastinoscopy. The surgeons were blinded to the cytopathology results, and each patient served as his or her own control. The patients who had no evidence of N2/N3 disease on EBUS-TBNA and mediastinoscopy then underwent pulmonary resection with systematic lymph node resection, enabling correlation of the results with prior EBUS-TBNA and mediastinoscopy results. EBUS-TBNA and mediastinoscopy were comparably accurate, with respective sensitivity, negative predictive value, and diagnostic accuracy of 81% vs. 79%, 91% vs. 90%, and 93% vs. 93%. Both tests had a specificity of 100%. There were fewer complications with EBUS-TBNA than with mediastinoscopy. These results suggest that EBUS-TBNA is equivalent to mediastinoscopy for staging of NSCLC, even without the addition of EUS-FNA as was done in the trial by Annema [56].

Endoscopic ultrasound (EUS) with FNA, generally performed by gastroenterologists, preceded the development of EBUS by several years. EUS-FNA has also been used to diagnose mediastinal lesions and assist in the mediastinal staging of lung cancer. EUS alone has somewhat limited application for sampling mediastinal lymph nodes because it is unable to sample those nodal stations anterior to or to the right of the trachea and also unable to sample hilar lymph nodes. EBUS, on the other hand, is able to reach those nodal stations anterior to the trachea as well as the hilar nodes. Its anatomic limitations for nodal staging are primarily in reaching the lymph nodes of the aortopulmonary window, the lower esophageal nodes, and the nodes of the inferior pulmonary ligament [50]. The two techniques are complementary in their reach and at least theoretically should be able to reach all the mediastinal lymph node stations except for the aortopulmonary window and perhaps the upper retrotracheal stations. Several groups have assessed their collaborative use in staging the mediastinum of patients with NSCLC. Small preliminary studies of a combined EBUS-TBNA/EUS-FNA approach using separate bronchoscopes and endoscopes appeared promising, and these have led to subsequent larger studies evaluating such a combined approach [57, 58]. Herth et al. assessed 150 consecutive patients with non-small cell lung cancer and no evidence of extrathoracic metastases. The investigators included 139 patients who were confirmed to have NSCLC in their analysis. The same operator performed both EBUS and EUS for each procedure using a single CP-EBUS bronchoscope. Endoscopic mediastinal diagnosis was confirmed with thoracotomy, thoracoscopy, or 6–12 months of clinical follow-up. The prevalence of mediastinal lymph node metastasis was 52% (71/139 patients). EBUS-TBNA detected the malignant nodes in 65/71 patients (91%), and EUS-FNA detected the malignant nodes in 63/71 patients (89%). The combined technique found the malignant lymph nodes in 68/71 patients (96%). The negative predictive value of the combined approach was 96% and was superior to that of either EBUS-TBNA (92%) or EUS-FNA (82%) alone [59]. Hwangbo et al. also assessed EBUS-TBNA and EUS-FNA using a single EBUS bronchoscope for each procedure. They enrolled 150 patients with confirmed or suspected NSCLC who required mediastinal staging. All underwent EBUS with 299 mediastinal lymph node stations sampled. EUS was performed in 149 patients, with FNA of 64 mediastinal nodal stations obtained in 53 patients. Mediastinal lymph node metastasis was found by EBUS in 38 patients and by EUS in an additional three patients. Of the remaining 109 patients, 102 were evaluated—seven were excluded because they either did not have surgery, did not have lymph node dissection performed, or were given an alternative diagnosis precluding surgery. Of the 102 patients with negative mediastinal lymph nodes by EBUS + EUS who underwent surgery with lymph node dissection, only four had mediastinal lymph node metastases. The combined approach did not differ significantly from EBUS-TBNA alone in terms of sensitivity, specificity, negative predictive value, and diagnostic accuracy. The combined approach did show a significantly higher proportion of accessible mediastinal lymph node stations when compared to EBUS-TBNA alone (85% vs. 79%; $p=0.015$) [60].

Although combined EBUS and EUS staging of the mediastinum by a single operator using an EBUS bronchoscope holds great promise, limitations of operator training, credentialing, and possibly equipment may restrict its generalizability.

Restaging mediastinal lymph nodes after induction chemotherapy for stage IIIA-N2 NSCLC is another potential application of EBUS-TBNA. Ongoing studies are assessing the role of surgery for these patients after potential downstaging with neoadjuvant chemotherapy, but the optimal method for restaging the mediastinum has yet to be determined. Imaging techniques, including CT and PET, are insufficiently sensitive or specific to restage the mediastinum. Mediastinoscopy has been used for this purpose, but is significantly more technically difficult in this setting due to fibrosis induced by both the initial procedure and the subsequent chemotherapy. This has resulted in decreased yield and increased complications for mediastinoscopy for restaging. Herth et al. assessed EBUS-TBNA for restaging of the mediastinum in such patients after induction chemotherapy. The investigators enrolled 124 patients with stage IIIA-N2 NSCLC who had undergone neoadjuvant chemotherapy and then shown either a response to therapy or stable disease on follow-up CT. All patients then underwent EBUS-TBNA with a plan to proceed to surgical resection and lymph node dissection regardless of the results of EBUS-TBNA. Residual N2 disease was confirmed in lymph node aspirates of 89 patients (72%), with 35 patients (28%) without any evidence of residual disease by EBUS-TBNA. Thoracotomy confirmed persistent N2 disease in all 89 of the patients who had positive lymph node aspirates. Additionally, 28/35 patients (80%) of the patients without evidence of persistent N2 malignancy on EBUS-TBNA had malignant cells present on thoracotomy. EBUS-TBNA demonstrated a sensitivity for residual mediastinal N2 disease after neoadjuvant chemotherapy of 76%, with a specificity of 100%, a negative predictive value of 20%, and an overall diagnostic accuracy of 77%. Of the 28 false-negative N2 lymph nodes, 91% had been correctly identified by EBUS, and the failure to diagnose persistent malignancy was due to sampling error. This may be in part due to changes produced in the lymph nodes by the neoadjuvant therapy. When the results of this study are considered, the real utility of EBUS-TBNA in restaging NSCLC after neoadjuvant therapy may simply be as a way to identify patients with persistent disease who may therefore not need to proceed to surgery. Those with negative results on EBUS would still require surgical restaging to reach an acceptable negative predictive value [61].

Two groups have also evaluated the ability of ultrasonographic features of mediastinal or hilar lymph nodes to predict nodal metastasis when staging the mediastinum using CP-EBUS. Fujiwara et al. performed a retrospective analysis of 1,061 lymph nodes from 461 patients who underwent EBUS-TBNA for staging of NSCLC at a single center. Images of all the nodes that were sampled using CP-EBUS during the period of the study were evaluated in JPEG and digital video formats by three reviewers who were blinded to the results of the TBNA. The ultrasonographic appearance of the nodes was classified using six characteristics, and these characteristics were compared to the final pathologic diagnosis for each lymph node. Four of these nodal features were found to be independently predictive of lymph node metastasis: round shape, distinct margin, heterogeneous echogenicity, and presence of coagulation necrosis sign (a hypoechoic area within the node that has no blood flow). The presence of any of the four features increased the risk of metastasis to the node. The absence of all four features had a negative predictive value of 96% for malignancy within the node [62]. Wang Memoli et al. prospectively evaluated 227 lymph nodes in 100 patients who had suspected or confirmed NSCLC, who had PET scan performed prior to the procedure, and who were referred for EBUS-TBNA to a single center. EBUS was performed and lymph node characteristics were recorded prior to TBNA. The ultrasound characteristics that were recorded and assessed were size, shape, echogenicity, border definition, and number of lymph nodes at each lymph node station. They found that the only

ultrasonographic characteristics that increased the probability of malignancy in their cohort were size >10 mm and round or oval shape. Interestingly, despite the increased probability of malignancy in lymph nodes larger than 10 mm, 10% of sampled lymph nodes <10 mm in size were confirmed to have malignant metastases. This suggests that while certain ultrasonographic characteristics may be correlated with an increased probability of lymph node metastases, their negative predictive value is not good enough to allow biopsy to be deferred because the characteristics in question are absent [63].

Summary

Since its advent endobronchial ultrasound has proven to be one of the most versatile and powerful diagnostic tools available to the bronchoscopist. Its most widespread uses have been found in the staging of non-small cell lung cancer, diagnosis of diseases of the mediastinum, evaluation of the airway wall, and sampling peripheral pulmonary parenchymal lesions. Other applications continue to be investigated, and EBUS should continue to be among the most valuable techniques available to the interventional bronchoscopist.

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Part V

Pleural Conditions

Pleural Anatomy

23

Juan Antonio Moya Amorós and
Anna Ureña Lluberas

Pleural Embryology

The pleural membranes are originated from the embryonic coelomic cavity lining, from which vital organs such as the heart, intestines, and lungs also develop. Coelomic cavity is divided into peritoneal and pleural cavity, which in turn is divided into two by the pericardium. Later, the lungs develop through primary buds that grow from a central mesenchymal mass, and as they grow laterally, they invaginate into each pleural space, thus taking the pleural lining. The pleura covers the entire chest cavity (parietal pleura) and the lungs (visceral pleura).

Histologically, the pleura is composed by five layers:

- A single layer of mesothelial cells
- A thin submesothelial connective tissue
- A thin elastic superficial layer
- A layer of loose connective tissue
- A deep fibroelastic layer

The surface of mesothelial cells contains microvilli. These microvilli are believed to function in liquid absorption, but recently it has been shown that they contain glycoproteins to lubricate the sliding of the two pleural layers.

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Pleural Layers

Parietal Pleura

The parietal pleura is lining the pleural cavity internally, and it can be divided into three parts, costal, diaphragmatic, and mediastinal:

1. *Costal pleura*: It lines the inner part of the chest wall, extending over the ribs and intercostal muscles, cartilage, and a small portion of the sternum. Its upper limit is the first rib, and the lower limit is formed by the diaphragmatic fingerings; backwards, it reaches the side of the vertebral bodies and anteriorly the anterior pleural sinus (Fig. 23.1a).
2. *Diaphragmatic pleura*: It is tied closely to the corresponding hemidiaphragm. It has a firm connection to the phrenic center level (preventing its cleavage) and a looser union at the muscular portion of the diaphragm (Fig. 23.1b).
3. *Mediastinal pleura*: It extends over all mediastinal organs, between the costo-vertebral canal in the back and the sternum interiorly, interrupted by the pulmonary hilum. The pulmonary hilum divides the mediastinal pleura into three parts: anterior mediastinal pleura, superior mediastinal pleura, and posterior mediastinal pleura. In the right hemithorax, it produces the inter azygus-esophageal recess and in the left hemithorax the interaortic-esophageal recess (Fig. 23.1c).

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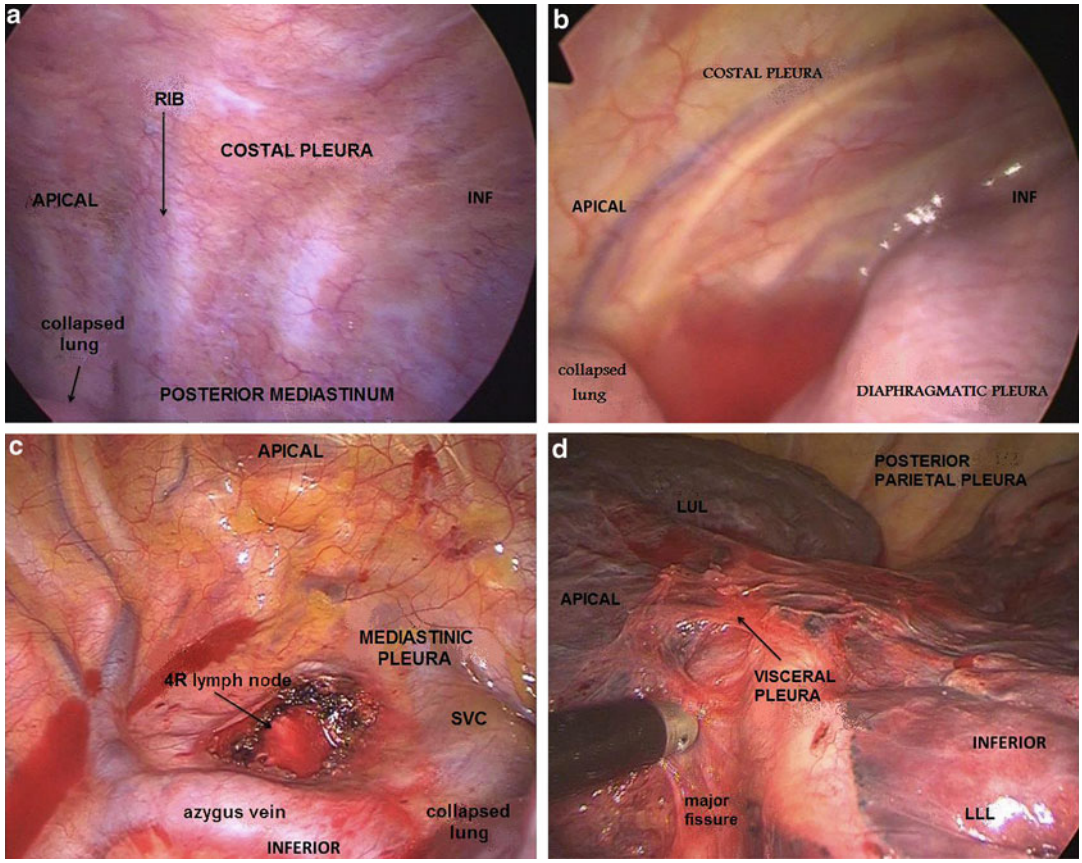

Fig. 23.1 Pleural endoscopic images. *INF* inferior, *4R* right paratracheal lymph node region according to Naruke's classification, *SVC* superior vena cava, *LUL* left upper lobe, *LLL* left lower lobe. (**a**) Endoscopic image of the costal pleura. (**b**) Endoscopic image of the diaphragmatic pleura. (**c**) Endoscopic image of the mediastinal pleura. (**d**) Endoscopic image of the visceral pleura (*left* lung)

Visceral Pleura

The visceral pleura is intimately attached to the outer surface of the lung (Fig. 23.1d). There is no cleavage plane, so that it cannot be dissected without injuring the lungs. It covers all lung surface, penetrating and producing the lung fissures; however, on the internal lung surface (lung hilum), it reflects to continue with the mediastinal parietal pleura. Here, there is a small lung surface without pleural lining, and the pleural reflection extends down to the diaphragm, and it is called the triangular or inferior pulmonary ligament. The hilar region is shaped as a long inverted teardrop, with a rounded superior end covering the lung pedicle and a triangular space whose base is superior, that elongates downward, and it is called triangular ligament as discussed above. This ligament helps fixing the lung not only to the mediastinum but also to the diaphragm where it ends. Between the two pleural reflection sheets that form the triangular ligament, nodal station 9 is found (Naruke's classification).

Pleural Recesses

The pleural space is a virtual space delimited between the parietal and the visceral pleurae. This space has important anatomical accidents, and the most important of them are called sinuses or pleural recesses, which are the following:

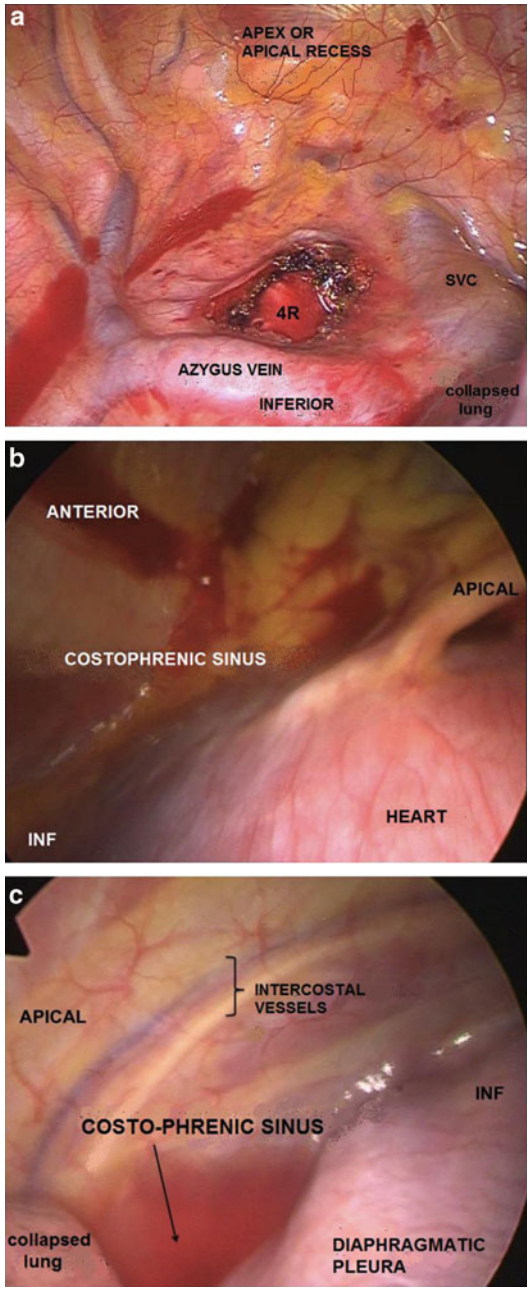

Fig. 23.2 Pleural endoscopic images. *INF* inferior; *4R* right paratracheal lymph node region according to Naruke's classification, *SVC* superior vena cava, *LUL* left upper lobe, *LLL* left lower lobe. (**a**) Apical pleural recess. Endoscopic view. (**b**) Anterior costo-mediastinic or cardiophrenic recess. Endoscopic view. (**c**) Posterior costo-diaphragmatic or costophrenic recess

1. *Pleural apex or superior pleural sinuses*: They are cervical since they are situated above the clavicle, at the base of the neck. At the apex, the costal and mediastinal pleurae join forming the upper cone (Fig. 23.2a).

On the outer side, the three suspensor ligaments of Sebileau insert:

- Transverse-pleural ligament: It goes from C7 transverse apophysis to the pleural apex and issues an expansion to the first rib. If it contains muscle fibers, it is called scalenus minimus muscle.
- Costo-pleural ligament: It runs from the first rib neck to the pleural apex.
- Vertebro-pleural ligament: It runs from C7 vertebral body to the pleural apex.

2. *Anterior costophrenic recesses or cardiophrenic*: At a retrosternal level, they form an acute angle. They represent the point where the parietal costal, diaphragmatic, and mediastinal pleurae intersect. In the left side, the costophrenic recess is displaced by the heart 2.5–4 cm from the vertical line (Fig. 23.2b).
3. *Posterior costophrenic recesses*: They are located posteriorly at the level of the intersection of the diaphragmatic parietal, costal, and mediastinal pleurae on the vertebral body. Those recesses represent the most dependent points in the pleural cavity.
4. *Costo-diaphragmatic or costo-lateral recesses*: They are the greatest of all pleural recesses and the first ones that come to mind when speaking of pleural recesses. They are formed by the reflection of the costo-parietal pleura with the diaphragmatic pleura. They extend from the seventh costal cartilage in the front, to the neck of the twelfth rib in the back, running along the entire length of the costal diaphragmatic insertions and surpassing them behind the arcuate ligament. They may exceed the lower edge of the twelfth rib (Fig. 23.2c).

Fissures

They are recesses of the visceral pleura. If they are complete, they can cross the entire lung from front to back. They divide each lung into different

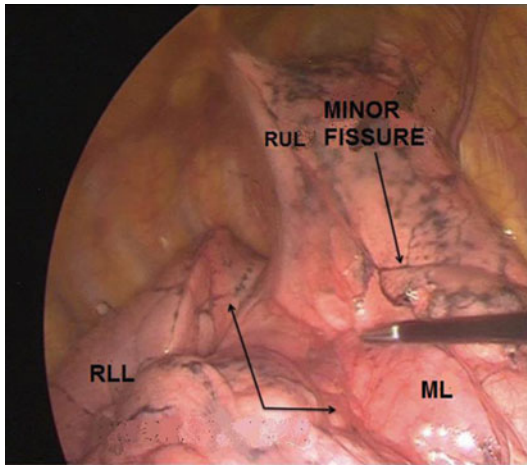

Fig. 23.3 Pulmonary fissures. Endoscopic image of a collapsed right lung. Both pulmonary fissures, separating the three lobes of the lung can be seen

lobes, three lobes in the case of the right lung and two lobes in the left lung. Supernumerary fissures may exist and also fissures defects (Fig. 23.3):

1. *Major fissure/oblique*: It originates from the fourth thoracic vertebra and ends up in the fifth intercostal space. In the right lung, it starts at the level of the fourth rib in the spinal portion of the costal side of the lung. It then descends obliquely downward and forward to reach the diaphragmatic surface. It crosses this side from lateral to medial, reaches the mediastinal prehilar side, and reflects up and backward to get to the front and bottom of the hilum. In the postero-superior portion, it separates the upper lobe from the lower lobe. In the infero-anterior portion, it separates the lower lobe from the middle lobe. In the left lung, there is only a major fissure, and it has a slightly different path as it descends in a helical manner from the top, anteriorly, and downward.
2. *Minor fissure/horizontal*: It ascends slightly from the level of the fourth intercostal space upward to the third. It is directed forward and medially, reaching the anterior edge of the lung through the mediastinal prehilar side and reaches the hilum. The minor fissure separates the lung into two lobes: middle lobe and upper lobe. In an anterior view, the lower lobe, which is posterobasal, cannot be observed.
3. *Accessory fissures*: Superior accessory fissure or azygos fissure is caused by the azygos vein arch, which in its embryonic movement cuts the mesenchyme of the upper lobe. It separates the upper lobe into two parts, a medial or Wrisberg azygos lobe and a lateral or upper lobe (proper upper lobe). Inferior accessory fissure is located in the lower lobe separating the lobar segment 6. When it is present, the portion of the lung related to this segment is called Fowler lobule.

Blood Supply and Venous Drainage

The parietal pleura receives its blood supply from systemic capillaries: Small branches of the intercostal arteries supply the costal pleura, while the mediastinal pleura is mainly irrigated by pericardium–phrenic arteries. The diaphragmatic pleura is supplied by the superior phrenic arteries. The blood supply of the visceral pleura comes from the systemic circulation through the bronchial arteries. Venous drainage of the parietal pleura goes to the intercostal veins (systemic veins), while the visceral pleura drains into the pulmonary veins.

Lymphatic Drainage

The parietal pleura lymphatics drain pleural fluid and harmful particles that reach the pleura. The lymphatic system starts with small nests that communicate with lymphatic foci draining through lymphatic vessels to the lymph nodes that run along the internal thoracic artery and internal intercostal nodes (along the ribs heads). Pleural lymphatics can eliminate 20 times the fluid generated under normal conditions (up to 0.2 ml/kg/h approximately). The visceral pleura drains through two systems (a) a superficial system that floats on the surface of the lung reaching the hilum and (b) a deep system that penetrates into the lung parenchyma to reach the hilar lymph nodes.

Pleural Innervation

Sensory nerve endings are present in the costal and diaphragmatic parietal pleurae. The intercostal nerves innervate the costal pleura and the peripheral portion of the diaphragmatic pleura. When any of these areas is stimulated, pain is referred to the adjacent chest wall. By contrast, the central part of the diaphragmatic pleura is innervated by the phrenic nerve, and the stimulation of this part of the pleura causes referred pain at the ipsilateral shoulder The visceral pleura does not contain pain fibers.

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Medical Thoracoscopy

24

Francisco Rodriguez-Panadero

Summary

Medical thoracoscopy, synonymous to "pleuroscopy," refers to the exploration of the pleural cavity under local anesthesia plus general sedation/analgesia. As opposed to *video-assisted thoracoscopic surgery* (*VATS*), general anesthesia or tracheal intubation is not necessary, and it can be performed either by trained pulmonologists or thoracic surgeons in a well-equipped endoscopy suite. Main indications are diagnosis of unexplained pleural effusions and treatment of recurrent pleural effusions or pneumothorax (pleurodesis, *talc poudrage*). Calibrated talc with particles no smaller than 10 μm (in order to prevent extrapleural dissemination with subsequent systemic complications) is mandatory whenever pleurodesis is attempted.

Introduction and Historical Perspective

According to an excellent review from Hoksch and coworkers, the term "thoracoscopy" was well known in the second half of the nineteenth century, and a thoracoscope was defined in some French dictionaries as an "Instrument for observing changes of the respiratory tract and of the lungs" [1]. Today thoracoscopy is defined as "a procedure involving internal examination, biopsy, and/or resection of disease or masses within the pleural cavity and thoracic cavity." In that article and in another two detailed historic reviews by Moisiuc and Colt [2] and Marchetti et al. [3] there is agreement in that the first reported thoracoscopy was performed in Dublin in 1865 by the Irish urologist Francis Richard Cruise, who designed a binocular cystoscope [4], and that first procedure was reported in 1866 by Dr. Samuel Gordon at the end of a case presentation of an 11-year-old girl with empyema [5]. However, Cruise himself never published anything on the thoracoscopy that he performed and there is no further reference to that procedure until Jacobaeus, who still deserves the honor to be considered as the father of thoracoscopy, because he used thoracoscopy both as a diagnostic and therapeutic tool and also overcame the problems with lack of lung collapse by inducing pneumothorax through cutting adhesions using galvanocautery (the *Jacobaeus operation*) [6]. After 1950s, due to the success of antibiotic treatment for tuberculosis, the "Jacobaeus operation" was gradually abandoned, and use of thoracoscopy subsequently declined.

Thoracoscopy began to recover in the 1970s, in particular in continental Europe where some pulmonologists became reference persons for this technique: Boutin in France, Brandt and Loddenkemper in Germany, Sattler in Austria, Swieringa in the Netherlands, Viskum in Denmark, and Cantó in Spain, among others.

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Although this technique has been performed for more than one century, the term "medical thoracoscopy" appeared about 15 years ago in order to distinguish "video-assisted thoracoscopic surgery" (VATS) from the old conventional thoracoscopy technique that had been introduced by Jacobaeus in 1910 [7]. Medical thoracoscopy is performed by pulmonologists in the endoscopy suite under local anesthesia and with intravenous conscious sedation/analgesia in most of the cases, while VATS requires general anesthesia and double-lumen tracheal intubation, and is performed almost exclusively by thoracic surgeons in the operating room [8]. Medical thoracoscopy is mostly used for diagnostic purposes (especially in pleural effusions) and for talc pleurodesis ("poudrage") to prevent recurrence of persistent pleural effusions or pneumothorax. Instead of *medical thoracoscopy*, I would support the old term *pleuroscopy*, which allows for an easy distinction between the so-called medical thoracoscopy and VATS and was used in the past by many physicians (prior to the introduction of VATS in the last decade of the twentieth century) [9].

Indications for Medical Thoracoscopy

Thoracoscopy can be performed for diagnostic as well as therapeutic purposes. The most frequent indication for diagnostic thoracoscopy relates to pleural effusion, but it can also be useful in spontaneous pneumothorax. The main indication for therapeutic thoracoscopy is pleurodesis (mostly chemical) to prevent recurrence of pleural effusion or pneumothorax.

Medical Thoracoscopy in Pleural Effusions

The primary aim of diagnostic thoracoscopy is to obtain a specific diagnosis when facing a pleural effusion of unknown origin. Most of the current guidelines recommend the addition of a biopsy procedure when a first cytology is negative in effusions of unknown origin [10, 11]. Percutaneous needle pleural biopsy is frequently advised in those cases [12], but with the recent advances of image techniques, some authors prefer CT-guided needle biopsy that could replace blind needle biopsy in more than two-thirds of the cases [13]. CT-guided pleural biopsy is especially recommended in cases with marked pleural thickening or lesions clearly visible on CT scans, while direct thoracoscopy is preferred for patients showing only pleural effusion of unknown origin [14].

Percutaneous pleural biopsy aims to obtain diagnosis only in cases where histology is crucial, like in tuberculous pleurisy and malignancy. However, and in contrast to thoracoscopy, it does not have any therapeutic implication, and the choice between those two techniques must be based on the availability and the clinical aggressivity of the effusion [15] (Figs. 24.1 and 24.2). All available biopsy needles provide a better yield in pleural tuberculosis than in malignancy, and this is due to the different degree of diffuse involvement of the parietal pleura in those conditions. In cases where only scarce or hardly accessible neoplastic lesions are present in the pleural cavity or when large specimens are needed for histological diagnosis (like in mesothelioma or non-Hodgkin lymphoma), blind needle biopsy is unlikely to yield satisfactory results and thoracoscopy is the preferred choice (Figs. 24.3–24.5, and 24.6).

In a prospective study including 150 patients, Boutin and coworkers [16] found a positive yield of Abrams needle in 36% of the cases, whereas thoracoscopy obtained the diagnosis in up to 87%. In another prospective study, Loddenkemper et al. obtained similar results comparing simultaneous Tru-Cut needle biopsy and thoracoscopy [17]. On the other hand, pleural needle biopsy can be performed in an outpatient basis [18], whereas thoracoscopy is much more complex and requires hospitalization, at least when pleurodesis is performed. Our current policy is therefore to perform needle biopsy of the pleura only in young patients (in whom tuberculous pleurisy is more likely, at least in countries with relatively high prevalence) and in those patients who reject thoracoscopy or are too sick to tolerate it. If blind needle biopsy does not provide diagnosis, thoracoscopy is the best option [19].

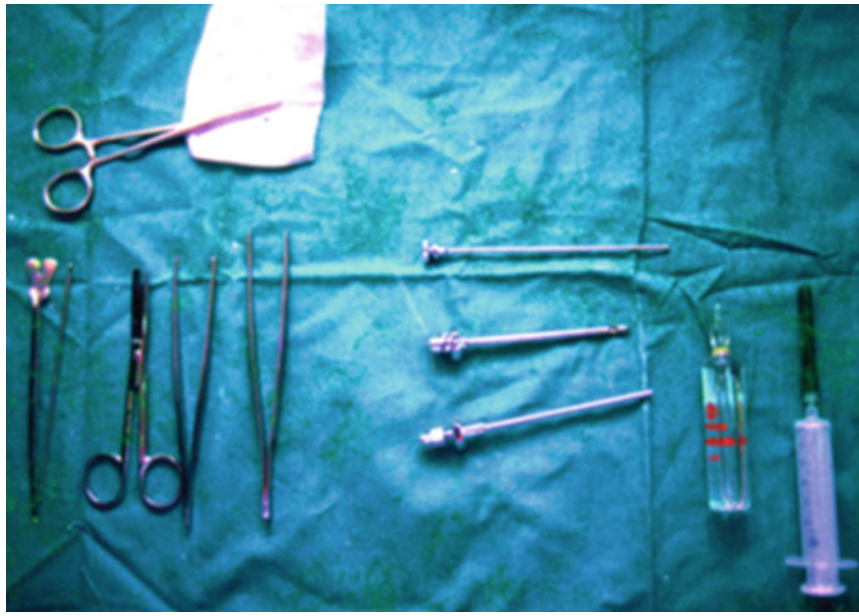

Fig. 24.1 Equipment for pleural biopsy with Abrams needle

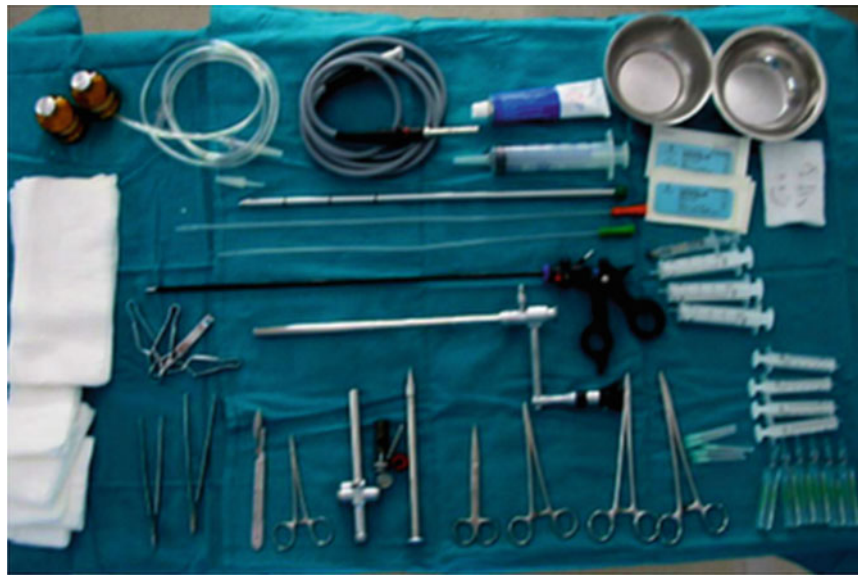

Fig. 24.2 Equipment needed for medical thoracoscopy and talc poudrage (plus video and light source)

The average yield of cytology in malignant pleural effusions is around 60%, and it varies with the type of tumors [20] (see Table 24.1). In our experience, mesotheliomas and lymphomas are the most problematic in yielding positive results by cytology, while thoracoscopy is very good in those cases.

Medical Thoracoscopy in Lung Cancer with Ipsilateral Pleural Effusion

The finding of a pleural effusion coexisting with lung cancer is usually associated with a poor prognosis [21]. In one series including 971 consecutive patients with lung cancer, Martin Diaz

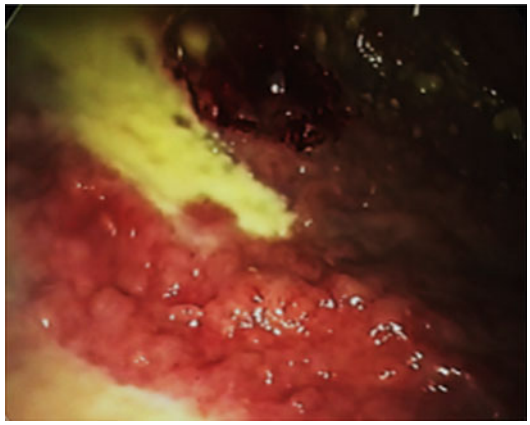

Fig. 24.3 Diffuse malignant mesothelioma coexisting with pleural plaques in one patient with history of asbestos exposure. Several biopsies have been taken with no significant bleeding (*top* of the figure)

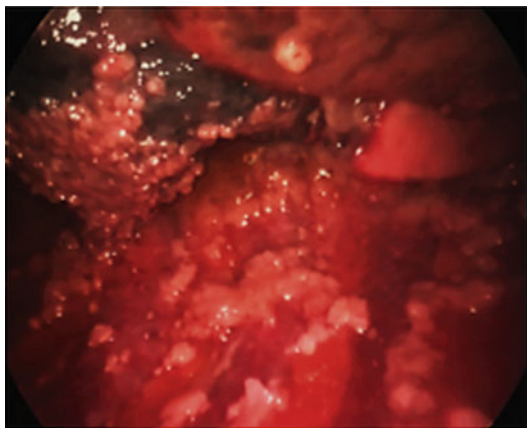

Fig. 24.4 Diffuse malignant mesothelioma involving parietal and visceral pleura. No pleural plaques are identified

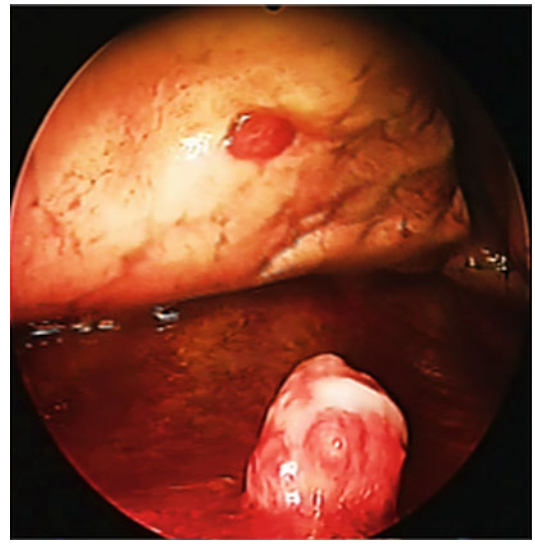

Fig. 24.5 Tumoral mass in the parietal pleura in a patient with metastatic renal carcinoma. A "kissing lesion" is seen opposite in the visceral pleura (*top* of the figure)

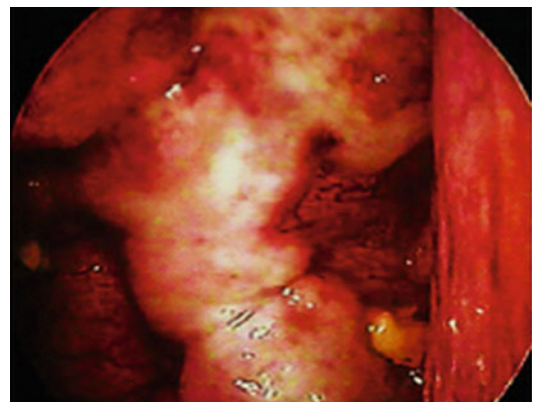

Fig. 24.6 Localized pleural involvement by non-Hodgkin lymphoma in the *lower* part of the parietal pleura (diaphragm seen on the *right*). A previous blind needle biopsy was nondiagnostic

and coworkers found pleural effusion in 188 cases (19%), but it was visible on chest X-ray films only in 72 of them (38%, 7% of the total series). The remaining 116 effusions were detected on CT or ultrasound examination or were found only at thoracotomy [22]. Although cytology was positive in only 40% of the effusions that were visible on chest radiographs, pleural metastases were actually found in up to 75% of those cases. We therefore recommend performing exploratory thoracoscopy before attempting resection, in order to detect unsuspected pleural metastases [23, 24].

If the mediastinum is midline or shows an ipsilateral shift, obstruction of the mainstem bronchus should be suspected, and bronchoscopy performed prior to thoracoscopy, in order to debulk the tumoral obstruction and then assess the lung expandability.

When the effusion is found at thoracotomy only, one could think about the possibility of a *paramalignant* pleural effusion (associated to obstructive pneumonitis, atelectasis, or lymphatic blockade), and resection of the tumor has to be considered.

Table 24.1 Yield of simultaneous cytology and thoracoscopic biopsy in our series of 556 consecutive malignant pleural effusions (Adapted from Rodriguez-Panadero, [20])

Origin of tumor	Biopsy + (%)	Cytology + (%)	B-/C- (%)
Total (556)	95	60	4
Lung (135)	91	57	9
Breast (101)	98	78	–
Mesothelioma (81)	94	41	6
Ovary (27)	100	83	
Lymphoma (51)	86	18	14
Colon (18)	92	62	–
Kidney (24)	100	54	–
Others (56)	100	67	–
Unknown origin (63)	95	71	5

However, the prognosis is poorer in those patients than in those without pleural effusion [25].

Pleural cytology can be eventually positive without macroscopically visible lesions on the pleural surface, and this appears to be associated with a better prognosis [26]. The finding of a positive cytology in pleural lavage performed at thoracotomy has been associated with a worse prognosis in cases submitted to resection [27, 28].

Medical Thoracoscopy in Pneumothorax

There is no consensus about treatment of spontaneous pneumothorax, especially on the first event. However, there is general agreement in that some treatment is mandatory when pneumothorax recurs. Treatment options include pleurodesis, pleurectomy associated with bullectomy by thoracotomy or VATS, or talc poudrage by medical thoracoscopy. Many therapeutic approaches combine talc or surgical pleurodesis with bullectomy or bleb resection or coagulation. Jannsen et al. showed that there was no difference in videothoracoscopic appearance between first and recurrent pneumothorax and concluded that the presence of bullous lesions did not predict recurrence [29]. *Fluorescence thoracoscopy* can be of great help to identify lesions responsible for air leak in spontaneous pneumothorax [30]. In a multicenter prospective study, Tschopp et al. demonstrated that simple thoracoscopic talc poudrage under local anesthesia is a safe, low-morbidity, cost-effective treatment for patients with primary spontaneous pneumothorax requiring chest tube drainage, although efficient control of pain by opioids is always necessary [31].

Advanced Indications in Medical Thoracoscopy

Management of pleural effusions and pneumothorax is the most common indication for medical thoracoscopy. However, and depending upon the medical facilities and the availability or not of a thoracic surgery service, there are other situations that can be managed by pulmonologists using medical thoracoscopy [32]:

- *Thoracoscopy in empyema*. The management of complicated parapneumonic pleural effusions requires a careful clinical control and early intervention whenever loculations are seen in ultrasound examination. Early instillation of fibrinolytics with ultrasound guidance can be very helpful in solving complicated effusions [33], but thoracoscopy can be necessary in some cases, especially when performed early after failure of chest tube drainage [34, 35]. In more complex cases, VATS would be the preferred choice [36].
- *Lung biopsy by thoracoscopy*. Forceps lung biopsy—with or without electrocautery—has

been performed for many years by pulmonologists using medical thoracoscopy, and I have done it in more than 50 patients with pleural effusion of unknown origin who had relevant findings on the visceral pleura and underlying lung parenchyma at thoracoscopy examination. However, a VATS procedure with endoscopic stapling that can obtain large specimens, more suitable for extended pathological examination, is clearly recommended for management of diffuse lung diseases.

– *Other thoracoscopic procedures*, such as sympathectomy for control of severe hyperhidrosis, can be easily performed by well-trained thoracoscopists. Again, VATS would be the preferred technique in order to completely collapse the ipsilateral lung during the procedure, thus providing a better access to the paravertebral sympathetic nervous structures.

Contraindications for Medical Thoracoscopy

Most complications can be avoided by proper selection of patients for thoracoscopy. Patients with *severe COPD and respiratory insufficiency*, with hypoxemia ($PO_2 < 50$ mmHg) and hypercapnia, will not tolerate induction of a pneumothorax without further deterioration of the gas exchange and are therefore no suitable candidates for thoracoscopy. When there is a *contralateral lung or pleural involvement*, thoracoscopy is not advisable, unless general anesthesia and tracheal intubation is used. Any patient with a history of *cardiovascular disease*—especially those with unstable angina or recent history of myocardial infarct—should be carefully evaluated before undertaking thoracoscopy. *Cough, fever, and infection* are relative contraindications for thoracoscopy, and treatment should be considered before a procedure is scheduled. Coagulation defects should also be corrected before thoracoscopy. Thoracoscopy will not be feasible in case of *complete symphysis of the visceral and parietal pleura*. In case of localized pleural adhesions seen on ultrasound examination, an alternative point of entry might be chosen. In some select cases it might be possible to create a pleural space by extended thoracoscopy using digital dissection on the chest wall, and then introduce the thoracoscope to take biopsies from suspicious lesions [37]. However, this technique should be performed only by experienced thoracoscopists. Medical thoracoscopy is not safe in *advanced pulmonary fibrosis*: after induction of pneumothorax, a severe acute hypoxemia might occur, and re-expansion of the lung can be difficult due to the loss of elasticity of the pulmonary tissue. Pulmonary biopsy in case of honeycombing lung may result in prolonged air leakage and impaired re-expansion of the lung. Also, pulmonary biopsy should be avoided in *hydatid cyst disease*, *arteriovenous malformations, and other highly vascularized lesions*.

Equipment for Medical Thoracoscopy

Jacobaeus demonstrated that pleuroscopy could be performed simply with an optical instrument (cystoscope) inserted into the pleural cavity through a trocar. With the technical improvements achieved in the instruments and video cameras for endoscopy, the quality of the vision has been greatly enhanced and the safety of the procedure increased. In order to keep both up to the highest standards, there are a few recommendations to follow.

Be Acquainted with the Equipment You Are Going to Use in Advance

– The *light source* for the thoracoscope has to be of good quality, and the last-generation lamps are recommended. Make sure that the connecting cables between the source and the thoracoscope are correctly attached.

– *Telescopes*. There are both *rigid* and *semirigid* instruments available for thoracoscopy, and each type has some advantages over the others. The rigid thoracoscope provides excellent vision, allows for big biopsy samples using a single port of entry (in most of the versions available), facilitates the orientation inside the pleural cavity, and also is of great help when

biopsies have to be taken from hard lesions (or located over the ribs). On the other hand, the semirigid thoracoscope is a little more familiar to pulmonologists who are used to the flexible bronchoscope in everyday practice; in addition, it allows for *lateral vision* very easily (we would need a telescope with oblique view for that purpose when using the rigid ones), or even retrovisualization of the point of entry. However, it is more expensive and fragile than the rigid thoracoscope, the working channel is smaller, and biopsies consequently smaller too.

– *Trocar*. Obviously, a large trocar would permit insertion of a large telescope too, thus enhancing the quality of the exploration, but—especially when working in local anesthesia—we need a compromise between the size of the instruments and the width of the intercostal spaces. I have done most of my thoracoscopies with a 10 mm thoracoscope in local anesthesia plus intravenous analgesia (mepivacaine), but I readily accept that a 7- or even 5 mm thoracoscope is the best choice for medical thoracoscopy, especially if it has a working channel that allows taking biopsies through a single port of entry. The *shape of the tip of the trocar* is important, and the *conical* one is much preferred to the others, in order to prevent damage to the intercostal vessels or nerves during insertion in the pleural cavity [38].
– *Other aspects regarding the equipment*. A good *suction system* is absolutely necessary in every endoscopy procedure, and thoracoscopy is no exception, in order to remove all the pleural fluid before exploring completely the pleural cavity and taking biopsies. Also, *monitorization of the patient* (including oxygen saturation and electrocardiogram) should be prepared before starting the procedure. We also prefer preparing the drain and the water-seal system prior to the thoracoscopy procedure, in order to act quickly should a complication occur and then we need to re-expand the lung immediately. The physician performing thoracoscopy has to be well trained in management of pleural drainage during the recovery period also, including lung re-expansion after the procedure.

One or Two Ports of Entry for Medical Thoracoscopy?

Though it is clear that several entries are needed for VATS, I much prefer using one single entry for diagnosis and treatment of pleural effusions (talc poudrage) and have needed two ports in very few occasions. They have to be created when there is no thoracoscope with working channel available, when electrocautery has to be used, whenever a hardly accessible area of the pleural cavity needs to be explored, and when very small telescopes are used (for pediatric patients or other selected cases). The second point of entry is located one intercostal space superior or inferior to the main entry, and rather close to it, in order to manipulate the instruments easily under visual control. Recently, minithoracoscopy was developed as an alternative for diagnostic thoracoscopy under local anesthesia. Tassi and Marchetti used a 3 mm thoracoscope for diagnostic thoracoscopy under local anesthesia [39], and the diagnostic yield was 93% in their study. Janssen et al. compared minithoracoscopy—using a 3 mm set and a 2 mm set—to standard thoracoscopy using the 7 mm set. The diagnostic yield of the 3 mm set was 100%, the same as for the 7 mm one, but the yield of biopsies using the 2 mm set was only 40% [37]. It is necessary to create a second port of entry to take biopsies using a minithoracoscope, in contrast to the standard larger equipment.

Technique for Thoracoscopy

Preparation of the Patient

Although medical thoracoscopy is safe and relatively simple when the performing physician is well trained and familiar with the *endoscopic anatomy* of the thorax (which is not always the same than conventional anatomy, due to the point of view and the limited field of vision, as compared with open thoracotomy or autopsy), a few rules have to be followed carefully:

(a) Explanation of the technique to the patient. This is especially important when the proce-

dure is going to be done in local anesthesia plus intravenous analgesia, because he or she will be more confident during the exploration when knowing the details of the procedure in advance.

(b) Evaluation of the performance status of the patient. We have to be especially careful with patients who are in very poor clinical condition, hypoproteinemic, or with diffuse neoplastic infiltration of the chest wall. Also, patients with uncontrollable cough should be deferred for medical thoracoscopy because the exploration is likely to be very difficult and with more complications (subcutaneous emphysema!).

(c) Studies to be done prior to thoracoscopy. A posteroanterior and lateral *chest X-ray film* is mandatory, in order to evaluate the most convenient port of entry, to exclude presence of *contralateral pulmonary lesions* (that could lead to acute respiratory insufficiency at the time of inducing pneumothorax for thoracoscopy), and to evaluate the size and shape of the pleural effusion to be explored. A *contrast CT scan* that is strongly recommended in the evaluation of every pleural effusion of unclear origin and *ultrasound examination* prior to the exploration can be very useful. *Electrocardiogram*, *coagulation tests, and blood gas analysis* are also necessary.

Premedication for Thoracoscopy

Preoperative preparation may involve chest physiotherapy, bronchodilators, antibiotics, and corticosteroids to optimize pulmonary function in patients with obstructive lung disease. Routine prophylactic antibiotics are not necessary, unless the patient is neutropenic.

The role of preoperative medication has not been subjected to randomized studies. We routinely administer 0.4–0.8 mg of atropine (intramuscular or subcutaneous) prior to the procedure, to prevent vasovagal reactions [40]. Intravenous midazolam can be very useful, especially in young patients, and titrated propofol has also been proposed [41], but propofol requires permanent assistance of an anesthesiologist in many countries. Instead, we have used titrated intravenous pethidine—keeping the patient awake—in more than 500 procedures involving talc poudrage. Sedation during the procedure can also be performed using incremental dosages of a narcotic (morphine, pethidine, or fentanyl) and a benzodiazepine. Agents to antagonize both morphine and benzodiazepine should be available [42].

In order to prevent pulmonary embolism, especially in patients with malignant pleural effusions who are submitted to talc pleurodesis, we advise giving prophylactic during all the hospital stay.

Endoscopy Room

Whenever available, a well-equipped operating room is excellent for every invasive procedure, including thoracoscopy, but this is not the case in most of the centers, where operating rooms are very busy with other major procedures or operations. Instead, medical thoracoscopy can be performed safely in the respiratory endoscopy suite, provided that a sterile setting can be prepared, the electrical installation and patient monitorization is adequate, and the mandatory resuscitation equipment is available.

Thoracoscopy Procedure

Patients should have an intravenous cannula. Basic monitoring includes ECG and pulse oximetry. Supplementary oxygen should be provided to the patient to maintain oxygen saturation above 90%.

The patient is positioned in lateral decubitus position, with healthy lung in the dependent side. Keeping the ipsilateral arm to the exploration above the head helps to widen the intercostal spaces, thus allowing for an easier introduction of the trocar. The optimal point of entry depends upon the disease to be investigated: thus, a higher entry is preferred for pneumothorax, in order to explore more easily the

upper part of the pleural cavity, where most of the bullae are located; on the other hand, the mid-axillary line of the fifth or sixth intercostal spaces is the best option to explore patients with pleural effusions. A few technical details are important, as follows:

- *Local anesthesia* has to be applied generously and carefully around the chosen point of entry. A common mistake with beginners is the application of large amounts of anesthetics in the subcutaneous tissue, while the deep tissue and intercostals muscles are neglected. The lack of deep local anesthesia would provoke acute pain when the trocar compresses the intercostal nerves during the exploration of the pleural cavity.
- We prefer applying the *sutures for the drain* in advance at the beginning of the exploration (just before inserting the trocar) in order to get everything prepared if an emergency insertion of the chest tube is needed for rapid lung re-expansion.
- *The trocar* should always be inserted perpendicularly to the chest wall with a rotating motion. It is safer to locate the tip over the inferior rib in the chosen port of entry, in order to prevent damage to the intercostal vessels and nerves. Introduction of the trocar can be difficult in presence of pleural adhesions, and it should be performed slowly and carefully. Again, previous ultrasound examination is strongly recommended. The inner part of the trocar must be withdrawn when a reduction of resistance is felt after passage of the parietal pleura.
- Once the trocar has been inserted into the pleura, suction should be gently applied and all the pleural fluid removed to have an optimal vision of the cavity. Keeping the catheter in continuous motion helps prevent cough, which could be provoked by the attachment of the catheter to the visceral pleura and the underlying lung during suction maneuvers. While fluid is removed, air is entering passively into the pleural cavity to keep the lung collapsed.
- If there are adhesions found, the thinner ones can be severed with the biopsy forceps or cautery, but this maneuver has to be performed very carefully and by experienced thoracoscopists to prevent bleeding.
- For the complete exploration of the pleural cavity, a slow circular motion of the scope is recommended, taking into account that—in order to identify organs inside—the diaphragm shows respiratory movements, the lung has a transmitted pulsating motion, and the costal pleura appears to be still. Biopsies should be preferably taken from lesions located at the inferior and posterior zone of the parietal pleura and preferably *over* (*and not between*) the ribs, whenever possible.
- A *chest drain* should be inserted in every case just at the end of the procedure and then connected to a water-seal system; gentle step-by-step suction is applied afterwards and the drain kept in place until a complete re-expansion of the lung has been achieved. This is especially important when talc poudrage for pleurodesis has been performed. In this case, the drain stay should not be less than 2 days, in order to achieve a tight symphysis between the visceral and parietal pleura.

Complications of Thoracoscopy

When performed by well-trained personnel, thoracoscopy is a safe procedure. O_2 desaturation during thoracoscopy under local anesthesia is unusual, and—in our experience—it is remarkable that the procedure is especially well tolerated when facing large pleural effusions that are removed just after insertion of the trocar, thus improving the respiratory function. Very few deaths associated to thoracoscopy itself have been reported in the literature (see Tables 24.2 and 24.3), but we have to be aware that fatal complications can occur [43]. When talc poudrage is added to the procedure, the rate of complications is expected to rise a little [44], especially in patients with poor general condition.

In order to understand better how to manage complications, it is convenient to separate them in several categories:

Table 24.2 Complications of thoracoscopy reported in the literature

• Viskum and Enk (Poumon-Coeur 1981;37:25–28): Revision of 2,298 reported procedures in 15 (general) series
– Subcutaneous emphysema: 1.3%
– Empyema: 2%
– (Significant) bleeding: 2.3%
– Air embolism: 0.2%
– Death due to the technique: 0.09%
• Viallat et al. (Chest 1996;110:1387–93): (360 patients submitted to *talc poudrage*)
– Subcutaneous emphysema: 0.6%
– Empyema: 2.5%
• Ribas et al. (Chest 2001;119:801–806): 614 pts with *talc poudrage*
– Empyema: 2.7%
– Re-expansion pulmonary edema: 2.2%
– Respiratory failure: 1.3%
– Air leak: 0.5%
– Postoperative bleeding: 0.4%

Table 24.3 Complications of thoracoscopy in patients submitted to thoracoscopic talc poudrage in our personal series

Complications of thoracoscopic talc poudrage in MPE	Patients $N=512$
Transient dyspnea after talc	50 (9.8%)
Acute pain after talc	44 (8.6%)
Prolonged air leak	46 (9%)
Subcutaneous emphysema	25 (4.9%)
Neoplastic invasion of the thoracoscopy tract	14 (2.7%)
Pulmonary embolism	12 (2.3%)
Skin infection (at the port of entry)	15 (2.9%)
Empyema	12 (2.3%)
Bleeding (requiring blood transfusion)	2 (0.4%)
Acute respiratory distress	1 (0.2%)

Complications Associated to Thoracoscopy Technique Itself

– *Laceration of the lung during insertion of the trocar*. Some authors advise to create a pneumothorax a few hours or even the day before thoracoscopy. This technique may reduce blood flow in the periphery of the lung and may prevent damage to the lung after introduction of thoracoscopy instruments. However, direct introduction of a blunt trocar into the thoracic wall, without prior induction of pneumothorax, is in our experience safe and effective if there is enough pleural fluid. Ultrasound examination can be also very helpful to identify loculations in the pleural cavity and to locate the best entry for thoracoscopy [45, 46].

– *Bleeding*. Patients with pancytopenia or coagulation disorders can be at risk, and no invasive procedure should be done at all when platelets are below 60,000/mm^3. To take a safe biopsy in patients using anticoagulant medication, INR should be <2.0. The use of aspirin may prolong bleeding time, but is not an absolute contraindication for biopsies. Clopidogrel or other antiplatelet agents might be more problematic and should be discontinued before thoracoscopy. In order to prevent inadvertently taking biopsies from vascular structures, a perfect knowledge of the anatomy is mandatory. One should never take biopsies inside the fissures of the lung (because large vessels are close to the surface on those zones), and special care is also necessary when sampling areas near the internal mammary artery and vein (anterior mediastinal pleura). Although they can be identified easily by expert thoracoscopists, those vessels might sometimes be covered by tumor lesions or fibrin, and then be inadvertently sampled, with fatal consequences if emergency surgery is not immediately available.

  In case of excessive bleeding after biopsy, we would recommend compressing with the forceps and local application of *tranexamic acid* (antifibrinolytic agent) that—according to our experience—can help in stopping the hemorrhage, both in thoracoscopy and bronchoscopy [47]. Anyway, availability of electrocautery is highly advisable.

– *Infection*. Although routine prophylactic antibiotics are not necessary, they should be used in neutropenic patients. Deep antiseptic cleaning of the chest wall is mandatory and very strict care of the drain and the chest wound is essential. The likelihood of occurrence of empyema is higher in neutropenic

patients and in those with prolonged chest drains: we never leave the drain for more than 5 days after thoracoscopy, even in cases with talc poudrage performed.

– *Neoplastic invasion of the thoracoscopy tract*. It is frequently seen in mesothelioma, but can be found also in long-surviving patients with pleural metastatic carcinoma. To prevent invasion by mesothelioma, application of local radiation therapy to the scar 10–14 days after thoracoscopy is recommended (7 Gy/day for 3 days).

Complications Associated to Lung Re-expansion

A chest drain should be inserted in every case just at the end of the procedure and then connected to a water-seal system; gentle step-by-step suction is applied afterwards and the drain kept in place until complete re-expansion of the lung has been achieved.

– *Pulmonary re-expansion edema* can occur if suction is too strong, especially in patients with a trapped lung. In order to prevent it, careful and graded suction should be applied, especially when a pleurodesis procedure has been performed: we usually leave the drain connected to water seal without suction for at least 3 h following the pleurodesis procedure and then apply increasing suction gradually. Pulmonary edema can occur when expanding the lung in pneumothorax and malignant effusions, even without application of any sclerosant. Although the edema usually appears on the ipsilateral hemithorax, it can happen on the contralateral side in some cases [48, 49]. Mahfood and coworkers reported three cases in which the edema was contralateral, with fatal outcome in two cases [50]. The mechanism for this complication is not fully understood; however, a too rapid re-expansion, especially if the lung was collapsed for several weeks, may play an important role, as pointed out by several authors [51] and also confirmed by our experience. It also appears that a high production of IL-8 and other proinflammatory cytokines has some role in the development of this complication [52].
– *Prolonged air leak*. According to our experience, it can happen most frequently in neoplastic patients who have undergone prior chemotherapy. In those cases, necrotic tumor nodules can be seen on the surface of the lung, and some of them could eventually get broken during lung re-expansion. If this occurs, suction must be stopped immediately, and the drain left only in water seal (without suction) until the air leaking stops.
– *Subcutaneous emphysema* is frequently associated to prolonged air leak and would require specific surgical measures in some cases, especially if there is any compromise to the upper airways. It can also be observed in patients who have persistent cough during thoracoscopy exploration. If this occurs, the trocar should be left open, so that development of high intrathoracic pressures will be prevented. Manual compression over the area surrounding the port of entry and the trocar may prevent the subcutaneous spreading of air (that is expelled around the trocar by coughing, especially if the trocar´s valve is closed).

Complications Associated to Pleurodesis

Thoracoscopy is associated with a transient impairment in lung function, which is more pronounced when pleurodesis is performed [53]. With the exception of some complications related to the technique itself [54]—that could be prevented with good training and the support of ultrasound examination—the most relevant are systemic complications associated to intrapleural instillation of the sclerosant:

- *Acute respiratory distress or pneumonitis*. This has been described in some cases of talc pleurodesis [55, 56], but the pathophysiologic mechanism responsible for this severe complication is still unclear. There is a concern about systemic inflammation, which appears to be common with almost all agents instilled into the pleural space [57] and with talc containing small particles (<10 mm in diameter) [58]. Acute respiratory

complications arise more frequently in patients with poor clinical condition at the time of pleurodesis, and careful evaluation of the performance status of those patients prior to thoracoscopy and pleurodesis is therefore highly recommended.

- *Possible activation of systemic coagulation after pleurodesis*. There is evidence that thoracoscopy—like many other interventional procedures—can provoke some systemic inflammation, but it is clear that talc pleurodesis induces a stronger reaction in many cases [59]. According to some studies from our group, an activation of the systemic coagulation might be observed after talc poudrage [60], and this side effect can be partially controlled with prophylactic heparin [61].

The complication rates in our thoracoscopy series—including talc poudrage—are reported on Table 24.3.

In conclusion, medical thoracoscopy can be performed by well-trained pulmonologists in the endoscopy suite using local anesthesia with proper general analgesia and mild sedation, both for diagnostic and therapeutic (pleurodesis) purposes, with no major complications.

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Overview of the Spectrum of Chest Tubes with Focus on the Tunneled Pleural Catheter: Disease-Specific Selection

25

Ghazwan Acash and Carla R. Lamb

Introduction

Chest tube placement has been a long-standing therapeutic intervention in the setting of pneumothorax, empyema, and hemothorax. Competency in placement is required by surgeons, intensivists, pulmonologists, emergency room physicians, and radiologists.

There is a core set of medical knowledge and procedural technique that must be understood by the physician placing a chest tube. Over the past decade, there is an ongoing evolution of tube sizes available along with variation in technique that allows for improved patient comfort while providing optimal management of the pleural disease warranting chest tube placement. This chapter will review the approach to the patient with specific pleural diseases requiring chest tube placement. The indications, contraindications, spectrum of tubes available, basic technique, and management will be discussed with a focus on the indwelling pleural catheter. Review of the existing literature regarding optimal chest tube size for disease-specific pleural diseases will be included.

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Indications and Contraindications

The primary indications for chest tube placement include pneumothorax, pleural effusion specifically malignant pleural effusion, empyema, and hemothorax.

Early intervention is the key to management of the symptomatic patient with any of these pleural diseases. Contraindications include the uncorrected coagulopathy, an uncooperative patient, absence of informed consent, and lack of proper procedural training. Patient preparation and technique will be reviewed followed by disease-specific tube selection.

Pre-procedure preparation of the patient is fundamental. After consent has been obtained, platelet count, PT, INR, and PTT should be assessed. The patient's current medication should be reviewed specifically screening for antiplatelet agents or other anticoagulants. Discontinuation of the medication and reversal of the effect of these agents whenever possible are required. The patient should be placed in the supine position or decubitus position dependent on chest tube site location with elevation of the head of bed approximately 30°. For example, with a pneumothorax, the second intercostal space along the midclavicular line is recommended. In the setting of pleural effusion, placing the patient with the noninvolved side down in the decubitus position placing the chest tube in the 4th or 5th intercostal space in the midaxillary line is recommended. Locating the xyphoid process

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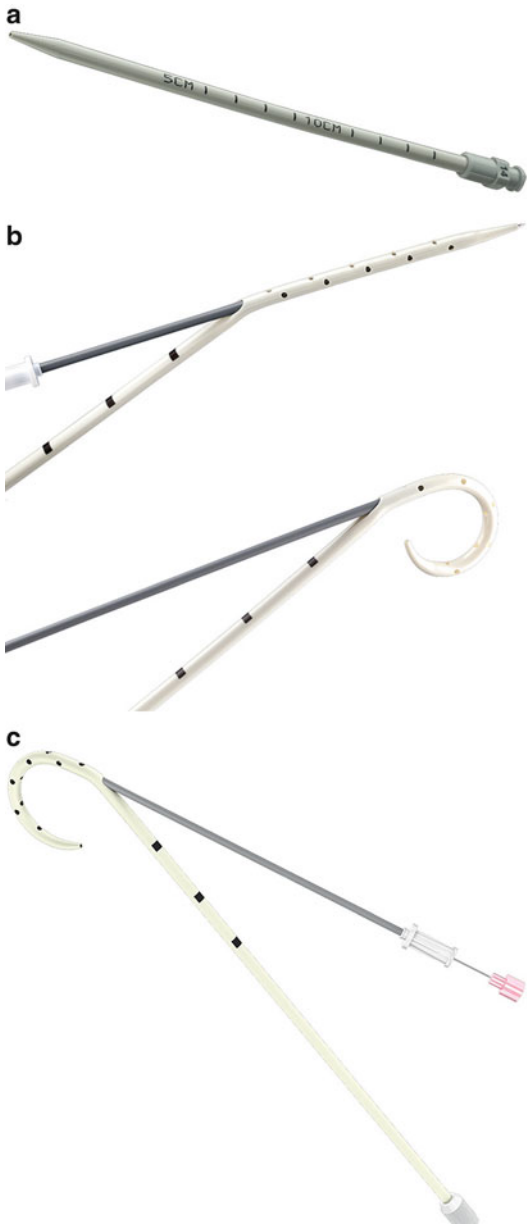

Fig. 25.1 (**a**) Thal-Quick introducer needle. (**b**, **c**) Wayne trocar

and drawing a mental line at that level to the midaxillary line are a practical way to find this location. Physical exam, chest imaging review, and thoracic ultrasound are utilized to confirm the location for chest tube entry followed by marking the site. Universal protocol is exercised with final verbal confirmation of the correct anatomic side by the medical team. Intravenous analgesia and/or anxiolytics are recommended prior to chest wall preparation to alleviate patient symptoms in addition to topical anesthetic with 1% lidocaine. The site is then cleaned with chlorhexidine followed by placement of a sterile drape. Topical 1% lidocaine (not exceeding 5–7 mg/kg) is generously introduced subcutaneously, intercostally, and along the periosteum. Often pleural fluid or air (in the setting of pneumothorax) will be identified during this process, confirming entry into the pleural space. There are two basic techniques for chest tube placement defined as operative or the wire-guided modified Seldinger technique. The trocar method will not be discussed as it is not recommended. The operative technique requires a 1–2 cm intercostal incision parallel to the rib just above the rib that is the desired point of entry.

Using a sterile clamp applying steady controlled pressure over the rib, a tactile "pleural pop" will be felt. Once the pleural space has been entered, the clamp is spread apart to dilate an entry tract. The operative method allows for placement of a gloved sterile finger into this entry to perform a 360° finger sweep to remove any fibrous adhesions and to manually confirm that the lung is not against the chest wall.

The wire-guided modified Seldinger technique is less tactile; however, it is equally effective in placing a chest tube. The manufactured kits include the addition of a guidewire with one to three sequential dilators to gently dissect the intercostal muscles creating the entry tract for the chest tube and introducer. The available chest tube sizes range from 8 to 36 Fr using the Seldinger technique (Figs. 25.1–25.3).

Pneumothorax

Chest tube placement in this setting will be directed anterior and apically in the supine patient. The anterior second intercostal space along the midclavicular line is the standard location. The exception to this would be in the setting of the iatrogenic pneumothorax from cardiac pacemaker or defibrillator placement. In order to avoid the risk of possible subcutaneous chest wall

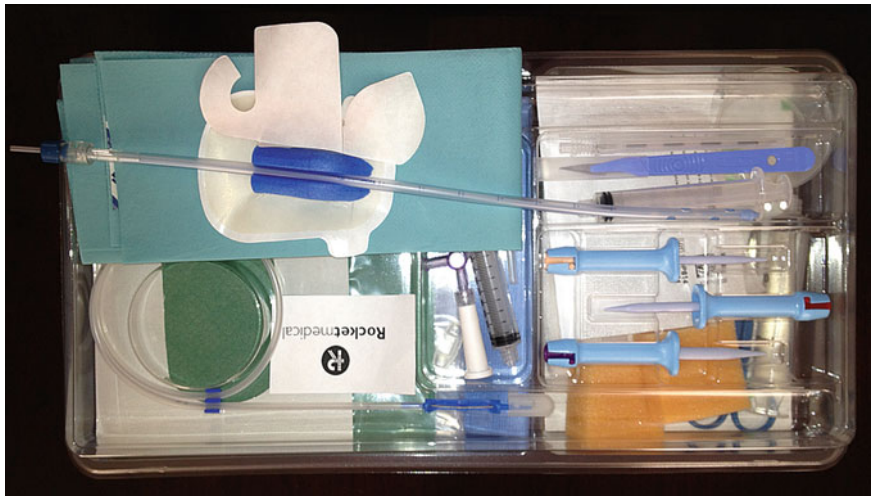

Fig. 25.2 Insertion kit: trocar and catheters

Fig. 25.3 Thal-Quick chest tube

infection in a newly placed device, it is recommended to place the chest tube along the fourth or fifth intercostal space in the midaxillary line. If the patient is noted to have a loculated pneumothorax with varying pleural adhesions, then CT guidance for chest tube placement would be advised. With the availability of smaller-bore chest tubes and literature supporting that these are as effective and better tolerated by the patient, the larger-bore tubes have been replaced by the smaller-bore tubes ranging from 8 Fr to 14 Fr. At the time of chest tube placement, manual aspiration of the pneumothorax with a Luer lock syringe until resistance is met can result in a quicker resolution of the pneumothorax.

Empyema

When a diagnosis of pneumonia is made and a pleural effusion is identified, a thoracentesis should be performed immediately with complete evacuation and analysis of the pleural fluid. This may prevent the need for further intervention. However, if the fluid accumulates again and the patient does not demonstrate clinical improvement with antibiotics, or the initial pleural fluid analysis suggests diagnosis of an empyema, then a chest tube should be placed. There is evidence that small-bore chest tubes defined as <14 Fr are as effective as the traditional larger-bore chest tubes for evacuating pleural space infections.

The smaller tubes are better tolerated by the patients. The British Thoracic Society guidelines also suggest that to prevent premature clogging of the smaller-bore tubes, routine saline flushes of 30–50 ml every 6–8 h is effective. We recommend use of the 14 Fr catheter due to its resilience and lower incidence of fibrin clogging as compared to the smaller-bore tubes. Fibrinolytics can be utilized such as tissue plasminogen activator (TPA) (2–50 mg) instilled at varying intervals to further maintain an existing chest tube. If the patient has clear evidence of multiple loculations from the outset, then image-guided placement of more than one chest tube may be required and thoracic surgical consult would also be recommended in the event that surgical decortication is required.

Table 25.1 Complications of chest tube insertion

Complication	No.	%
Unsuccessful insertion	10	4
Symptomatic loculation	21	8.4
Asymptomatic loculation	10	4
Empyema	8	3.2
PTX, SQ air/BPF	6	2.4
Cellulitis	4	1.6
Recurred fluid	4	1.6
Dislodged	3	1.2
Bleeding	2	0.8
Tumor seeding	1	0.4
Pain requiring removal	1	0.4
Extrapleural catheter	1	0.4

PTX pneumothorax, *BPF* bronchopleural fistula 1

Hemothorax

This is most often associated with thoracic trauma or iatrogenic thoracic complications. It is recommended to utilize a 28 Fr to 32 Fr chest tube since due to the viscosity of the hemothorax, there is a higher risk for occlusion with a smaller tube. It is critical in this scenario to be able to have a patent tube in order to accurately assess the rate of output as this would determine the need for surgical intervention.

Malignant Pleural Effusion

Malignant pleural effusion is common in lung cancer, breast cancer, and lymphoma. This impacts the patient's quality of life. After the initial pleural diagnosis is made, a definitive management plan to prevent recurrence should follow. This will be fully discussed later with the indwelling pleural catheter.

Complications and Troubleshooting Chest Tubes

While the complication rate is 1–2%, it is important to recognize the potential complications that may occur with chest tube placement, maintenance, and removal (Table 25.1). Managing the chest tube after placement is equally important.

Once the chest tube has been placed, there are a number of daily assessments that must be performed. Patient symptoms, pain management, respiratory variation, degree and duration of air leak, amount of drainage output per 24 h, character of output, chest tube entry site, radiographic imaging, and timing of tube removal are indicators as to whether the chest tube is optimally managed. While there may be controversy in the literature regarding some of these factors, we will review practical clinical pearls regarding these aspects. If there is a persistent air leak, assess all of the chest tube connections by removing the dressing to assure that the chest tube has not migrated out resulting in air entering into the pleural space from one of the open side ports. Proceed from the chest wall along all of the tubing to assure that all of the connections are sealed. If you do not identify a leak in the system, consider replacing the pleural drain tubing as small punctures in the tubing are difficult to isolate. If there is still an ongoing air leak, then there is most likely a bronchopleural fistula. If there is no respiratory variation with deep inspiration or cough, this could suggest that the chest tube may be occluded with fibrin or clot. Manual milking of the chest tube and adjacent tubing can remedy this; however, saline or fibrinolytics may be required. The chest tube or connector tubing could be kinked due to patient positioning but can be easily identified and corrected at the bedside. This can be recognized when drainage output markedly decreases or there is evidence of reaccumulation of a pneumothorax. Lastly, it could signify that the lung has not fully expanded and is now occluding the chest tube. Criteria for determining the timing of chest tube removal varies in the literature. For pneumothorax, it is the resolution of a visible air leak in the drainage system and radiographic resolution. Generally, once this is established, the chest tube is placed to water seal for 12–24 h, and if there is no recurrence, then the tube can be clamped for several hours and then removed.

Most would maintain a functioning chest tube while a patient is receiving positive pressure with mechanical ventilation when used to treat a pneumothorax; however, similar steps for standard

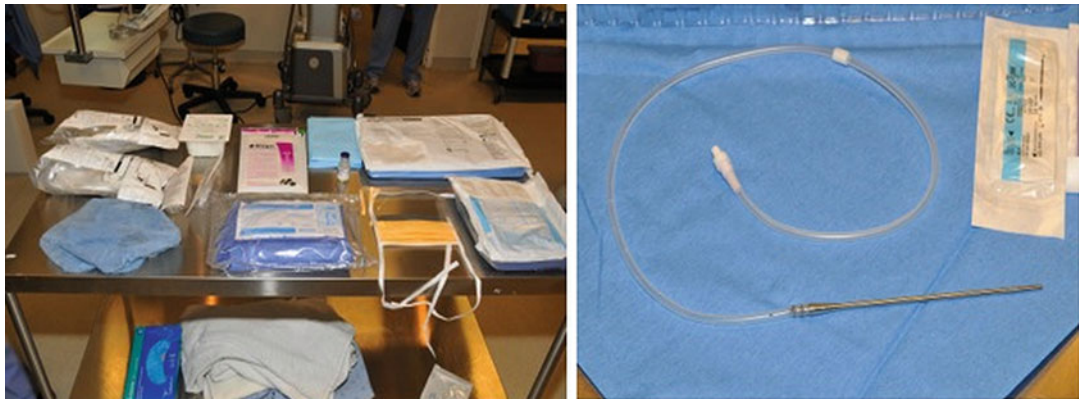

Fig. 25.4 Pleural catheter and equipment needed

removal as previously described may be considered as well. When treating empyema, the chest tubes are maintained until there is no spontaneous output, clinical status has improved, and chest imaging confirms resolution of the fluid collection. In the setting of malignant pleural effusion and pleurodesis, the chest tube may be removed with drainage output of <150 ml in a 24 h period without consequence.

Pleural Drainage Systems

Since the pleura space pressure is negative, the pleural drainage systems must prevent air entry while draining fluid, pus, blood, or air. There are two primary drainage systems.

The Heimlich one-way valve consists of a flutter valve that is effective for the treatment of pneumothorax. This valve closes when the pressure inside the tubing is less than atmospheric pressure (during patient inspiration) to prevent entrainment of unwanted air into the pleural space. It opens when the pressure inside the tubing is above atmospheric pressure (during patient exhalation).

The three-bottle system is made up of (1) a water pressure chamber that determines the cm H20 of suction applied relative to the amount of water placed into this chamber, (2) air leak chamber that identifies the presence of air and respiratory variation, and (3) drainage chamber to allow for volume assessment of fluid output.

Indwelling Tunneled Pleural Catheter

An indwelling tunneled pleural catheter (TPC) is a device involving a minimally invasive procedure typically performed to alleviate dyspnea resulting from recurrent malignant pleural effusion (MPE) with or without a partially trapped lung. There is also a role in the recurrent benign pleural effusion that is refractory to medical management as in the case of congestive heart failure or end-stage liver disease. It may also be used in conjunction with medical thoracoscopy in a rapid pleurodesis model (Fig. 25.4). Generally speaking, the procedure is performed in the outpatient setting and requires drainage by a visiting home nurse, a trained family member, or the patient after appropriate education.

The Denver PleurX catheter is a 66 cm long, 15.5 F, silicone rubber catheter with fenestrations along the distal 24 cm. A valve at the proximal end of the catheter is a one-way valve and can be accessed only by using the special drainage line provided in the kit. There is a polyester cuff which serves to prevent infection and anchors the catheter in place just beneath the skin (Fig. 25.5).

History

Malignant pleural effusion (MPE) is a significant cause of morbidity in patients with advanced cancer and usually signifies a poor prognosis.

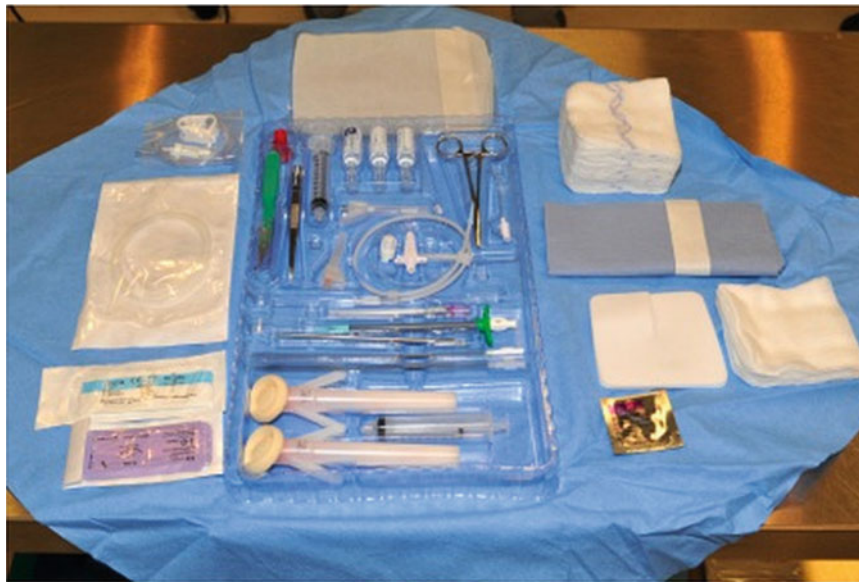

Fig. 25.5 Pleural catheter kit

The median survival following diagnosis ranges from 3 to 12 months dependent on the originating tumor type of underlying malignancy. The Karnofsky score has also been found to be a predictor for survival in the setting of malignant pleural effusion.

Lung cancer is the most common cause of MPE in men, while in women breast cancer is the leading cause of MPE. Three other malignancies such as ovarian, gastric, and mesothelioma can also cause MPE to a lesser extent. Options in the management of MPE include chest tube insertion with subsequent injection of sclerosing agent such as talc or doxycycline, TPC with or without chemical pleurodesis, medical thoracoscopy with talc poudrage with or without TPC, and surgical thoracoscopy with chemical pleurodesis or mechanical pleural abrasion. Patient selection for management of symptomatic malignant pleural effusion should include several factors such as the relief of shortness of breath with the initial thoracentesis, patient preference, performance status, life expectancy, comorbidities, as well as availability of procedural expertise. It is critical to plan a definitive procedure after the initial thoracentesis, and pleural diagnosis is made to minimize symptoms from the outset.

Indications

Malignant Pleural Effusion

- In the largest series published for TPC, Tremblay et al. reported placing 250 TPC for MPE in 223 patients during a 3-year period. Complete symptom control was achieved in 38.8% procedures, partial symptom control in 50% and failure to control symptoms in 3.6%, failure to insert the catheter in 4%, and 3.6% without assessment of symptoms at the follow-up visit. Spontaneous pleurodesis occurred in 43% of cases and the catheter stayed in place for a median duration of 56 days. No further ipsilateral pleural procedure was required in 90% of cases. The complication rate was low.

When compared to chest tube insertion and chemical pleurodesis, TPC was found to achieve equivalent relief of dyspnea and safety

with the advantage of a significant decrease in the need for a hospital stay and hospital expenses. TPC can be used in conjunction with other procedures such as medical thoracoscopy. In a study involving 30 patients with MPE who underwent medical thoracoscopy and talc poudrage pleurodesis, the insertion of TPC significantly reduced median duration of hospitalization and the duration of TPC use compared with historical controls of either procedure alone.

Partial Trapped Lung

Patients with partial trapped lung typically have a dense peel of tissue encasing the visceral pleura preventing the lung from fully reexpanding following thoracentesis. Accordingly, pleurodesis is frequently unsuccessful as pleural apposition is difficult to achieve. These patients are frequently symptomatic because of lung atelectasis secondary to pleural effusion as well as dysfunction of the affected diaphragm. After fluid removal, dyspnea in these patients improves because of partial lung expansion and relief of the ipsilateral diaphragm.

The use of TPC in patients with MPE and trapped lung was reported in a series of 11 patients with lung cancer, lymphoma, and mesothelioma. All patients reported symptomatic relief and the catheter remained in place till death in ten patients. Complications included cellulitis at insertion site and catheter infection.

Chylothorax

Chylothorax is defined as a pleural effusion with triglyceride level >110 mg/dl. It usually develops as a result of direct invasion of the thoracic duct by a tumor or as a result of obliteration of the lymphatics following radiation therapy. Of the malignant etiologies, lymphoma is the most common although any metastatic cancer from any organ to the thorax can cause it. Other causes of chylothorax can be divided into traumatic, nontraumatic, and idiopathic.

Recurrent chylothorax is debilitating and the management can be challenging despite treatment of the underlying condition. Options include recurrent thoracentesis, dietary management to reduce long-chain triglycerides, somatostatin analogue such as octreotide, thoracoscopy with chemical sclerosis, and insertion of a TPC.

In a case control study, Jimenez et al. reviewed the charts of 19 patients with confirmed chylothorax. Ten patients underwent TPC placement and nine patients had other palliative interventions including repeated thoracentesis, thoracoscopic talc pleurodesis, and pleuroperitoneal shunt placement. Patients with TPC were drained according to a specific protocol, and there was no baseline significant difference between the two groups regarding age, functional status, weight, albumin level, or absolute lymphocyte count.

TPC group had a statistically significant lower risk of requiring a second pleural intervention after the index procedure during the following 500 days compared to the other pleural interventions. There was a decrease in albumin following TPC insertion which was not worse than that observed in the other group and recovered to baseline after TPC removal. No statistically significant difference was noted in successful pleurodesis rate or symptom control between the two groups, and the author concluded that TPC may be considered as first-line palliative management for patients with symptomatic recurrent chylothorax poorly responsive to treatment of underlying malignancy.

Benign Recurrent Pleural Effusion

TPC is also an option for the patient with refractory pleural effusion in the setting of congestive heart failure that persists despite maximal medical therapy. In the setting of hepatohydrothorax and advanced liver disease, TPC placement can serve as a temporary bridge to transjugular intrahepatic shunt (TIPS) or as a palliative therapeutic measure in the patient who is not a candidate of liver transplant. This is especially beneficial in this patient population due to ongoing coagulopathy and rapid rate of pleural effusion

Fig. 25.6 Preparing the patient for TPC insertion and accessing the pleural space

recurrence by reducing frequent thoracentesis and hospital visits to manage a very debilitating component of disease.

Contraindications

The patient who does not experience any significant relief of dyspnea after initial thoracentesis will not benefit from the placement of TPC. Infection should be ruled out before placing TPC as an infected pleural space is a contraindication to TPC placement. The site of insertion should be intact and should have no evidence of broken skin or cellulitis. Uncorrected coagulopathy is a contraindication to TPC placement and checking of CBC, PT, and PTT is required before proceeding. Evidence of multiple loculations within the pleural space would also be a contraindication to TPC. If the patient does not have an adequate support system to maintain proper care and sterile drainage of the TPC, it would not be recommended.

Complications (Table 25.1)

How Do I Do It? (Figs. 25.5–25.10)

After informed consent is obtained from the patient, the patient is placed in a supine or decubitus position with the affected side slightly elevated. Thoracic ultrasound is employed in all cases to verify the point of entry and to ensure there is a safe pocket of fluid for TPC insertion. The correct site is marked as "yes" in the visible field of the operator, and a time-out is called where patient name, medical record number, and date of birth are verified. The skin is then prepped with chlorhexidine and covered with a large sterile drape. The patient is connected to a telemetry monitor and continuous pulse oximetry monitoring as well as placement of a peripheral IV in the event of any need for medication administration. The skin is anesthetized with 1% lidocaine at both the insertion site and the planned tunneling site. The pleural fluid pocket is accessed with the

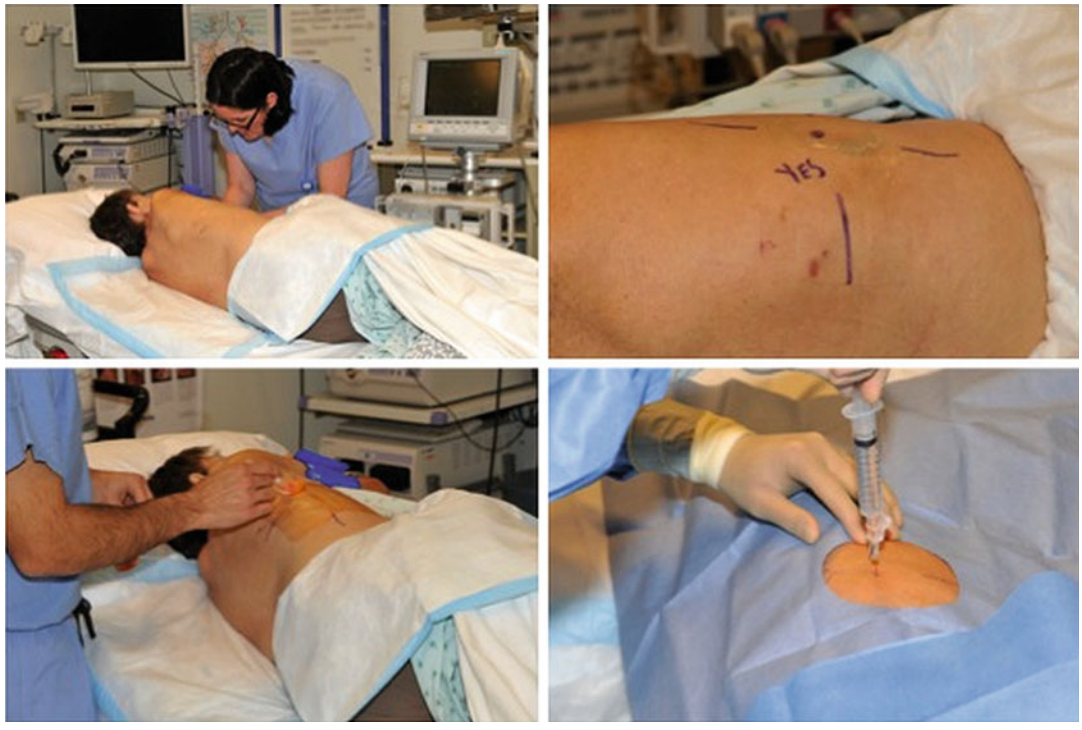

Fig. 25.7 Patient positioning and local anesthesia

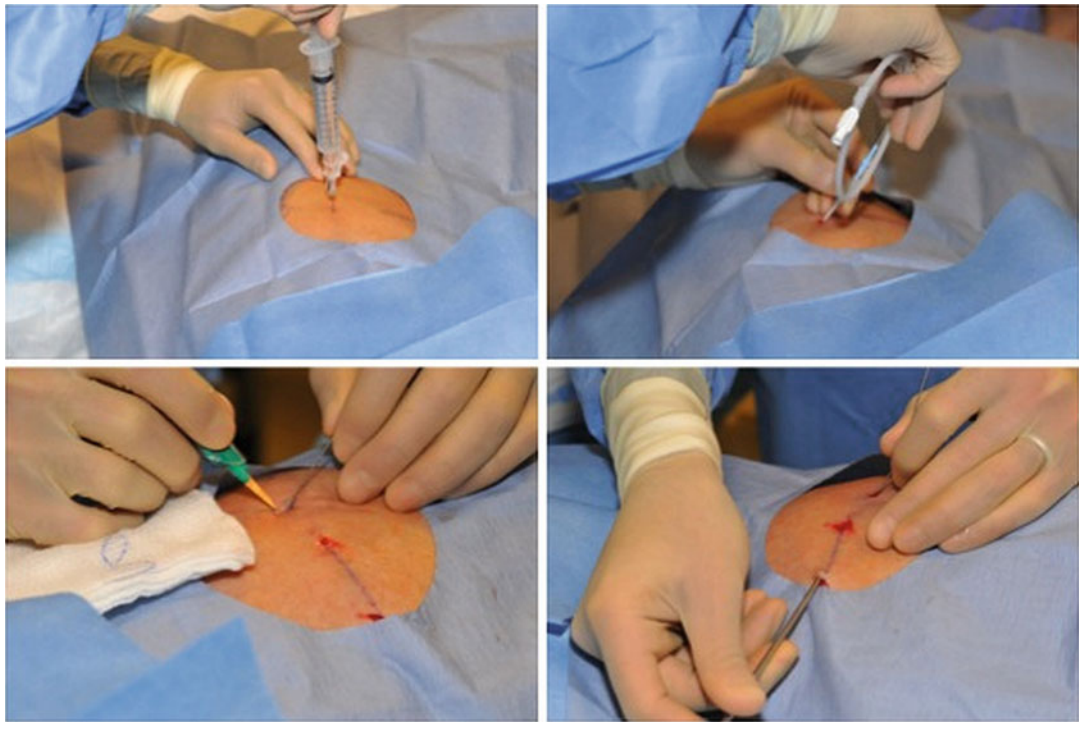

Fig. 25.8 Guidewire insertion, followed by pleural catheter tunneling

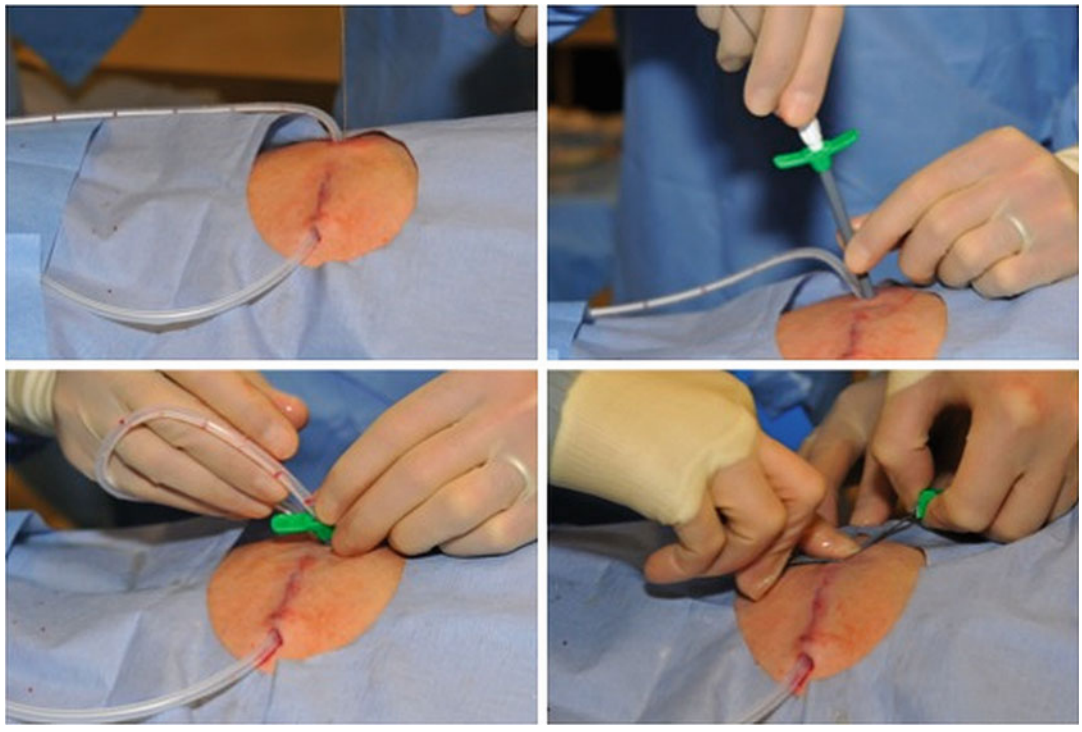

Fig. 25.9 Trocar insertion followed by feeding the catheter into trocar and finally peeling off the trocar

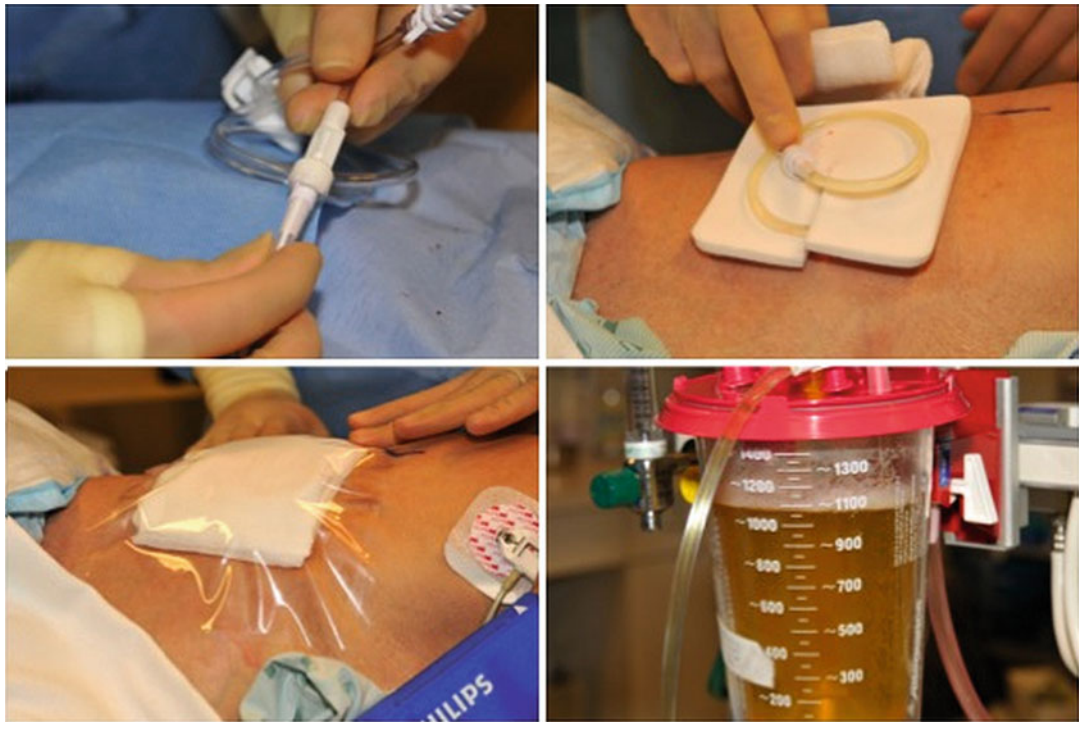

Fig. 25.10 Draining the fluid and placing the final dressing

Table 25.2 Karnofsky score

Able to carry on normal activity and work, no special care needed	100	Normal, no complaints, no evidence of disease
	90	Able to carry on normal activity, minor signs or symptoms of disease
	80	Normal activity with effort, some signs or symptoms of disease
Unable to work, able to live at home and care for most personal needs, varying amount of assistance needed	70	Cares for self, unable to carry on normal activity or to do active work
	60	Requires occasional assistance but is able to care for most of his personal needs
	50	Requires considerable assistance and frequent medical care
Unable to care for self, requires equivalent of institutional or hospital care, disease may be progressing rapidly	40	Disabled, requires special care and assistance
	30	Severely disabled, hospital admission is indicated although death not imminent
	20	Very sick, hospital admission necessary, active supportive treatment necessary
	10	Moribund, fatal processes progressing rapidly
	0	Deceased

needle using Seldinger technique and the guidewire is inserted through the needle and directed into the largest fluid collection seen on the ultrasound examination. A small incision (0.5 cm) is made at the guidewire entry to facilitate the insertion of the dilating trocar. A small incision (1 cm) is made at the skin level a few centimeters anterior to the insertion site with the catheter tunneled subcutaneously until the polyester cuff is buried 0.5 cm underneath the skin and catheter exits from the guidewire insertion site. Gentle dilatation with the sequential dilators is performed over the guidewire with eventual insertion of the trocar and removal of the guidewire. The catheter is then fed through the breakaway trocar which is peeled until the catheter is fully inserted into the pleural space. The catheter is then secured with sutures and drained to ensure proper function and provide the patient with immediate relief of dyspnea. A follow-up CXR is ordered to confirm proper placement. The patient is scheduled for follow-up visit in 7–10 days for suture removal and to review the drainage data.

Patient Selection

TPC is typically done in a patient with MPE who has poor performance status indicated by Karnofsky score less than 60% (Table 25.2). Patients with known MPE and a good performance status may elect for TPC rather than medical thoracoscopy and pleurodesis to further minimize hospitalization.

Karnofsky score (Table 25.2).

Pleurodesis

Patients with MPE have fluid accumulating in the pleural space and compressing the lung resulting in significant dyspnea and poor quality of life. Pleurodesis is the treatment used to drain that fluid and preventing it from reaccumulation. In many instances, pleurodesis involves injecting a sclerosing agent into the pleural space to induce inflammation and fibrosis to obliterate the pleural space.

Spontaneous pleurodesis with TPC alone can occur in 50–58% of cases in a mean of 39 days. Sclerosing agents can be injected into TPC by overcoming the one-way valve and inserting a three-way stopcock at the end of the drainage line. Doxycycline or talc is used to achieve pleurodesis. No significant differences in side effects or safety profile were found between these sclerosing agents although some studies reported concerns regarding the possibility of ARDS when using smaller particles of talc. Chest tubes are another option to achieve pleurodesis in MPE. Small-bore chest tubes (10–14 F) inserted with ultrasound guidance proved to be as effective as large-bore chest tubes in the management of

MPE. Two studies using those tubes reported pleurodesis success rate between 72 and 94%. A variety of small-bore chest tubes are available, and the sclerosing agent can be instilled through the three-way stopcock at the end of chest tube. The British Thoracic Society recommended starting pleurodesis once effusion drainage is achieved and lung expansion has been confirmed radiologically. Disadvantages of chest tube insertion include prolonged hospital stay, limited mobility, and increased chest wall pain as compared to the outpatient TPC.

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Part VI

Interventional Bronchoscopy in Asthma and Emphysema

Endoscopic Methods for Lung Volume Reduction

26

Luis M. Seijo

Introduction and Definition of the Procedure

Pulmonary emphysema is a chronic, debilitating, often fatal disease, characterized by progressive destruction of the lung parenchyma, hyperinflation, reduced lung elasticity, and impaired gas exchange. Patients with severe emphysema complain of progressive dyspnea as the hyperinflated lung becomes entrapped in a rigid chest wall. Medical treatment of emphysema offers limited symptomatic relief but has failed thus far to improve survival. Lung volume reduction surgery, a therapeutic option in advanced emphysema, while successful in a selected group of patients, is associated with considerable morbidity and mortality [1]. The landmark National Emphysema Treatment Trial (NETT) found a striking improvement in survival in patients undergoing surgery with upper-lobe predominant emphysema and poor exercise tolerance [1]. Despite such promising findings, the NETT may be credited with a widespread reluctance to refer patients for the procedure because of the reported 5% mortality, including a worrisome increase in mortality in some high-risk patients [2]. The NETT also found excess morbidity in 50% of the patients in the surgical arm, mostly related to prolonged hospitalizations, air leaks, and infection. Consequently, fewer than 200 surgical procedures were performed in the USA in 2007 [3].

Pulmonologists have been searching for a minimally invasive alternative to lung volume reduction surgery for years. The promise of a technique or device capable of reproducing the benefits of the surgical procedure without incurring the side effects, mortality, and morbidity of surgical lung volume reduction is appealing for obvious reasons. Not surprisingly, interest in endoscopic lung volume reduction (ELVR) peaked after the NETT findings were made public.

In general, ELVR can be defined as a minimally invasive bronchoscopic procedure devoted to the reduction of total or regional lung volumes in patients with severe emphysema and profound dyspnea [4]. Some procedures rely on device insertion, including endobronchial valves, coils, and bypass stents, while others instill bioactive substances such as a polymer or water vapor with identical therapeutic intentions. The methods are diverse but are usually applied using the flexible bronchoscope under deep sedation or general anesthesia. Most procedures last less than 1 h and may target one or both lungs. Patients may undergo pulmonary rehabilitation prior to treatment and must be on standard medical therapy for COPD, including bronchodilators and occasionally low-dose steroids. In general, patients with frequent exacerbations are excluded as they may be at greater risk for complications following device implantation, although there is no evidence to support this practice.

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Historical Perspective

Pioneers of ELVR focused on obtaining improvements in lung function and seeking measurable lung volume reduction, essentially attempting to reproduce surgical results [5]. However, the paradigm has shifted back and forth as failure to obtain true lung volume reduction despite improvements in quality of life made many investigators weary of attempting to match surgical outcomes. Also, while ELVR was initially reserved for ideal surgical candidates with upper-lobe predominant emphysema, subsequent studies have included patients with homogeneous emphysema as well as patients with heterogeneous emphysema not necessarily upper-lobe predominant.

The role of computed tomography (CT) has also widened. It was originally limited to patient selection but has become a useful tool for follow-up since it can quantify regional lung volume changes in the absence of overall lung volume reduction. Collateral ventilation, a major limitation of many ELVR approaches, has also been studied with CT as well as specific devices designed for this very purpose [6]. Such devices along with CT determinations of the integrity of a candidate's interlobar fissures may improve patient selection for a given procedure.

Indications and Contraindications

Endoscopic lung volume reduction is indicated for a highly selected group of patients with advanced emphysema. Originally, ELVR was reserved for patients with upper-lobe predominant disease. However, indications for ELVR have widened to include a more diverse population of patients suffering from emphysema in response to the recent proliferation in techniques and devices. New approaches have led to broader indications, including patients with homogeneous emphysema or lower-lobe predominant disease.

In general, candidates for ELVR must suffer from severe emphysema and moderate to severe dyspnea despite optimal medical therapy. Patients with alpha-1 antitrypsin deficiency are generally excluded, as are those 75 or older. Ideal candidates must be ambulatory and capable of walking at least 140 m with or without supplemental oxygen during a 6-min walk test. They must abstain from smoking and demonstrate severe obstruction on spirometry as well as air trapping and hyperinflation on plethysmography. Patients with extremely low diffusing capacities, as well as those with severe gas exchange abnormalities, especially CO_2 retainers, are not considered good candidates for ELVR. Giant bullous or reactive airways disease, severe pulmonary hypertension, frequent exacerbations, or major medical comorbidities are also considered important contraindications. Patients with FEV1s less than 20–25% of the age-adjusted predicted value are generally not treated. Most procedures are performed under general anesthesia or deep sedation so patients unable to tolerate either cannot be treated. One should keep in mind that each device or technique designed to achieve ELVR is unique. Endobronchial valves, for example, are never used to treat patients with homogeneous emphysema, a group specifically targeted by airway bypass. Polymer-induced lung volume reduction may also be indicated for these patients but only if the treatment targets the upper lobes.

Description of the Equipment Needed

ELVR can be performed in a variety of hospital settings. Many procedures are performed in the bronchoscopy suite and do not require special equipment beyond that which can generally be found in a well-stocked unit. A diagnostic or therapeutic flexible bronchoscope may be used, depending on the method chosen. Devices tend to require the larger 2.8 mm channel of the therapeutic bronchoscope. A calibration balloon is sometimes needed (Fig. 26.1). Airway bypass relies on the sonographic exploration of the treated airway in order to avoid puncturing a blood vessel and originally used a radiofrequency ablation catheter to create an airway fenestration which has since been replaced by a needle. Vapor-induced ELVR requires special equipment unique to this procedure.

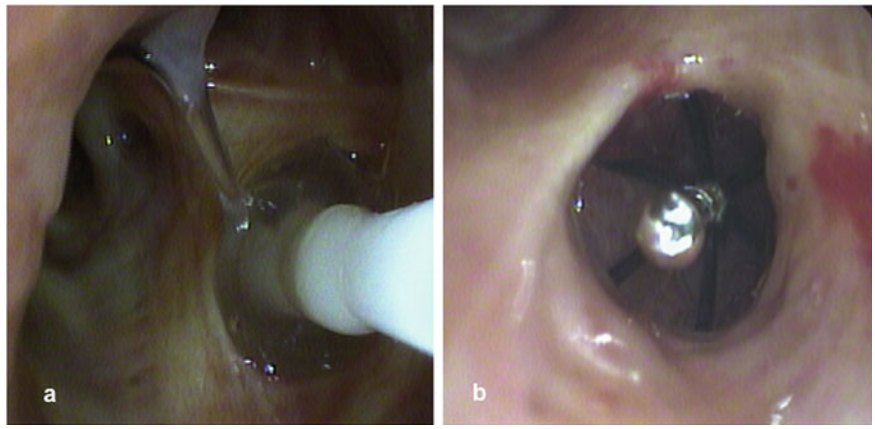

Fig. 26.1 Balloon calibration (**a**) and placement (**b**) of an IBV device in a patient with severe upper-lobe predominant emphysema

In general, deployment of most devices, including valves, is straightforward for an experienced bronchoscopist and requires little additional training. That notwithstanding, valve removal can be quite challenging if not impossible in some cases. Coil therapy is best performed under fluoroscopic guidance, a technique familiar to many bronchoscopists who perform transbronchial biopsies or stent implantation. Finally, some bronchoscopists prefer to treat patients under general anesthesia using the rigid bronchoscope or an endotracheal tube. Anesthesia support is mandatory in such cases. Others prefer conscious sedation which may be administered by the endoscopic team.

Evidence-Based Review

Endobronchial Valves

Endobronchial valves were among the first devices to be developed for ELVR. They have been widely studied, and results from well-designed randomized studies have recently been reported. The landmark VENT, a multicenter randomized controlled trial, demonstrated that endobronchial valves can achieve modest statistically significant improvements in a variety of endpoints, including lung function, exercise capacity, and quality of life [7]. The study was completed in 2007 and enrolled 321 patients. It compared the safety and efficacy of endobronchial valve therapy employing a unilateral lobar approach in patients with heterogeneous emphysema with optimal medical care. Despite achieving statistical significance, the results were considered by many, including the FDA, underwhelming (http://www.fda.gov/ohrms/dockets/ac/08/transcripts/2008-4404-t001.pdf). Improvements in FEV1 (60 ml), the 6-min walk distance (19 m), and reductions in the SGRQ scores with treatment (3.4 points) have been considered by some clinically insignificant. Careful scrutiny of VENT results, however, leaves some room for optimism. Improvements in the BODE index, more common among valve-treated patients, are provocative since this index correlates well with prognosis in COPD (http://www.fda.gov/ohrms/dockets/ac/08/transcripts/2008-4404-t001.pdf). In addition, patients with complete fissures who achieved a greater than 50% reduction in lobar volume demonstrated clinically relevant improvements in FEV1 (23%) which may have survival implications as demonstrated in a subsequent report from a group of investigators using the same valves as the VENT [9]. These authors found a survival benefit in a small cohort of patients among those who achieved atelectasis at the expense of more pneumothoraces, suggesting that ELVR may match surgical results in some patients with heterogeneous emphysema. In its ruling denying approval for the Zephyr device

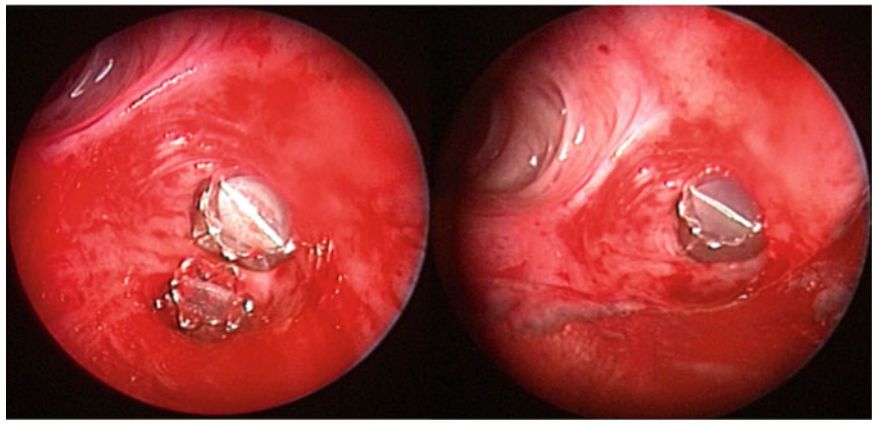

Fig. 26.2 Duckbill-shaped endobronchial valves (Zephyr) (courtesy Dr. Dutau)

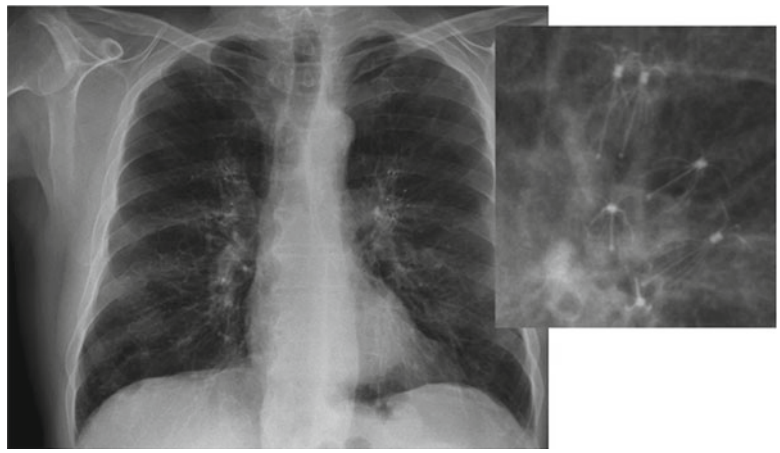

Fig. 26.3 Chest radiograph of a patient with upper-lobe predominant severe emphysema treated with ten endobronchial valves (IBV). The characteristic umbrella-shaped valves can be seen in both upper lobes. Lobar occlusion was avoided in this patient

(Fig. 26.2) employed in the VENT (a self-expanding nitinol stent with a silicon one-way duckbill valve), the FDA expressed concern regarding the complications of ELVR, including a major increase in the number of hospitalizations for COPD exacerbations in the treatment arm (17 vs. 1) and other complications such as hemoptysis (http://www.fda.gov/ohrms/dockets/ac/08/transcripts/2008-4404-t001.pdf). Fear of the risks undermined the modest benefits of the trial. As a result, more research was requested.

Results from a randomized sham-controlled trial, using the IBV system from Spiration (an umbrella-shaped, self-expanding device, Fig. 26.3), have recently been reported. This smaller trial was unique since it included sham bronchoscopy in the control group and kept patients blinded for the duration of the initial trial period of 3 months [10]. The treatment strategy differed significantly from the VENT, since it focused on a bilateral approach purposefully avoiding lobar occlusion. This trial also failed to achieve overall clinically relevant improvements in hard outcomes such as FEV1, gas exchange, or exercise capacity but demonstrated statistically significant improvements in a combined endpoint including quality of life and regional lung volume changes as measured by CT. At the conclusion of the Spiration trial, 31% of the treated patients demonstrated an improvement of eight points in

the SGRQ score and a significant regional lung volume reduction in the treated upper lobes.

The most striking finding of the European Spiration trial was the impressive magnitude of the placebo effect. Many patients undergoing sham bronchoscopy reported significant benefits in quality of life. Such findings match results from the most recent bronchial thermoplasty trial employing sham bronchoscopy [11]. A larger parallel study currently underway in the USA may better clarify the placebo effect of sham bronchoscopy since randomization lasts 6 months instead of 3 [12]. Interestingly, a pilot trial seeking lobar occlusion found significant improvements in lung function and more impressive reductions in SGRQ scores in patients who achieved atelectasis with the IBV system (Fig. 26.4) [13]. The risks associated with this complication motivated the subsequent change in treatment strategy. Whether avoiding atelectasis guarantees safety at the expense of efficacy remains to be seen.

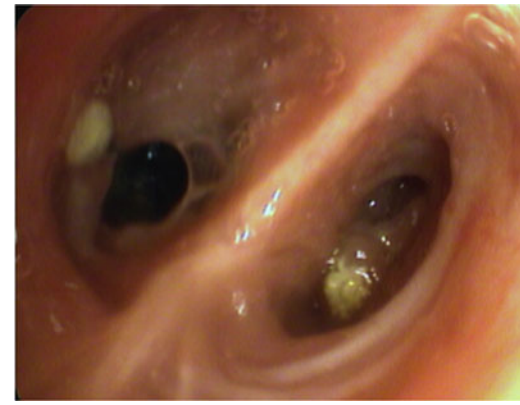

Fig. 26.4 Endobronchial valves (IBV) in the *right upper* lobe 3 years after deployment

Airway Bypass Tracts

While most ELVR techniques are designed to promote lung volume reduction by limiting flow to the most affected lung parenchyma, Broncus (Mountain View, CA) has developed a technique which reduces air trapping by promoting nonanatomic collateral flow. This method of ELVR known as the Exhale™ Emphysema Treatment system, pioneered by Joel Cooper in the USA, shuns atelectasis, a manifest goal of some valve treatments, striving instead to create airway fenestrations in order to facilitate exhalation of trapped air. A Doppler system is employed in order to avoid damaging major vessels and select the appropriate site for stent deployment using a needle. This approach reduces end-expiratory volume without altering lung recoil and has been tried in patients with homogeneous emphysema, although it should theoretically also work in patients with heterogeneous emphysema.

Preliminary evidence treating explanted lungs was quite encouraging. Improvements in FEV1 following deployment of multiple stents in one small study of 12 explanted lungs were dramatic [14]. Outcomes in vivo, however, have been frustrating, mostly as a consequence of stent occlusion by granulation tissue. Drug-eluting stents have been created to avoid this complication and seem to work in animal studies, prolonging patency [15]. An open-label study of the drug-eluting stents has shown that the Exhale™ system can reduce hyperinflation for a limited time in a selected group of patients with severe emphysema [16]. Unfortunately, while results at one month were impressive including improvements in FEV1, quality of life, and total lung capacity in more than 30 patients treated with more than five stents each, results at 6 months were less encouraging. Post-procedure complications including COPD exacerbations were relatively frequent, and one patient died as a consequence of massive hemoptysis induced by stent implantation.

The Exhale™ system was recently put to the test in a multicenter randomized, sham-bronchoscopy-controlled trial known as EASE (exhale airway stents for emphysema) [17]. Three hundred and fifteen patients with severe hyperinflation defined as a ratio of residual volume to total lung capacity of ≥0.65 from 38 centers worldwide were enrolled. Patients were followed for 12 months. Unfortunately, stented patients did not achieve the co-primary endpoints of a 12% improvement in forced vital capacity and 1 point improvement in the mMRC dyspnea score when compared to controls, though the latter did show a statistically significant improvement. In effect, only 30 out of

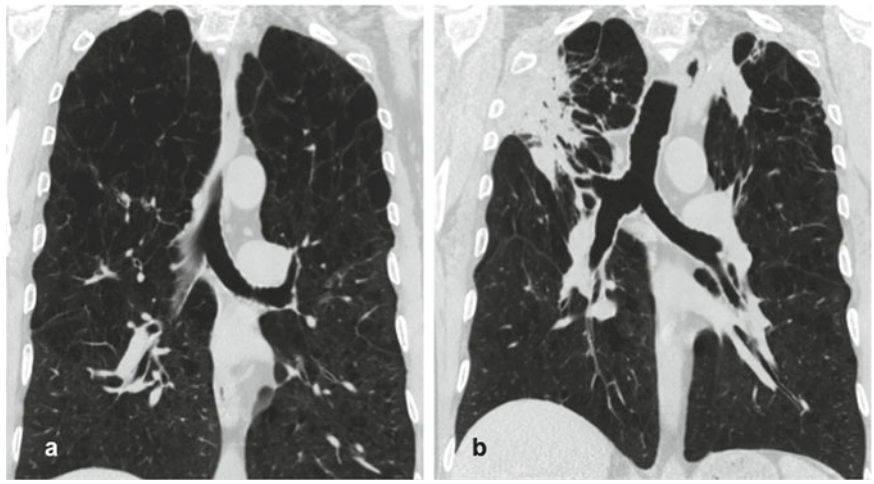

Fig. 26.5 Before (**a**) and after (**b**) coronal CT images of a patient with heterogenous upper-lobe predominant emphysema treated with AeriSeal. The patient's FEV1 improved by 69%, his SGRQ score diminished by 8.3 units, and the RV/TLC ratio dropped by 9% (courtesy of Dr. Ingenito)

208 treated patients met the co-primary endpoint. A considerable mean reduction in residual volume averaging 0.5 L was achieved in 40% of the treated patients. This finding predicted clinical success. The 6-month composite primary safety endpoint combining five severe adverse events was 14.4% for the treatment arm which compared favorably with 11.2% for the control group and was judged non-inferior. So at least the treatment was proven to be safe.

Biologic Lung Volume Reduction

Biologic lung volume reduction, unlike its predecessors, is not device based. This method of ELVR has been developed by Aeris Therapeutics (Woburn, MA) and seeks to achieve its goal employing tissue engineering principles (Fig. 26.5) [18]. Remodeling of damaged lung parenchyma by the newer polymer-based treatment creates progressive atelectasis in treated subsegments of the upper lobes, thus promoting true lung volume reduction. The ability of the polymer to spread through the airway limits the impact of collateral ventilation, a major concern with endobronchial valves. Treatment is irreversible and frequently associated with considerable, though relatively brief, inflammation which mandates prophylactic treatment with steroids and antibiotics, in effect causing a minor COPD exacerbation in all treated patients. Pneumothorax is not expected as tissue remodeling occurs slowly, although it is theoretically possible. A preliminary small open-label phase I trial showed the treatment to be safe and moderately effective in a small group of six patients [19]. Results from a phase 2 clinical trial enrolling 50 patients were recently reported [20]. High-dose therapy was effective in that trial and yielded sustained benefits, but COPD exacerbations were frequent, occurring in 28% of treated patients. Severe adverse events were reported in four subjects. A subsequent trial enrolling patients with homogeneous emphysema (Fig. 26.6) with depressed perfusion to the upper lobes also showed benefit with high-dose treatment and had a similar safety profile [21]. The AeriSeal System will be the subject of a randomized controlled trial in Europe scheduled to begin recruiting patients in 2012.

Other Methods of ELVR

Bronchoscopic thermal vapor ablation (Update Inc.; Seattle, WA) and nitinol self-actuating reduction coils (PneumRx Inc.; Mountain View, CA) are under development, but available data are insufficient for meaningful evaluation of safety and efficacy (Fig. 26.7) [22, 23].

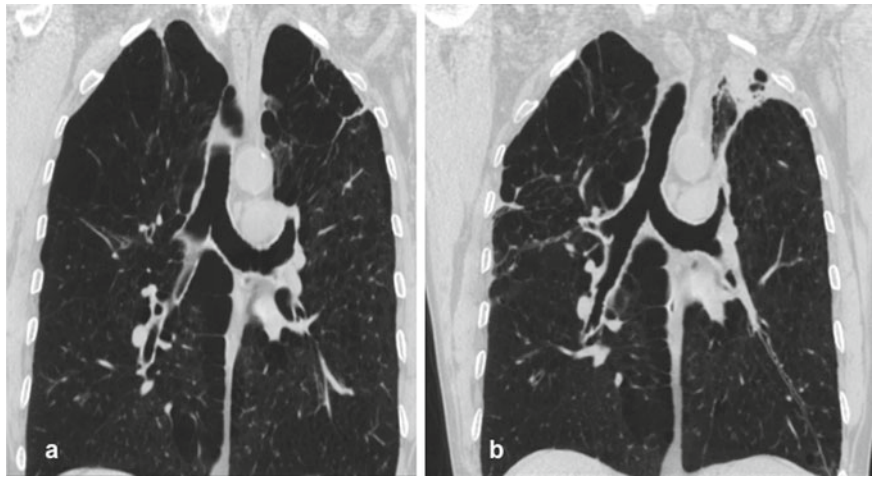

Fig. 26.6 Before (**a**) and after (**b**) coronal CT images of a patient with homogeneous emphysema treated with AeriSeal. The patient's FEV1 improved by 29%, his SGRQ score diminished by 8.5 units, and the RV/TLC ratio dropped by 8% (courtesy of Dr. Ingenito)

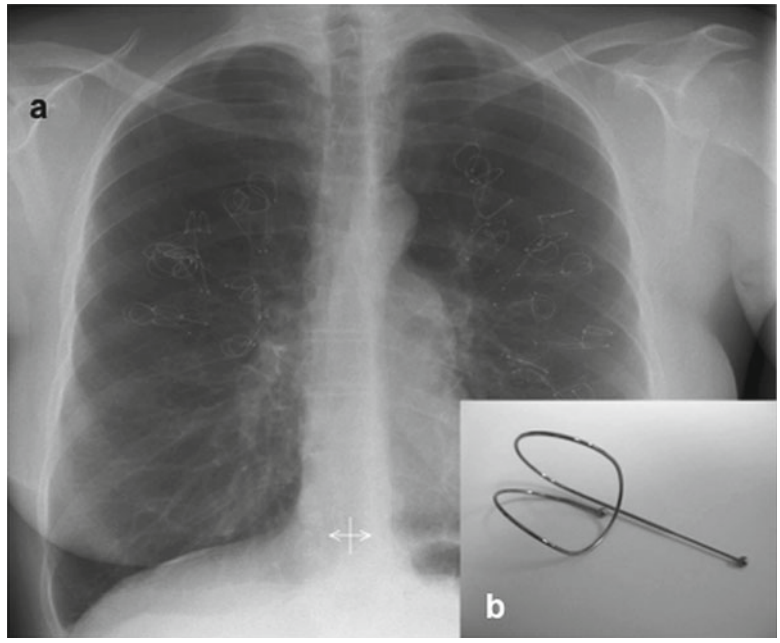

Fig. 26.7 Chest radiograph of a patient treated with the PneumRx coils (**a**). The coil in more detail (**b**)

Summary and Recommendations

The limited clinical data currently available suggest that ELVR is reasonably safe. We know that current approaches to ELVR achieve modest regional or total lung volume reduction and significant improvements in quality of life as measured by validated disease-specific questionnaires. However, lung volume reduction surgery outcomes cannot be expected with established approaches to ELVR. ELVR should not be considered an alternative to LVRS. Indeed, efficacy is lacking or underwhelming for most procedures. Patient selection must be

optimized, treatment strategies refined, and safety on a broader scale confirmed before ELVR can be considered standard of care for selected patients with severe emphysema. The placebo effect, a powerful confounder in studies focusing exclusively on soft outcomes such as quality of life, must be accounted for. Although modest gains in such endpoints may be considered a relative success of ELVR therapies since they often exceed those achieved with bronchodilators, I believe we should continue to strive for improvements in lung function and survival [24, 25]. Only then will device-related complications or significant increases in morbidity become acceptable in this patient population.

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Transbronchoscopic Emphysema Treatment with One-Way Zephyr Valves

27

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and Hugo G. de Oliveira

Introduction and Definition of the Procedure

Very few alternatives are available for the treatment of emphysema, which is still incurable and characterized by steady and sometimes devastating physical decay that is not countered by medication. Until recently, the most efficient palliative treatments for emphysema were lung volume reduction surgery (LVRS) and lung transplantation. However, the high morbidity and mortality associated with these procedures have greatly restricted their applicability. Nevertheless, it was the National Emphysema Treatment Trial (NETT), a prospective randomized trial of LVRS that contributed the most valuable data on emphysema in medical history, allowing other minimally invasive alternatives to be considered and developed.

To date, most minimally invasive (endoscopic) emphysema treatments have employed the same rationale underlying LVRS—to decrease or prevent air trapping in portions of the lung that are damaged by emphysema so as to allow reexpansion of the remaining tissue (the exhale system employs a somewhat different approach—see clinicaltrials.gov/ct2/show/NCT00391612). In emphysema, static or dynamic hyperinflation, that is, the expansion of the lung at rest or during exercise to a volume that cannot be contained in the rib cage, has a major deleterious impact on quality of life and survival, which is further worsened by nonpulmonary issues such as undernutrition and depression.

Historical Perspective

The first endoscopic approach for emphysema treatment was proposed by Crenshaw. In 1966, that author described a technique in which diluted sodium hydroxide was bronchoscopically applied as sclerosing agent to promote retraction of emphysema bullae. Despite the marked improvement obtained with two patients, with one being able to resume work, there is no record of this experience having been pursued further. Also pioneer was the work of Watanabe and colleagues, who proposed the use of an endoscopically delivered cork-like device, the spigot. One of the major limitations of the method was the occurrence of obstructive pneumonia and pneumothorax, possibly resulting from hyperinflation due to collateral ventilation. Therefore, the Watanabe spigot had limited clinical application.

Following these two founding approaches and the NETT, a range of techniques and devices has appeared for nonsurgical management of

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emphysema. Together with the vast amount of information obtained with the NETT, the effort to develop these minimally invasive treatments has greatly improved the understanding regarding the pathogenesis, clinical expression, and treatment response of chronic obstructive pulmonary disease (COPD). The advancement of physiological knowledge in the past years has shed light on the local inflammatory and systemic nature of COPD, and therefore clinical management currently emphasizes a more comprehensive approach that includes the use of anti-inflammatory drugs, rehabilitation, oxygen therapy, and nutritional and psychological support, among others.

The literature on endobronchial valves is largely limited to fairly preliminary results that agree regarding valve safety but are inconclusive in terms of many aspects or to reports of valve use to treat other conditions such as fistulae. Also, the only randomized trial available to date has produced unsatisfactory results. Therefore, it is important to discuss our own experience working with endobronchial valves since June 2002 and to report our results with patients with more than 6 years of follow-up.

In 2001 we were invited to take part in a phase II trial set up by endobronchial valve manufacturer Emphasys Medical. We performed our first endoscopic treatment on 4 June 2002. In the research phase, our group treated 19 patients (until 28 October 2004). Between the end of the trial and the approval for commercial valve use in Brazil, in August of 2008, we did another ten treatments (with one patient from the research stage being retreated). Since then, 38 additional patients have been treated. Considering the overall group, some patients were submitted to a second treatment, some were treated with a progressive strategy (staging), and some patients underwent valve reimplantation (two for valve dislodgment/migration and two due to pneumonia). Thus, our group has performed 86 treatments in 66 patients. This experience and the lessons we learned during this period (197 valves implanted) will be described in this chapter.

Indication and Contraindications

Endobronchial valve treatment was initially indicated for the treatment of patients with heterogeneous emphysema. Currently, we have added the presence of complete lung fissures as a major criterion supporting valve treatment in patients with homogeneous emphysema (heterogeneity gradient <15 pp) as well.

The most important prognostic factors to select patients for the various nonsurgical emphysema treatment modalities seem to be dynamic air trapping/hyperinflation, heterogeneity, and collateral ventilation, in addition to clinical aspects. Small airway disease has also emerged as a possible complicating factor. Together, dynamic air trapping and the presence of collateral ventilation indicate the cases in which valve treatment is more likely to succeed. Hypothetically, the study of collateral ventilation will be able, in the future, to assess the appropriateness of combined treatments, in which two techniques can be applied together to promote lung volume reduction through different mechanisms. Heterogeneity defines the parenchyma to be excluded.

Table 27.1 describes relative and absolute contraindications for valve treatment.

Air Trapping/Hyperinflation

In emphysema, the correlation between air trapping, dyspnea, and expiratory flow requires further elucidation. The loss of lung elastic recoil, typical of emphysema, is associated with the development of static and dynamic hyperinflation, dynamic airway collapse, and airway obstruction. It is known that in patients submitted to LVRS, lung elastic recoil is not recovered immediately after the surgery; rather, the observed increase in expiratory flow seems to result from an increase in pressure. In a situation of augmented air trapping, there is a decline in expiratory flow with increase in expiratory lung volume and residual volume. From the point of view of respiratory mechanics, increased pressures must be generated to over-

Table 27.1 Absolute and relative contraindications for valve treatment

Absolute contraindication	Relative contraindication
• Recurrent infection and daily sputum production judged clinically significant	• Bronchitis
• Refractory bronchospasm	• $FEV_1 < 20\%$
• Bronchiectasis	• $pCO_2 > 60$ mmHg
• Uncontrolled hypertension	• Multiple subpleural bullae in lobe adjacent to lobar exclusion
• Comorbidity or neoplasia compromising survival	• Giant bullae
• Current smoking	• Mean pulmonary artery pressure >50 mmHg

come the intrinsic positive end expiratory pressure and maintain tidal volume.

Dynamic air trapping is also an indication for valve treatment: that is, patients with more air trapping during exercise will probably obtain more benefit from endoscopic treatments. In our case series, 14/66 (21%) patients had an optimal response to valve treatment with volume reduction (>30%). This group includes patients with highly heterogeneous emphysema associated with high airway resistance (low collateral airflow).

Heterogeneity

The application of the available minimally invasive techniques depends, as previously proposed, on the radiologic distribution of emphysema (Fig. 27.1) and on the presence or intensity of collateral ventilation—more heterogeneity and less collateral ventilation being the strongest indicators of treatment success. Heterogeneity is defined as the difference in parenchymal density between adjacent lobes and segments, expressed as percent points (pp).

In the early days of endobronchial valve treatment, this difference in parenchymal density was visually assessed on CT scans, with subjective assignment of a parenchymal destruction score—0% corresponding to a score of 0; 1–25% corresponding to a score of 1; 26–50% corresponding to a score of 2; 51–75% corresponding to a score of 3; and >75% corresponding to a score of 4. Heterogeneity was then determined by the difference in the score of adjacent lobes and segments, with a difference of at least 1 in scores considered as desirable. This highly subjective method has been replaced with more objective techniques, especially multi-detector row computerized tomography (MDCT) imaging of the trachea-bronchial tree measured and reconstructed with targeted post-processing software. Our group agrees with other groups that define emphysematous tissue as parenchyma with density below −950 HU on CT. We then determine what percentage of each section corresponds to this density, and the difference in percentage between lobes and segments defines heterogeneity. For example, if an upper lobe has 58% parenchymal tissue with density <−950 HU, and a lower lobe has 23% parenchymal tissue <−950 HU, the heterogeneity score would be 35 pp. We adopted an arbitrary cutoff point of 15 pp between the upper and lower lobe to define heterogeneity. The right middle lobe is added to the untreated lobe for heterogeneity calculation.

Collateral Ventilation

Differently from LVRS, in which a part of the parenchyma is actually removed, transbronchoscopic endobronchial valve treatment merely introduces a barrier that allows one-way airflow in segment bronchi of specific lung regions. The contact surface and the degree of intralobar communication through foramens are difficult to evaluate. The pathophysiology of the opening and closure mechanisms in these interlobar orifices is complex and may vary in terms of airflow direction and volume, in addition to involving the participation of different time constants.

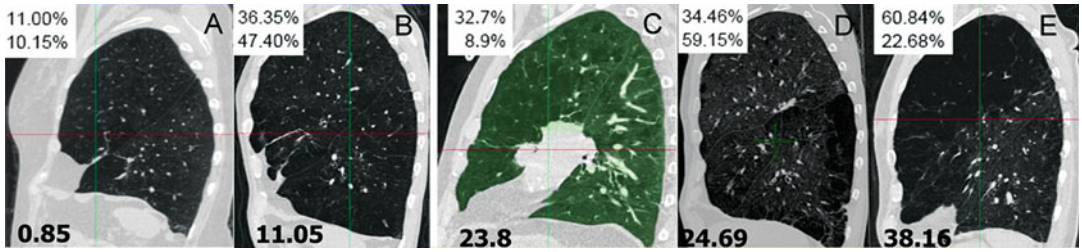

Fig. 27.1 Radiologic distribution of emphysema in left lung. (**a**, **b**) Homogeneous emphysema. (**c**) Heterogeneous emphysema with 23.8 pp gradient (LUL 32.7–LLL 8.9%). (**d, e**) Further examples of heterogeneous emphysema

Fig. 27.2 Chartis® system: monitor and disposable balloon catheter

Along these 10 years working with one-way valves, we came to understand the importance of interlobar collateral ventilation for the improvement of lung function after valve placement, that is, for the effective reduction of static volumes in treated areas. The teachings of the VENT suggest that in patients with a complete lung fissure, with high resistance to interlobar collateral ventilation, valve treatment may be beneficial even in the presence of homogeneous emphysema. In the VENT subgroup of 20 patients considered to be good responders—who presented significant volume reduction (89.4%) in the treated lobe—18 had a complete fissure and only ten had heterogeneous emphysema. More recently, Felix Herth and colleagues, from Germany, used a unique system that provides flow and pressure readings at the lobar or segmental level (Fig. 27.2). Of 97 patients selected for endoscopic treatment of advanced emphysema, 57 patients completing the evaluation and 30 (80%) of 37 patients with absent collateral ventilation had a volume reduction >350 ml in the treated lobe. In contrast, only 4 (20%) of 20 patients with collateral ventilation had volume reduction. The increase in FEV_1 in the 37 patients without collateral ventilation was 19.2 ± 23.9% vs. 0.9 ± 13.3% in patients with collateral ventilation. These results explain the increasing interest in measuring interlobar collateral ventilation as a criterion to select patients for endoscopic valve treatment of emphysema. The Chartis® Pulmonary Assessment System monitors airflow and pressure within the target lobe and quantifies the average collateral resistance.

Our group has developed a method for visual assessment of fissure integrity and is currently matching this visual integrity score with Chartis®

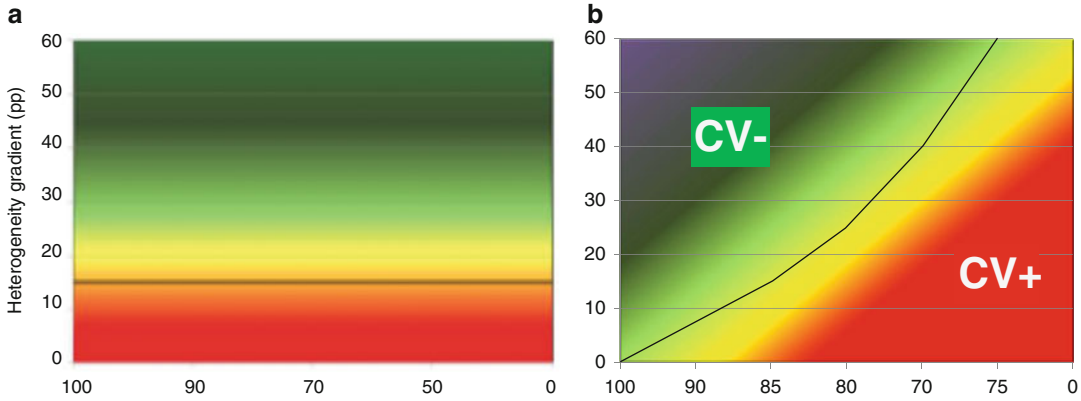

Fig. 27.3 Until 2010, we would only treat patients as in (**a**), based on heterogeneity score>15 pp. We currently treat patients as in (**b**), with *green* indicating the best candidates and *red* indicating the worst candidates or contraindication to treatment

and VIDA® software analyses (VIDA Diagnostics, Coralville, IA, USA; see Treatment Planning) to determine the absence of collateral ventilation and treat homogenous emphysema patients. This visual analysis is performed using a sagittal view through all slices of the lung CT scan in VIDA® to determine which percent of the overall slices were visually complete. Fissure integrity is categorized as incomplete (<70% integrity), partial (71–90%), or complete (91–100%). Our selection method has moved from one focused mainly on heterogeneity to one combining heterogeneity with collateral ventilation as an additional criterion (Fig. 27.3).

Small Airway Disease

The notion that the inflammatory process affecting small airways could be a prognostic indicator of functional response after LVRS was supported by the work by Kim et al. with 25 patients from the NETT. That study identified an important correlation between the absence of wall thickening in 2-mm airways and the functional response 6 months after LVRS. Perera et al. were the first to describe the behavior of biological markers collected in blood or in the airway as a means to diagnose COPD and consequently as a means of screening to initiate early treatment with antibiotics and corticosteroids. Interleukin-6 seems to play an important role as a marker of COPD.

The worsening causes limitation of expiratory airflow and greater air trapping. One of the most deleterious factors is the further lowering of the diaphragm. This set of factors leads to derangement of respiratory mechanics and to a feeling of dyspnea.

The inclusion of COPD exacerbation as an element to define severity as recommended by the 2011 GOLD guidelines is also evidence of the importance of small airway disease for improvement of patients with COPD. We foresee that small airway disease will soon become an additional selection criterion for candidates for endocospic emphysema treatments.

Clinical Factors

By 2020, chronic obstructive pulmonary disease (COPD) is expected to become the fifth most common cause of morbidity and the third most common cause of mortality worldwide. A mean of 1.3 COPD exacerbations per year can be predicted in affected individuals. The following are the main risk factors: old age, gastroesophageal reflux, chronic productive cough, and increased severity of COPD characterized by hospital admissions due to exacerbation. These individuals tend to score higher in the dyspnea scale, to have worse quality of life, remarkably decreased FEV_1, and greater air trapping as observed on CT. Many studies show

that the measures performed on CT can predict mortality in COPD patients. However, the findings of emphysematous alterations on CT do not predict COPD exacerbation. A more recent study shows that bronchial wall thickness is correlated to symptoms of chronic bronchitis and frequent exacerbations.

A comorbidity-based index such as the Charlson index, predicting mortality in 10 years, could be useful for the evaluation of clinical factors. As previously shown, a higher Charlson index score was a risk factor for COPD exacerbation and related to hospitalizations. Studies of patients with COPD have shown a phenotype for frequent COPD exacerbation, with prior exacerbations of COPD being the strongest risk factor for subsequent events.

Nutrition, psychological aspects (desire to improve and active participation in the treatment) such as anxiety and depression, and physical rehabilitation are also crucial components that must be addressed in emphysema patients. Even in the presence of heterogeneous emphysema and/or complete lung fissures, the undernutrition often associated with emphysema or the loss of muscle mass resulting from the chronic physical deterioration might compromise the results of valve treatment. Also, we have seen patients who feel much improved after valve treatment and who will then venture doing activities they are not ready for, with great risk of lesions. In one case, a patient broke a leg walking on a treadmill after being bedridden for a long time. Multidisciplinary care for emphysema patients encompasses physical therapy and psychological and nutritional support.

Description of the Equipment

The Zephyr valves that are currently used in flexible bronchoscopes (transcopic valve) have evolved from the classic endobronchial valve (EBV) model that was available between 2001 and 2003 (Fig. 27.4). In this initial, classic model, the valves were delivered using a guide wire and delivery system through (1) a rigid bronchoscope or (2) large orotracheal tube and flexible bronchoscope. Disadvantages of the classic valve were related to greater technical complexity and difficult implantation in upper lobe apical segments. Another important point was a higher risk of granuloma formation, since granulomas could easily obstruct the area close to the valve jeopardizing its unidirectional functioning (Fig. 27.5) (up to 70% of patients receiving the classic valve had some degree of granuloma on endoscopic follow-up after up to 1 year). Thus, the new design introduced important improvements for implantation, with the valve being totally compressed and loaded in a catheter with a diameter that is sufficiently small to be passed through a 2.8-mm bronchoscope channel. Also, the new valve design provided protection for the valve mechanism itself, facilitating grasping with the removal forceps when required. Our group was able to maintain a strict follow-up scheme in the phase II trial, with mandatory flexible bronchoscopies 30, 90, 180, and 365 days following the procedure. This allowed us to verify a significant reduction in granuloma formation with the Zephyr valve.

Fig. 27.4 Classic endobronchial valve

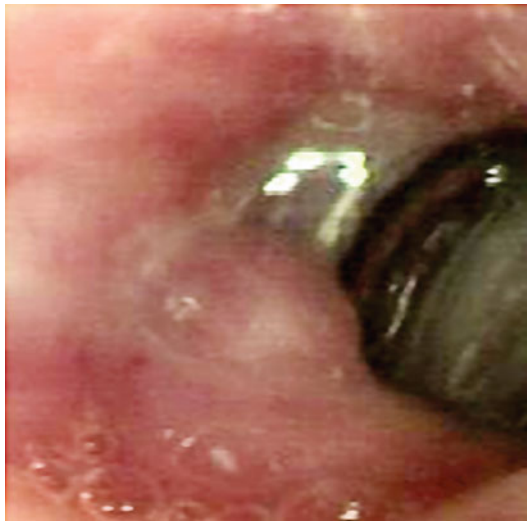

Fig. 27.5 Large granuloma associated with classic valve, possibly compromising valve mechanism

Reversibility of the procedure was also improved by the transcopic valve. We were able to remove a valve more than 5 years after implantation in one case.

Two Zephyr sizes are available (4.0 and 5.5), both built on a nitinol frame that provides structural support and is covered by a silicone layer that prevents the inclusion of material in the mucosa and creates a one-way airflow. The new model mimics airflow flexibility, decreasing friction, minimizing granuloma formation, and reducing valve migration/dislodgment. In summary, the newer model can be delivered directly through a 2.8 bronchoscope channel, streamlining the procedure. Valve mounting has also been greatly simplified.

System Components (Fig. 27.6)

- Endobronchial valve Zephyr 4.0 or 5.5 in diameter
- Delivery catheter
- Loader system

There are separate delivery catheters and loader systems for each valve size. Each system is color-coded: blue for the 4.0 system and green for the 5.5 system.

Application of the Technique

Treatment Planning

Even though it is not universally employed for this purpose, virtual bronchoscopy plays a major role in the planning of endoscopic emphysema treatment. In our experience, (1) it greatly reduces procedure duration, an important aspect for patients who are severely ill, as is usually the case of emphysema patients; (2) it is very helpful in selecting the exact sites for implantation and to get the interventional endoscopist acquainted with the anatomy of that particular patient.

There are no reports in the literature describing the use of this tool for this specific purpose; however, our group has long relied on Volumetric Imaging Display and Analysis (VIDA®) software (VIDA Diagnostics, Coralville, IA, USA), which reconstructs the tracheobronchial anatomy from CT scans. VIDA® software (current version is called Apollo®) produces results that are very accurate, even though its use is limited by the need for an expert operator who is capable of interpreting the tracheobronchial tree and making the necessary corrections in the reconstruction offered by the software.

However, the use of VIDA® software enables a detailed analysis of the airway (Fig. 27.7), providing information on bronchial diameter that determines if and which valve, 4.0 or 5.5, can be used to block the airway. Zephyr 4.0 is indicated for bronchi with 4–7-mm diameter and Zephyr 5.5 for bronchi with 5.5–8.5-mm diameter. It is also important to select segments with at least 9 mm in length. This pretreatment evaluation has practical advantages for reducing the duration of the procedure and estimating the exact number of valves that will be required. Rat tooth grasping forceps must be available during the procedure to remove the valve if implantation is not adequately accomplished. For valve removal, the bronchoscope must be introduced through the mouth.

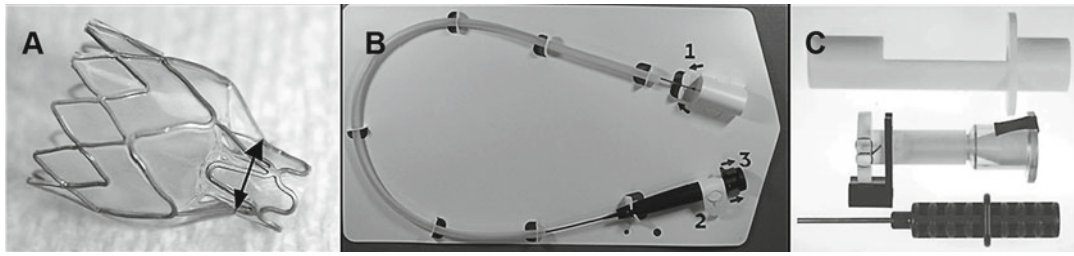

Fig. 27.6 (**a**) Zephyr valve (4.0 or 5.5 mm). *Arrow* shows diameter considered for valve size. The 4.0 model is used in bronchi measuring 4.0–7.0 mm in length, and the 5.5 model in bronchi measuring 5.5–8.5 mm. (**b**) Delivery catheter. (**c**) Loader system

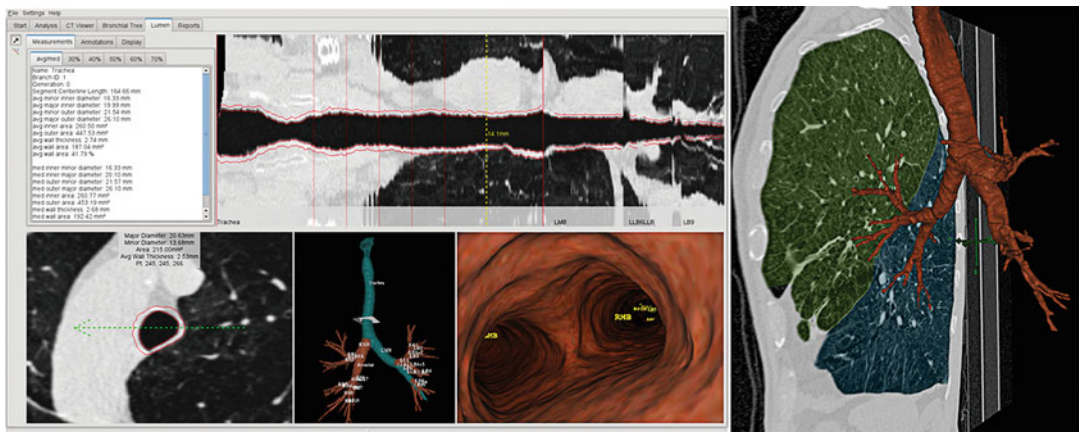

Fig. 27.7 VIDA® analysis of CT scan

Treatment

A flexible bronchoscope with a channel of at least 2.8 mm must be used. The device must be properly cleaned and rinsed, since any residual detergent in the working channel may cause severe bronchospasm. Angulation must also be verified to match the manufacturer's recommendations, especially when placing valves on RUL and LUL apical segments. Radioscopy is not required. Antihypertensive medication and bronchodilators are routinely administered before the procedure. Anticoagulant use is interrupted immediately before the procedure (depending on the drug used), and acetylsalicylic acid use is interrupted 5 days before. Valve implantation is easily performed in a well-equipped endoscopy suite (Fig. 27.8) under propofol-based sedation with spontaneous breathing. Topical anesthesia with one swallow lidocaine 5% gel in oral cavity is used, as well as intratracheobronchial instillation of lidocaine 1% during the initial phase of endoscopy. The procedure usually lasts 15–30 min without analysis of collateral ventilation with the Chartis® system and 45–60 min with Chartis® measurement of collateral ventilation (Fig. 27.9).

After the procedure, the patient is kept under observation with digital oxymetry for 2 h and has a chest X-ray performed right before returning to the room. Some degree of bronchospasm is observed in 20% of patients, usually mild, managed with usual medication. Corticosteroid prophylaxis is used only in patients with history of bronchospasm. Local patients are discharged from the hospital usually after 24–48 h, and patients living sufficiently far to prevent them from a fast return to the hospital, or those who need to travel by air are usually admitted for 5–7 days. Patients are guided to contact the team after discharge if any unusual event occurs. A procedure report is given to the patient, and the primary physician is contacted to discuss the patients and ensure a close supervision. To describe treatments, the following scheme is used:

Fig. 27.8 Endoscopy suite at Hospital Moinhos de Vento, Brazil

Side	Type	Lobe	Gradient	Valves	Segments	Fissures
		RUL				
		RLL				
	NLE	ML	15	3X4.0		
Un	LE	LUL	20	2X4.0+1X5.5	RB1,2,3...	IVS0.7
Bil	LE+	LLL	30	1X4.0+1X5.5	LB1+2,3....	Ch15

Where: side is unilateral or bilateral; type is nonlobar exclusion (NLE), lobar exclusion (LE) or lobar exclusion plus additional segment (LE+); lobe is right upper lobe (RUL), right lower lobe (RLL), middle lobe (ML), left upper lobe (LUL) or left lower lobe (LLL); gradient is the difference between lobes in heterogeneity scores expressed as percent points; valves show the number ofeach size valve used; segments refer to valve insertion place; and fissure refer to visual fissure integrity score in % of integrity. This is then an example of how cases are identified:

Un/LE/RUL/G25//V2X4.0+1X.5.5/RB1,RB2,RB3/VIS0.78 – corresponding to a

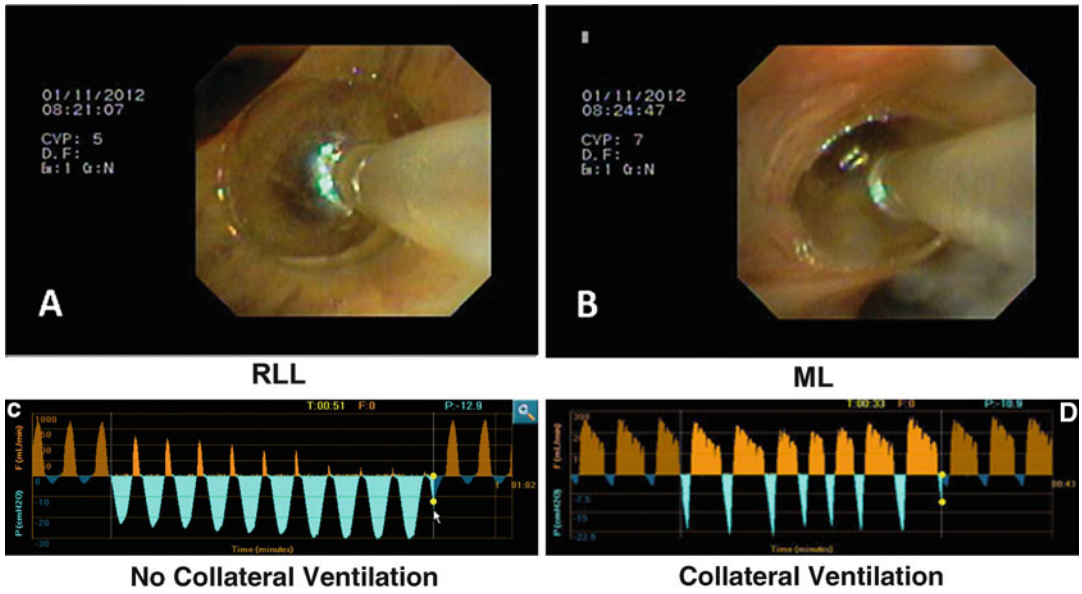

Fig. 27.9 Chartis® study. (**a, b**) Balloon insertion for blocking airflow to diseased lung. Resistance graphs showing absence of airflow (**c**) and presence of collateral ventilation (**d**)

unilateral treatment, with lobar exclusion of the right upper lobe, heterogeneity gradient of 25 pp, placement of two 4.0 valves and one 5.5 valve in RB1, RB2, and RB3, respectively, and a visual integrity score of 0.78 (partial integrity).

Our group has no restriction to lower lobe treatment, with ten cases treated using this strategy. Our preferred strategy, however, is unilateral lobar exclusion. Figures 27.10, 27.11, 27.12, 27.13, 27.14, and 27.15 show examples of cases treated in different areas of our selection continuum described in Fig. 27.3.

Follow-Up

The patient is contacted 1 week after the procedure, then monthly during the first 3 months. After 90 days, a follow-up evaluation is carried out including tomography (for VIDA® evaluation), pulmonary function tests, 6-min walk test, Saint George's Hospital Respiratory Questionnaire (SGRQ) for assessment of quality of life, and other tests at the discretion of the team. In the VENT trial, those treated with valves had more COPD exacerbation than the control group in the first 3 months following the procedure, which could be reflecting exacerbation of the underlying inflammatory process after the placement of a foreign body in the airway. Bronchoscopic revision is carried out at any time when a valve-related problem is suspected or else in the presence of intense mucus production. It should be noted that a CT (acquired with the correct parameters for VIDA® analysis) is sufficient to confirm the correct functioning of the valves. In patients without atelectasis, if mucus is clogging the valve, bronchoscopic cleaning and aspiration is carried out. This procedure does not endanger valve positioning. After this 3-month follow-up, a similar 6-month follow-up is carried out, and after that the patient is reviewed yearly.

Just like in patients receiving other types of tracheobronchial stents, we aim at maintaining physiological hydration levels and occasionally employ *N*-methylcysteine for fluidification. Continuation of physical therapy after the procedure is mandatory.

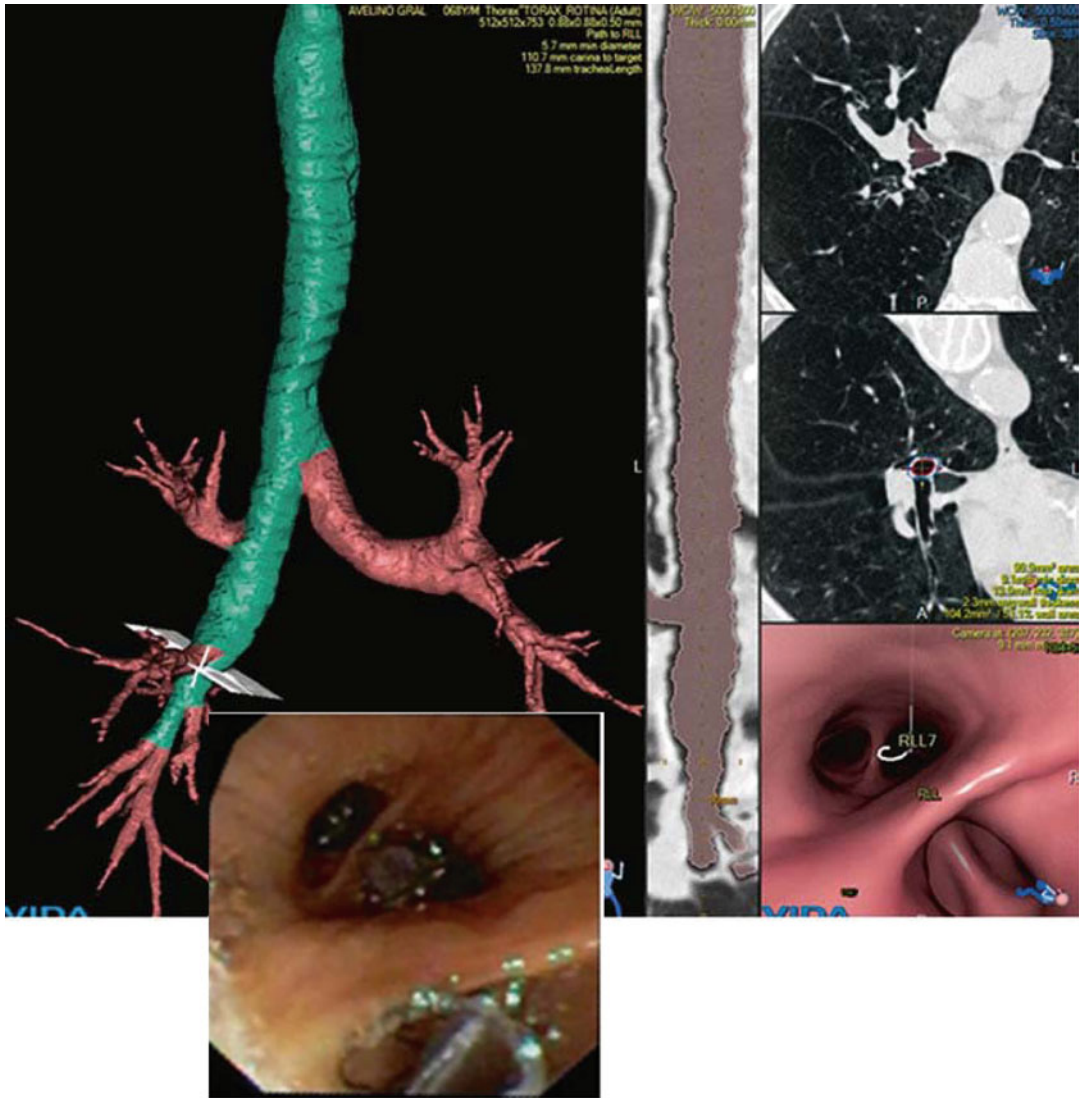

Fig. 27.10 CT image of implanted valve superimposed on Apollo image used for treatment planning. Patient with homogeneous emphysema (gradient 9.53 pp for RLL) and complete fissure on visual inspection. The patient had been submitted to LVRS 10 years earlier. After the absence of collateral ventilation was confirmed with the use of Chartis®, the *right lower* lobe was excluded with three valves placed in segments RB8 + 9 + 10, RB7, and RB6 (treatment scheme: Un/LE/RLL/G9.7/V1 × 5.5, 2 × 4,0/ RB8 + 9 + 10, RB7, RB6/CV-). This patient experienced lung volume reduction (184 ml) and improvement of functional parameters at the 30-day follow-up

Evidence-Based Review

Perhaps the major aspect about which there seems to be agreement in the literature is that valve treatment is safe and reversible. Also, there seems to be increasing evidence that endobronchial valve treatment is especially beneficial to improve functional capacity, which is not always reflected by the usual lung function parameters. Atelectasis is the ideal response to BLVR, such as the resection of diseased parenchyma is the aim of LVRS. In both cases the decrease in lung volume will improve respiratory mechanics. In our case series, 9 out of 22 patients submitted to

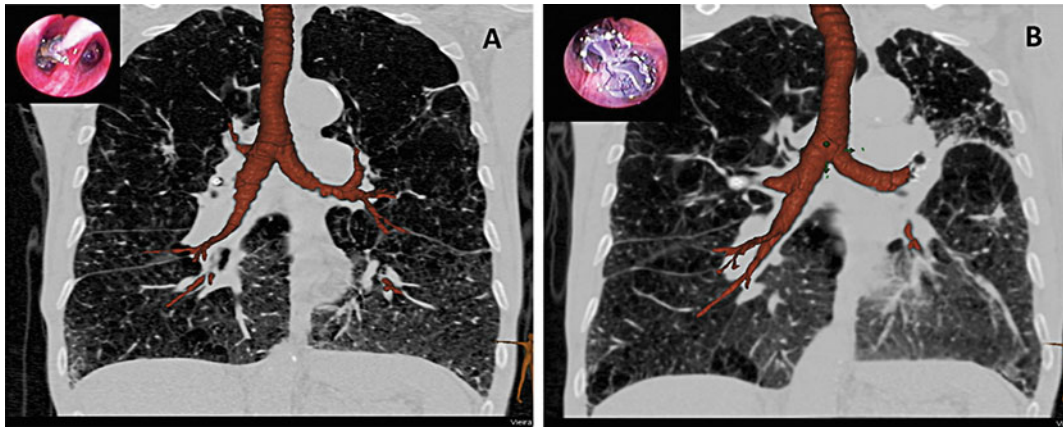

Fig. 27.11 Seventy-year-old male treated in (**a**) May 2003 and (**b**) January 2010. This is a case of high heterogeneity (>15 pp) with collateral ventilation, in which improvement was achieved despite the absence of atelectasis. After the second treatment with LUL exclusion (almost 7 years later), atelectasis was achieved

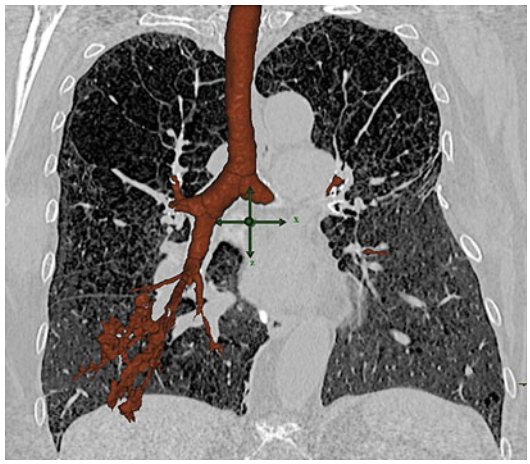

Fig. 27.12 Seventy-five-year-old female treated in December 2007 following 45 days of mechanical ventilation with unsuccessful weaning. The patient was treated again in March 2009. The patient was doing well at a follow-up bronchoscopy performed in January 2012

lobar exclusion and included in our analysis of fissure integrity experienced volume reduction. It is expected that these patients will have increased survival, as previously reported by the Royal Brompton group in London.

As previously stated, the principles underlying endobronchial valve treatment are those learned from LVRS. Because of that, the initial selection criteria were also those of LVRS. In 2009, the National Institute for Health and Clinical Excellence in England evaluated bronchoscopic lung volume reduction based on the results of six case series (total of 312 patients) deemed as scientifically relevant by that Institute. Our group contributed patients to one of these studies (multicenter study with 98 patients). Our core phase II article describing 19 patients with follow-up of up to 24 months was also cited. Our longest follow-up so far was 7 years (May 2003–June 2010), providing evidence of safety and possibly increased survival despite the natural decline associated with emphysema.

Up to that point, all groups working with endobronchial valves were using selection criteria described in the NETT, according to which the ideal patient had severe heterogeneous emphysema affecting predominantly the upper lobes. However, there was no uniformity regarding definitions such as emphysema severity and heterogeneity.

In 2010, the results of a randomized clinical trial sponsored by Emphasys was published. The Endobronchial Valve for Emphysema Palliation Trial (VENT) included patients enrolled and treated between December of 2004 and April 2006. The conclusions reported by the investigators were frustrating for those working with the method: "*Endobronchial-valve treatment for advanced heterogeneous emphysema induced modest improvements in lung function*, *exercise tolerance*, *and symptoms at the cost of more frequent exacerbations of COPD*, *pneumonia*, *and hemoptysis after implantation*" (p. 1233). The article caused much disappointment with the

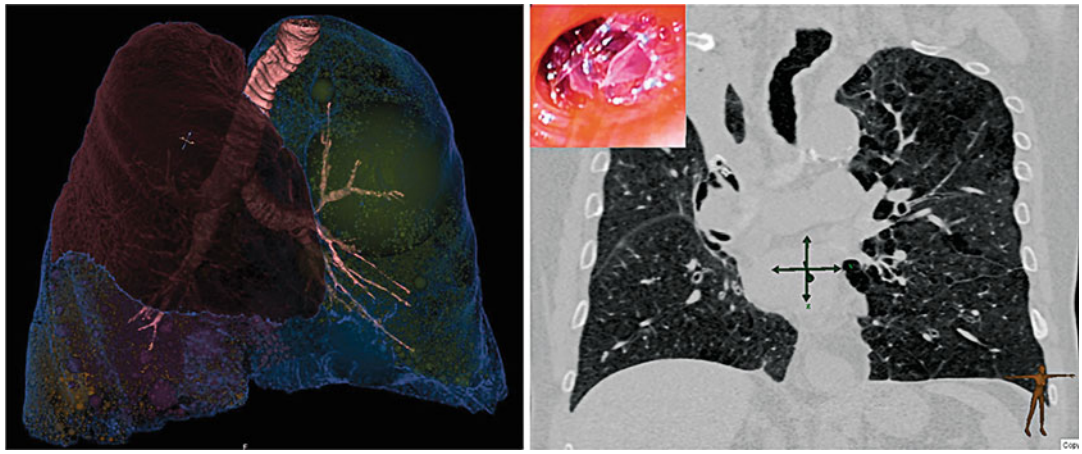

Fig. 27.13 Seventy-one-year-old male treated in October 2009. Oxygen was discontinued, and he resumed an almost normal life (see RUL complete atelectasis)

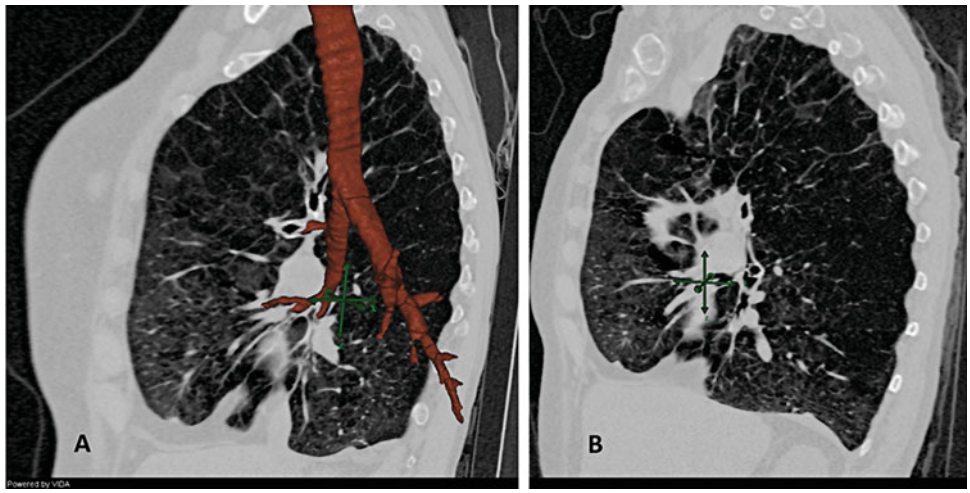

Fig. 27.14 Sixty-year-old female treated in (**a**) October 2004 and (**b**) August 2009. Improvement without volume reduction (no fissure can be seen)

method around the world despite the identification of a subgroup of good responders.

However, a close analysis of the VENT reveals a gross selection bias: half the patients included in the study had homogeneous emphysema despite the study's proposal to enroll patients with heterogeneous disease. The main flaw was the conversion of "objective quantitative analysis of high resolution CT scans" and "density histogram analysis, using a −910 Hounsfield unit thresholds to define indices of severity and heterogeneity" into Likert scores. The study assigned an emphysema score described in Table 27.2.

An example of how this system may result in the selection of patients with homogeneous emphysema, and exclusion of heterogeneous emphysema, is the following:

1. A patient with 74% of CT Hounsfield units below −910 in the left upper lobe (ES score = 3) and 52% of CT Hounsfield units below −910 in the left lower lobe (ES score = 3) has HS = 0 and is therefore not eligible for treatment despite a 22 pp difference between LUL and LLL.
2. A patient with 52% of CT Hounsfield units below −910 in the left upper lobe (ES

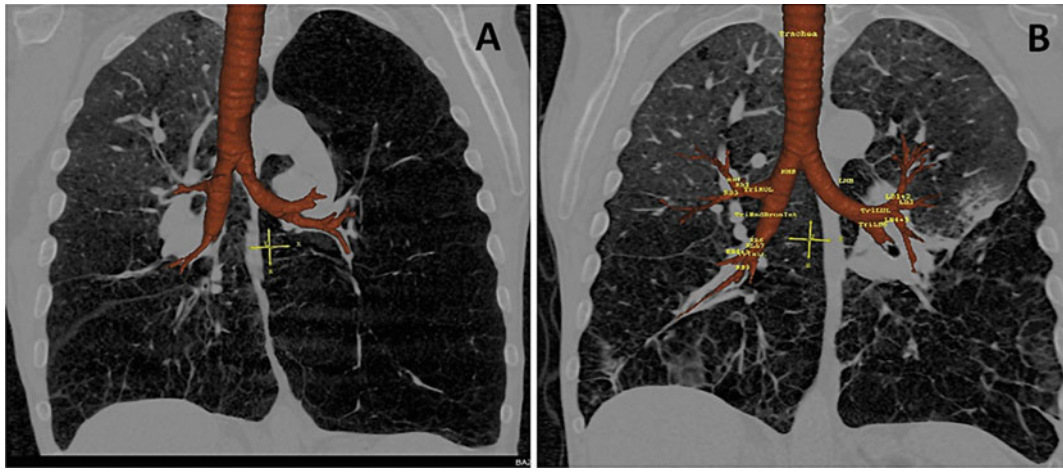

Fig. 27.15 Sixty-nine-year-old male treated in (**a**) June 2008 with LLL lobar exclusion using two valves at LB6 and LB8+9+10 and (**b**) 11-day follow-up. This patient was released from oxygen therapy after treatment and now leads a normal life. Note previous compression atelectasis of LUL

Table 27.2 Emphysema scores in the VENT trial

Emphysema score	Tissue with density <–910 HU (%)
1	1–25
2	26–50
3	51–75
4	>75

Heterogeneity score: *upper lobe* emphysema score—*lower lobe* emphysema score. Targeted lungs: *upper* or *lower lobe* ES >3 and HS score of at least 1

score = 3) and 50% of CT Hounsfield units below −910 in the left lower lobe (ES score = 2) has HS = 1 and is eligible (even with a difference of only 2 pp—homogeneous emphysema).

Retrospective analysis showed that the subgroup with heterogeneity >15pp had relatively greater improvements in FEV_1 and 6-min walk test at 6 months after EBV compared with control. Intact fissures translated into incremental improvements in FEV_1 of 16.2% at 6 months and 17.9% at 12 months as compared with incomplete fissures.

Summary and Recommendations

There are many aspects that still require better understanding for patient selection, prognostic evaluation, and treatment with endoscopic methods for the treatment of lung emphysema. Taking into consideration the doubts that remain concerning the pathophysiological mechanisms of improvement and the best selection criteria, it is essential to establish standardized protocols for the use of this technology and also to revise and update these protocols periodically. Meta-analyses of published results are also important and also a carefully designed randomized study taking into consideration the knowledge acquired by experience this far. Finally the use of mixed bronchoscopic techniques may soon become an alternative to treat emphysema patients. To date, patients with absent or little collateral ventilation are the best candidates for valve treatment. High heterogeneity is the best indicator of improvement. The best treatment strategy is lobar exclusion.

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28 Endoscopic Lung Volume Reduction for Treatment of Advanced Emphysema Using Injectable Hydrogels

Edward P. Ingenito

Introduction

Current recommendations for the treatment of patients with irreversible airflow obstruction involve the stepwise addition of bronchodilator and anti-inflammatory medications to improve airflow through narrowed and obstructed bronchioles [1]. While this approach effectively treats individuals with chronic obstructive pulmonary disease (COPD) caused by reactive airway disease and mucous hypersecretion, including those with chronic bronchitis and asthma, it is less effective in individuals whose disease is primarily due to pulmonary emphysema. In this latter group, the fundamental problem is tissue destruction caused by chronic inflammation associated with prolonged exposure to toxic inhalants. This results in the loss of elastic recoil, progressive hyperinflation, and airflow limitation that is minimally responsive to bronchodilator and anti-inflammatory medications [2].

Lung volume reduction therapy, reintroduced into clinical practice in the mid-1990s as a surgical procedure, directly addresses the problem of lung hyperinflation through elimination of damaged tissue [3–7]. While surgical volume reduction (i.e., lung volume reduction surgery, or LVRS) can be highly beneficial in selected patients with advanced emphysema, the procedure can also be associated with substantial risk [8, 9]. Results from the National Emphysema Treatment Trial (NETT), a large multicenter randomized controlled trial comparing optimized medical treatment alone to medical treatment combined with LVRS, showed that while LVRS patients with upper lobe predominant emphysema and low baseline exercise capacity did well, LVRS was associated with a 90-day mortality of approximately 5% and an incidence of significant cardiac and pulmonary morbidity of approximately 50% [9]. For these reasons, LVRS has been largely abandoned as a treatment for patients with advanced medically refractory emphysema and has not had a substantial impact on the management of this disease [10].

While the NETT results demonstrated the potential risks of LVRS in this patient population, they also highlighted the potential benefits of lung volume reduction therapy (LVRT), confirming the underlying premise that it is a physiologically sound concept [2, 11]. Endoscopic approaches to LVRT have subsequently been developed with the goal of achieving the same responses without the risks of major thoracic surgery [12, 13]. One endoscopic approach that has shown promise in initial trials involves the use of specially designed hydrogels to collapse damaged areas of lung and reduce hyperinflation. These hydrogels are administered endoscopically in liquid form to the lung periphery where they polymerize and trigger a therapeutic response.

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Two hydrogel systems for achieving lung volume reduction have been advanced into clinical trials during the past decade, and both have shown promise in clinical testing. One product, the AeriSeal System, has received CE Mark registration and is being further evaluated in a large randomized international clinical trial involving selected centers in the USA, Europe, and Israel [14]. If the safety and efficacy of this system are confirmed, hydrogel therapy could have a substantial impact on the treatment of patients with advanced emphysema in the near future and serve as a bridge to, or in some instances, a replacement for orthotopic lung transplantation.

Hydrogels for Treatment of Advanced Emphysema

Hydrogels are water-based semisolids comprised of networks of cross-linked hydrophilic molecules that maintain their state of hydration by trapping water through hydrogen bonding. They have been used in medicine for a variety of applications, most notably as vehicles to achieve timed release of water-soluble drugs [15–17]. Hydrogels have also been developed for delivering cells for orthopedic, dental, cosmetic, and wound surgery applications [18–20].

The two hydrogel systems developed and tested for treatment of patients with advanced emphysema are both designed to achieve lung volume reduction therapy by exerting their effects in the periphery of the lung. The first system, biologic lung volume reduction (BioLVR), completed preclinical testing in 2003 and was introduced into clinical trials in 2004. This treatment was classified as a biologic and regulated in the USA by the Center for Biologics Evaluation and Research (CBER). BioLVR completed phase 2 clinical trials in the USA, but development was halted in 2008 prior to beginning phase 3 testing. BioLVR, which was based on a fibrin hydrogel system, was replaced by a second-generation synthetic polymer-based hydrogel system. This system functions as a tissue sealant and therefore, like other tissue sealants, is regulated as a device. Initially designated polymeric lung volume reduction (PLVR) therapy, it is now recognized commercially as the AeriSeal® System and is marketed by Aeris Therapeutics, a biotechnology company based in Woburn, MA, USA.

Hydrogel systems have unique and desirable features for use in designing an endoscopic lung volume reduction treatment. A range of biocompatible hydrogels exist that can be delivered as liquids at physiological temperature and pH and be designed to polymerize once they have reached the periphery of the lung. This allows the delivery of therapeutically active materials to the small airways and alveoli, an important characteristic for achieving consistent, effective lung volume reduction therapy. Because they are comprised largely of water, hydrogels tend to be soft and therefore do not cause mechanical damage to the fragile tissues of the lung. This contributes to a favorable safety profile. They can be also used to deliver a wide range of water-soluble materials to lung periphery, and their pore size and chemical characteristics can be prospectively designed to modulate pharmacokinetics.

Although both the BioLVR and AeriSeal System are hydrogel-based systems, they achieve lung volume reduction through distinct mechanisms. The fibrin hydrogel components of BioLVR were used as a carrier to deliver a pharmacologically active polyanion–polycation complex to the periphery of the lung. This ionic complex caused localized injury and scarring that collapsed damaged lung tissue during the process of scar contraction [21]. The polymer-based hydrogel incorporated into the AeriSeal System functions as a tissue sealant. AeriSeal System treatment is delivered as a liquid foam that blocks the small airways and coats the surface of the target area, leading to absorption atelectasis and permanent collapse [14]. Both systems promote lung volume reduction through effects at both the airway and alveolar levels.

Clinical results using BioLVR and AeriSeal System therapy indicate that both approaches can be effective in treating a broad range of patients with advanced emphysema. The efficacy of these hydrogel-based therapies presumably derives from their unique abilities to (1) treat hyperinflation and reduce gas trapping, (2) block

small airways in diseased target areas shunting gas towards more functional lung tissue, and (3) block collateral ventilation pathways that would otherwise allow gas to enter the treated areas from adjacent untreated lung zones and prevent lung volume reduction from occurring.

Biological Lung Volume Reduction Hydrogel Therapy for Emphysema

BioLVR was initially conceived as a way to achieve endoscopic lung volume reduction using a fibrin glue. Current fibrin glues are designed for topical application and are quite viscous, but more dilute fibrinogen solutions can be developed for delivery through a small bore catheter for use with a standard flexible bronchoscope. Pilot testing in isolated calf lungs confirmed that simultaneous administration of dilute fibrinogen and thrombin solutions in the appropriate ratios through a dual lumen catheter resulted in formation of a hydrogel in the distal lung that could obstruct airflow and produce volume reduction. Testing in healthy, experimentally naïve sheep demonstrated that in vivo, simple fibrin hydrogels produced only transient collapse and were rapidly cleared due to the high plasmin activity that exists on the lung epithelial surface [22].

A modified fibrin hydrogel containing human fibrinogen and thrombin with plasmin inhibitors was tested in sheep ($n=4$) with experimental emphysema, and responses were compared to sham (saline-treated) control animals ($n=4$) and those undergoing surgical lung volume reduction ($n=4$) [23]. Lung mechanics and computed tomography (CT) imaging were performed at baseline following development of experimental emphysema and again 3 months following treatment. In these animal studies, BioLVR and surgical resection were associated with nearly equivalent reductions in total lung capacity (TLC) and residual volume (RV), while sham therapy had minimal effect on lung volumes. At necropsy, 3 sites treated with this BioLVR hydrogel formulation showed abscess formation, and only 11 sites demonstrated sustained collapse.

To improve its safety and efficacy profile, modifications to the initial BioLVR hydrogel system were made. Tetracycline was added as an antimicrobial, and polylysine complexed to chondroitin sulfate was added to block hydrogel degradation, improve durability, and promote regional sclerosis and scarring. Six sheep with experimental emphysema were treated with 10 ml doses of modified BioLVR solution at six subsegments each. Responses were assessed at 1 and 3 months posttreatment by comparing lung mechanics, diffusing capacity (DLco), and CT imaging posttreatment to measurements performed at baseline. BioLVR treatment was associated with reductions in lung volumes and gas trapping and improvements in DLco at 1 and 3 months. Necropsy results showed evidence of collapse at 33 of 36 treatment sites with no abscess formation [21].

The BioLVR treatment system developed for clinical testing is shown in Fig. 28.1. The chemical components of the fibrinogen solution, including polylysine, tetracycline, and chondroitin sulfate, form a precipitate that is resuspended by passing the materials through a stopcock between two 20 ml syringes (Fig. 28.1a). The 20 ml syringe containing the final fibrinogen suspension is clipped into a molded administration device along with a 5 ml syringe containing 2.5 ml of thrombin solution (Fig. 28.1b). The fibrinogen and thrombin solutions are then delivered simultaneously through a dual lumen catheter (Fig. 28.1c) that is positioned in the distal airway through the instrument channel of a bronchoscope. The system components mix at the distal tip of the catheter and polymerize to form the BioLVR hydrogel (Fig. 28.1d).

The safety and potential efficacy of the BioLVR hydrogel system was subsequently approved for testing in patients in a first-in-man phase 1 dose escalation study at two medical centers in Boston, MA, USA. Six (6) patients with upper lobe predominant emphysema and GOLD stages III and IV airflow obstruction without significant comorbidities were treated under general anesthesia. Three (3) patients received treatment at two subsegments in one lobe, and three received treatment at four subsegments in one lobe. Spirometry, plethysmographic

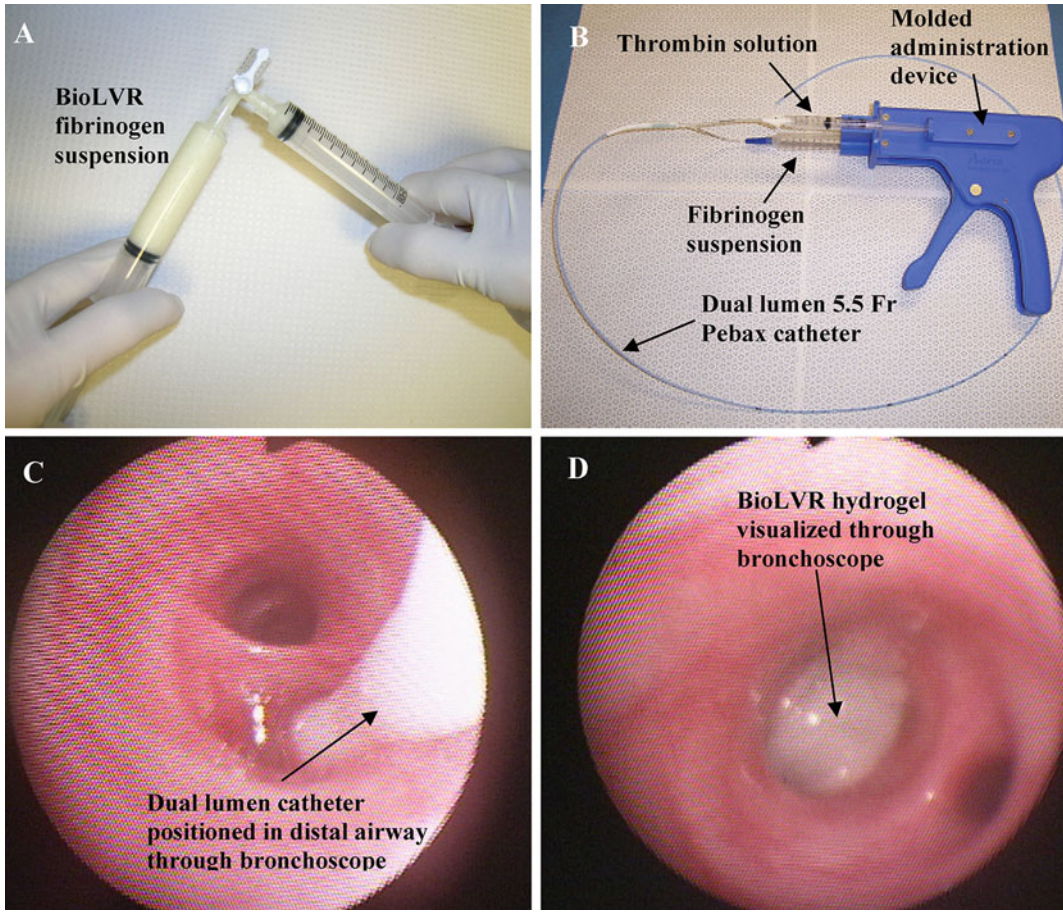

Fig. 28.1 (**a**) The precipitate formed by the chemical components of the fibrinogen hydrogel BioLVR reagent is resuspended by passing through a stopcock between 2 syringes. (**b**) The syringes containing the fibrinogen suspension and thrombin solution are shown attached to the dual lumen catheter and clipped into the molded administration device. (**c**) The BioLVR hydrogel components are administered through the dual lumen catheter positioned within the distal airway. (**d**) The polymerized BioLVR hydrogel is visualized through the bronchoscope posttreatment

lung volumes, Medical Research Council dyspnea (MRCD) scores, and 6 min walk test (6MWT) distance were assessed at baseline and 12 weeks posttreatment [24]. Safety was favorable with only minor side effects. Improvements in spirometry, gas trapping, dyspnea, and exercise capacity were observed at 3-month follow-up with greater improvements in the four-site treatment group, indicating of a dose–response relationship to therapy. Four-site unilateral treatment was associated with improvements in forced vital capacity (FVC; +10.3 ± 7.8%), RV/TLC (−9.3 ± 4.9%), 6MWT distance (+21.7 ± 25.0%), and MRCD score (−1.33 ± 1.15 U).

Phase 2 testing of BioLVR hydrogel therapy was conducted in 4 small international trials, two involving patients with upper lobe predominant disease and two involving patients with homogenous emphysema. Results are summarized in two recent publications. The first describes results in patients with upper lobe predominant emphysema who received either low-dose treatment (consisting of 10 ml BioLVR hydrogel doses at eight subsegments, 4 per side) or high-dose treatment (consisting of 20 ml BioLVR hydrogel doses at eight subsegments, 4 per side) [25]. The study included ten centers in the USA and Israel. All patients had severe airflow obstruction and

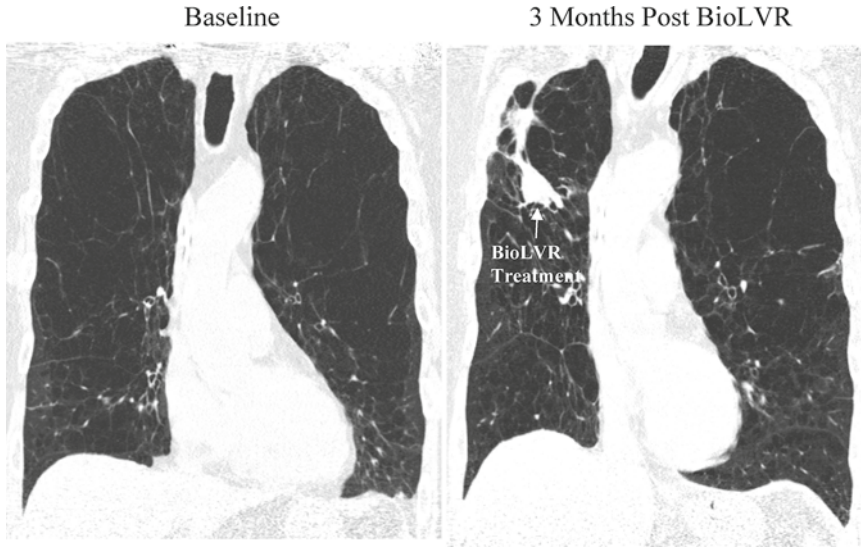

Fig. 28.2 Coronal CT images at baseline and 3 months following bilateral *upper lobe* BioLVR hydrogel treatment. Images show a marked reduction in lung volume in the *right upper lobe* associated with scarring and contraction at the treatment site and normalization of the diaphragm position in the *right* lung

were either ineligible for or had refused surgical lung volume reduction. Eligible candidates were required to have nonbullous emphysema and no significant comorbidities. Procedures were performed either under general anesthesia or moderate sedation (a.k.a. conscious sedation), and patients were followed out to 6 months. Safety was assessed in terms of the incidence of adverse events posttreatment. Efficacy was assessed in terms of reduction in gas trapping (RV/TLC ratio) and improvements in spirometry, diffusing capacity, exercise capacity, symptoms, and health-related quality of life compared to baseline at 3 and 6 months.

Bilateral BioLVR therapy was associated with a satisfactory safety profile and evidence of efficacy. Improvements in spirometry, lung volumes, dyspnea, and health-related quality of life were observed at 3 and 6 months in both low- and high-dose treatment groups. Physiological responses were uniformly better in the high-dose group at 6-month follow-up (high-dose responses: ΔFEV_1 (forced expiratory volume in 1 s)=+15.6±16.8%, p=0.002; ΔFVC=+9.1±15.5%, p=0.034; DRV=−9.0±11.2%, p=0.006; ΔTDI=+3.2±4.0 U, p=0.004; ΔSGRQ (St. George's Respiratory Questionnaire)=−9.7±18.8 U, p=0.057). Volume reduction was associated with radiographic evidence of tissue contraction and remodeling visualized by CT imaging out to 6 months (Fig. 28.2).

Responses in patients with advanced homogeneous emphysema were reported in the second study [26]. Eight (8) patients received low-dose therapy (10 ml doses at eight subsegments, four in each upper lobe) and 17 received high-dose therapy (20 ml doses) in similar fashion. The study design and participating centers were the same as those for the upper lobe study summarized above.

The safety profile of BioLVR in patients with advanced homogeneous emphysema was also favorable. At 6-month follow-up, low-dose therapy was not associated with physiological or functional benefit, but high-dose therapy was associated with improvements in spirometry (ΔFEV_1=13.8±20.3%, p=0.007), dyspnea (ΔMRCD=−0.8±0.73 U, p=0.001), and health-related quality of life (ΔSGRQ=−12.2±12.4 U, p=0.0001).

BioLVR hydrogel therapy for advanced emphysema demonstrated potential safety and efficacy in clinical studies but was not advanced into phase 3 testing because of the emergence of a superior second-generation synthetic hydrogel system, the polymeric lung volume reduction system, which is now known as the AeriSeal System.

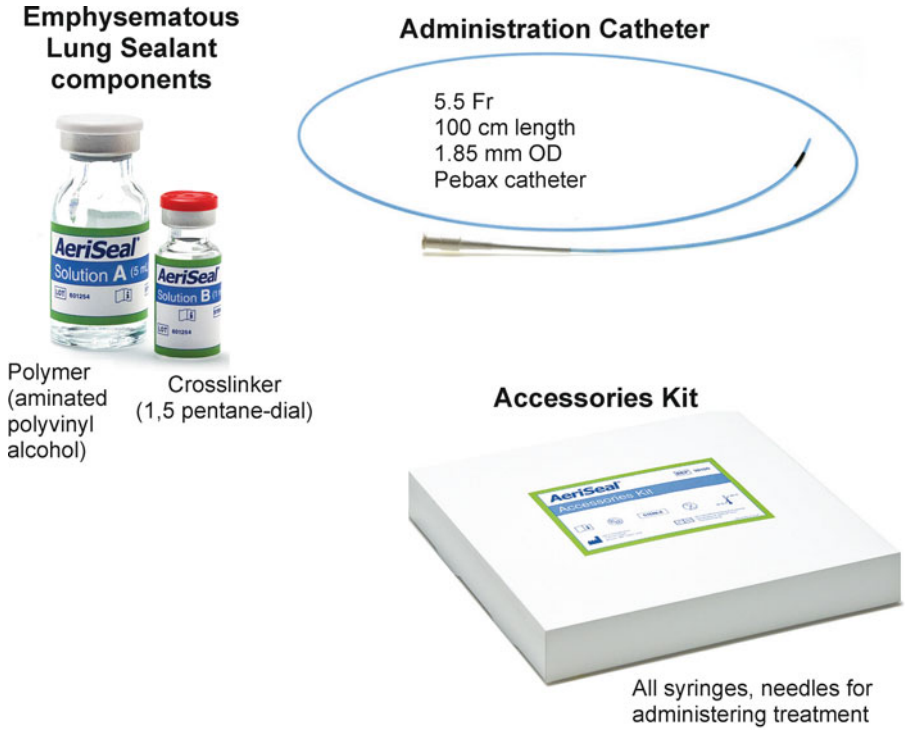

Fig. 28.3 The AeriSeal System hydrogel components are shown. The polymer consists of a dilute solution of aminated polyvinyl alcohol. The hydrogel is formed by mixing this polymer with a dilute solution of 1,5-pentanedial. When combined, the two components polymerize over 2–3 min. The polymer components are mixed with air to generate a liquid foam that is delivered to the lung using the administration catheter positioned in the distal airway through the instrument channel of the bronchoscope

The AeriSeal System: Polymeric Hydrogel Therapy for Advanced Emphysema

The hydrogel component of the BioLVR system was used to deliver an active pharmaceutical ingredient to the periphery of the lung. The hydrogel component of the AeriSeal System is the active component of the system, a lung-specific tissue sealant. Like other tissue sealants which act on the mucosal surface, the AeriSeal System is regulated as a device, not a pharmaceutical. Physiological benefit results from the sealing of the target area and the ensuing atelectasis that develops as the gas within the treated area is absorbed.

The hydrogel system used in the AeriSeal System, depicted in Fig. 28.3, has several advantages over the BioLVR hydrogel system. Because it is synthetic and does not utilize human blood products, there is no risk of transmissible infection. Furthermore, in preclinical testing, the AeriSeal System was more effective than BioLVR in producing consistent volume reduction. Preclinical responses following AeriSeal System treatment were larger in magnitude and more durable than those associated with BioLVR.

The polymeric component of the AeriSeal System is aminated polyvinyl alcohol (aPVA), an amphiphilic molecule that generates a stable foam when mixed vigorously with gas. AeriSeal Foam Sealant is formulated by mixing 4.5 ml of aqueous polymer solution in a 10:1 ratio with 1.25% 1,5-pentanedial, a nonspecific homobifunctional cross-linker, to generate a soft flexible foam that polymerizes over 2–3 min. This allows sufficient time for the mixture to be injected through a single lumen catheter positioned using a flexible bronchoscope in the distal lung.

Initial preclinical testing in large animals indicated that 5 ml of polymer + cross-linker could be mixed with 15 ml of air to generate 20 ml of liquid foam, a volume sufficient to seal a lung subsegment. Dosing was escalated by increasing the number of sites treated, not by increasing the dose per site.

First-in-man testing was initiated in December 2008 in a study involving six leading interventional centers across Germany [27]. Twenty-five (25) patients with upper lobe predominant emphysema and GOLD stage III/IV airflow obstruction were treated unilaterally in a dose escalation study at 2, 3, or 4 subsegments. Patients were followed for 6 months posttreatment. Safety was assessed in terms of the incidence of adverse events during follow-up. Efficacy was assessed in terms of improvement from baseline in physiological, functional, and quality-of-life outcomes.

Safety was satisfactory given the severity of disease in the treatment cohort. However, treatment was associated with an acute inflammatory reaction more pronounced at higher treatment doses. Signs and symptoms included fever, shortness of breath, cough, and chest discomfort lasting from 24 to 72 h. Within the first 120 days, there was a 30% incidence of COPD exacerbations.

Unilateral AeriSeal System treatment was associated with benefits out to 6 months. Significant improvements in spirometry ($\Delta FEV_1 = 10.0 \pm 19.8\%$, $p = 0.028$; $\Delta FVC = 15.8 \pm 22.2\%$, $p = 0.004$), gas trapping ($\Delta RV/TLC = -4.7 \pm 9.5\%$, $p = 0.039$), and health-related quality of life ($\Delta SGRQ = -7.5 \pm 14.4$ U, $p = 0.049$) were observed across the entire cohort with the larger improvements in patients with baseline GOLD stage III airflow obstruction than GOLD IV obstruction.

A second study of the AeriSeal System was then conducted to assess (1) the utility of medical prophylaxis for reducing posttreatment inflammation, (2) the safety and efficacy of treatment in patients with heterogeneous lower lobe disease and homogeneous disease, and (3) the safety and efficacy of bilateral therapy performed in two separate sessions. Six (6) European and two Israeli centers participated in this study [14]. Fifty-six (56) patients were enrolled, 30 with homogeneous disease, 19 with upper lobe predominant heterogeneous disease, and seven with lower lobe predominant heterogeneous disease. Patients were classified as having heterogeneous or homogeneous emphysema based on CT imaging. Target sites in heterogeneous emphysema patients were selected by visual assessment of CT images. Target sites in homogeneous patients were selected based on perfusion scanning. All patients received initial unilateral treatment at two subsegments in one lobe and were eligible for a second treatment at 2 or 3 additional subsegments after 12-week follow-up. Thirty-nine (39) patients received a second treatment in this study.

Safety was assessed in terms of the incidence of serious adverse events. Efficacy was assessed in terms of physiological, functional, and quality-of-life outcomes out to 3 months post-completion of therapy.

Prophylaxis with 7 days of tapering steroids and antibiotics substantially reduced the incidence and severity of posttreatment inflammation and lowered the COPD exacerbation rate requiring hospitalization within 90 days of treatment. Efficacy was observed in patients with homogeneous and upper lobe predominant hete- rogeneous emphysema. Several subgroups that demonstrated particularly favorable responses were identified retrospectively. Patients with baseline DLco values between 20% and 60% predicted did better than those with baseline values outside this range. Patients who received bilateral treatment experienced greater improvement than those who received unilateral treatment. In addition, patients with homogeneous disease who received treatment in the upper lung fields experienced greater improvements than those treated in the lower lung fields.

A third study was performed to prospectively confirm these findings, evaluate the safety and efficacy of bilateral treatment AeriSeal System hydrogel therapy performed during a single treatment session, and characterize long-term durability of responses following AeriSeal System hydrogel therapy out to 1 year. This study was conducted at two centers in Israel and enrolled 20 patients, ten with homogenous emphysema and ten with heterogeneous emphysema as determined by visual CT assessment.

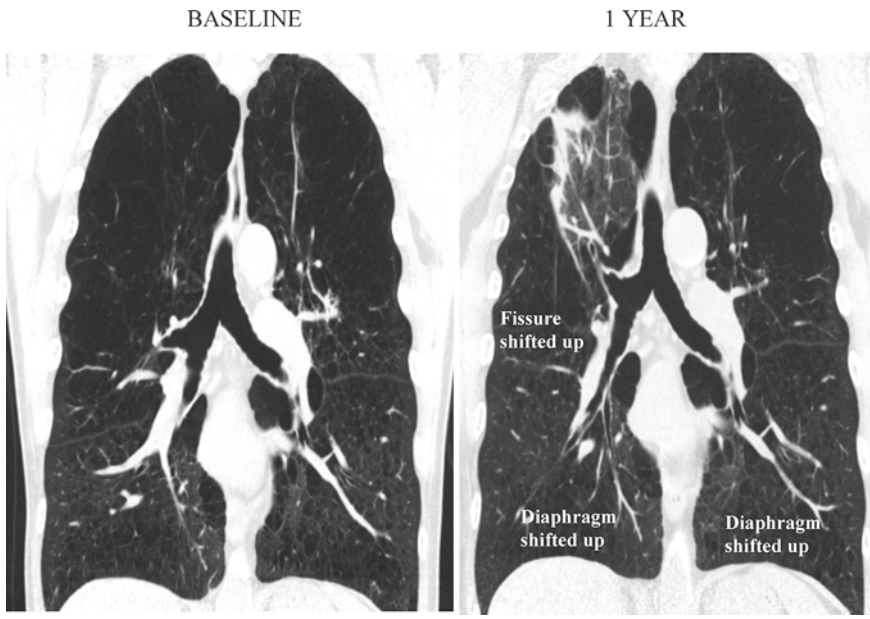

Fig. 28.4 Coronal CT images at baseline and 12 months following bilateral upper lobe AeriSeal System hydrogel treatment. Images show a reduction in lung volume in both upper lobes associated with scarring and contraction at the treatment sites, and normalization of the diaphragm position in both lungs

All patients had GOLD stage III/IV airflow obstruction and were on optimal medical therapy. Procedures were performed using moderate sedation anesthesia. Procedures took on average 15 min to complete, and 13 of 20 patients were discharged within 1 day of treatment.

The safety profile remained favorable. Procedures were generally well tolerated, and the incidence of COPD exacerbations requiring hospitalization during the first-year posttreatment was below that of historical controls [28]. Efficacy responses at 6 and 12 months posttreatment were quite favorable. Improvements from baseline in FEV_1 (25.0 ± 33.4%; $p = 0.013$), FVC (13.7 ± 16.4%, $p = 0.003$), RV (−15.9 ± 18.8%, $p = 0.004$), DLco (11.2 ± 21.2%, $p = 0.045$), MRCD score (−1.0 ± 0.87 U, $p = 0.003$), and SGRQ (−7.0 ± 15.8 U; 0.077) were comparable to those observed with surgical lung volume reduction at 1-year follow-up [29]. Treatment was associated with radiographic evidence of collapse and normalization of diaphragm position out to 1 year, as illustrated in the case example shown in Fig. 28.4.

Results obtained using AeriSeal System hydrogel therapy in these pilot studies are quite promising but must be interpreted with caution. Bilateral single-session treatment has been evaluated in only a limited number of patients in open-labeled studies. Confirmation in a large randomized trial is needed to further characterize effectiveness and long-term safety.

Conclusions

Hydrogels are versatile biocompatible systems that have found their way into a variety of therapeutic medical applications. They have unique properties that make them particularly useful for pulmonary applications. The success of BioLVR and AeriSeal System hydrogels for treating patients with advanced emphysema demonstrates the potential utility of this class of agent for use in lung volume reduction therapy for treatment of patients with advanced emphysema.

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Bronchial Thermoplasty

29

Adrian Shifren, Praveen Chenna, Alexander Chen, and Mario Castro

Introduction

Asthma is a chronic pulmonary disease characterized by recurrent episodes of bronchial hyperresponsiveness and airflow obstruction. During these episodes, patients experience coughing, wheezing, chest tightness, and dyspnea. The symptoms are typically reversible, either spontaneously or with treatment. These symptoms are the result of a number of pathophysiologic processes including airway remodeling characterized by airway epithelial injury, subepithelial fibrosis, excess mucus secretion, airway inflam-mation, and increased airway smooth muscle mass [1–3]. In a subgroup of patients with severe asthma, increased airway smooth muscle is thought to contribute considerably to persistent airflow obstruction that is difficult to manage, even with maximal medical therapy [4]. Bronchial thermoplasty was developed to reduce airway smooth muscle mass in the treatment of severe persistent asthma.

The Impact of Severe Asthma

Asthma is a major global health concern. Estimates suggest that almost 300 million people worldwide have asthma. In developed countries, the prevalence of asthma can exceed 15% [5]. While asthma is less prevalent in developing countries, the prevalence is increasing at an alarming rate [6]. Over 25 million people in the United States have asthma [7]. Poorly controlled asthma imposes a significant disease burden resulting in decreased quality of life, increased healthcare utilization, and significant economic burden [8]. There are almost 13.6 million unscheduled physician office visits, 1.8 million emergency room visits, 500,000 hospitalizations, and 4,000 deaths attributable to asthma in the United States each year [9]. The estimated annual cost of asthma in the United States is approximately $19.7 billion, including $5 billion in indirect costs like lost work days, and $14.7 billion in direct costs such as medications and healthcare utilization [10].

Asthma is currently managed with the use of long-term controller medications, to achieve and maintain control of persistent asthma, and quick-relief medications to treat acute symptoms and exacerbations. Long-term controller medications include inhaled corticosteroids (ICS), long-acting β_2-agonists (LABA), and, in a subset of patients, chronic oral corticosteroids. Approximately 15–20% of asthmatic patients have severe persistent asthma, defined by the presence of persistent asthma symptoms despite treatment with the best available medications [4]. The most severe asthmatic patients have refractory asthma. These patients constitute approximately 5–10% of all asthmatic patients and are defined by a requirement for treatment

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with high-dose inhaled corticosteroids, or the need for continuous or near continuous (>50% of year) oral corticosteroids [11]. Patients with severe persistent asthma present the greatest burden to the healthcare system [12], with refractory asthmatics having the most concentrated healthcare utilization including intensive care unit stays [4].

Limitations of Current Therapeutic Interventions

Although the current treatment of severe asthma has improved the level of asthma control, refractory asthmatics do not achieve disease control and have recurrent exacerbations requiring systemic corticosteroids [4]. Chronic oral corticosteroid use is associated with undesirable side effects ranging from mild annoyances to serious, irreversible organ damage. These side effects occur more frequently with higher doses and more prolonged treatment and include immunosuppression, adrenal suppression, growth retardation, osteoporosis, skin thinning, hypertension, cataracts, glaucoma, muscle weakness, and increased risk of infection. Short-term side effects include stomach upset, headache, dizziness, anxiety, agitation, trouble sleeping, fluid retention, weight gain, high blood pressure, hypokalemia, elevated cholesterol, and vision changes. There is, therefore, a critical need for additional therapeutic options for patients with corticosteroid-dependent asthma. Over the past decade, bronchial thermoplasty (BT) has been developed as a novel device-based approach for the treatment of severe persistent and refractory asthma.

The Rationale for Bronchial Thermoplasty

In normal airways, airway smooth muscle offers support, enables mucus clearance, enhances cough, and promotes lymphatic flow [13]. Chronic asthma is associated with a pathologic increase in airway smooth muscle mass [2, 14]. This excess airway smooth muscle constricts in response to asthma triggers resulting in airway hyperresponsiveness, bronchospasm, and severely reduced airflow, leading to difficulty breathing during asthma attacks. Early investigations into mechanisms of airflow obstruction and airway resistance demonstrated that 75% of postnasal resistance occurs in the first 6–8 generations of airways, indicating that larger airways are critically important [15]. Therefore, physical reduction of the increased airway smooth muscle mass of asthmatic patients, even in larger airways, could have significant conceivable benefits [16]. By reducing the amount of airway muscle present, the potential for bronchoconstriction may be reduced. The benefits of such an intervention might include less severe bronchoconstriction during exacerbations with fewer symptoms of airflow obstruction and less variability of disease [17]. Bronchial thermoplasty (BT) provides a new approach for treating severe persistent and refractory asthma through a reduction in this excess airway smooth muscle mass, with the goal of providing long-term relief of asthma symptoms.

Indications and Contraindications for Bronchial Thermoplasty

BT is currently only indicated for the treatment of severe persistent asthma in patients over the age of 18 whose symptoms are not well controlled with inhaled corticosteroids (ICS) and long-acting beta-2-agonists (LABA) [Alair package insert, Asthmatx, Inc, Sunnyvale, CA]. Patients are deemed appropriate based on inclusion and exclusion criteria from previous and current clinical trials of bronchial thermoplasty and accepted treatment guidelines for asthma [17, 18]. Table 29.1 outlines important patient selection criteria.

The Bronchial Thermoplasty Apparatus

Bronchial thermoplasty is performed using the Alair Bronchial Thermoplasty System® (Asthmatx, Inc, Sunnyvale, CA). The system is

Table 29.1 Inclusion and exclusion criteria for bronchial thermoplasty[a]

Inclusion criteria	• Age 18–65 years • Severe persistent asthma (symptoms present throughout the day, frequent nighttime awakenings, short-acting beta-agonist use for symptom control several times per day, extreme limitation of normal activity) • Currently using a regularly scheduled LABA **and** ICS • Pre-bronchodilator $FEV_1 \geq 60\%$ predicted at baseline **or** post-bronchodilator $FEV_1 > 65\%$ • Positive methacholine inhalation test • Nonsmoker for at least 1 year **or** <10 pack year smoking history if a current smoker
Exclusion criteria	• History of life-threatening asthma, defined by past intubations for asthma exacerbations • ICU admission for asthma, without intubation, within the last 24 months • ≥3 hospitalizations for asthma exacerbations in the last 12 months • >3 lower respiratory tract infections requiring antibiotics in the last 12 months • >3 pulses of oral steroids in the last 3 months • Known sensitivity to medications required to perform bronchoscopy • Patients with a pacemaker, internal defibrillator, or other implantable electronic device

[a]2007 National Heart, Lung, and Blood Institute/National Asthma Education and Prevention Program Guidelines (NHLBI/NAEPP) [19]; AIR2 Trial eligibility guidelines [20]

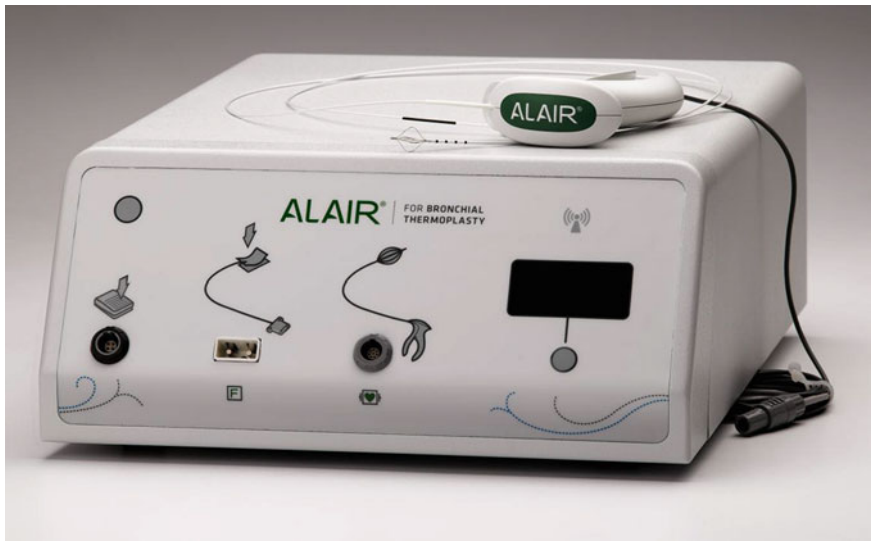

Fig. 29.1 The Alair radiofrequency controller with inputs for the footswitch (*left*), return electrode (*center*), and Alair Catheter (*right*). The Alair Catheter can be seen resting on the controller

composed of two principle components (Figs. 29.1 and 29.2):

1. The Alair Controller System, which includes a radiofrequency (RF) controller, a footswitch, and a patient return electrode
2. The Alair Catheter, which includes an expandable 4-arm array and an actuator

The Alair Catheter is a sterile, single-use device that is introduced into the airways through the working channel of an RF-compatible bronchoscope. The bronchoscope should ideally have an outer diameter of 4.9–5.2 mm and a working channel ≥2.0 mm [17]. The catheter has a distal 4-arm electrode array that expands to contact the airway wall when the proximal actuator is activated. The catheter is connected to the RF controller by a cable attached to its proximal end. The controller also has inputs for the footswitch and the patient return electrode. The footswitch allows the bronchoscopist to initiate delivery of RF energy. The return electrode completes the circuit, providing a pathway for the return of electrical current.

Fig. 29.2 The Alair Catheter inserted through the working channel of the bronchoscope with the 4-arm array fully expanded

This gel electrode is typically placed on the patient's chest or thigh. The RF controller delivers RF energy to the expanded 4-arm array in contact with the airway wall for a duration of 10 s. The RF controller utilizes sensory data from the catheter to limit current, power, voltage, time, and temperature of the RF energy delivered. This allows for the proper intensity and duration of RF energy to be applied while minimizing collateral airway damage. If the bronchoscopist determines that early termination of RF energy is needed, the footswitch can be pressed and released a second time to cease energy delivery [21]. The RF controller also safeguards against incorrect device setup. If any of the individual components are incorrectly connected or the catheter electrodes fail to contact the airway wall, the device will not deliver RF energy.

Overview of the Bronchial Thermoplasty Technique

BT is performed under conscious sedation to a moderate level. Visible airways distal to the main stem bronchi are treated by activation of the RF probe against nonoverlapping adjacent airway segments. Airways between 3 and 10 mm in diameter are systematically targeted, starting distally and moving proximally, being careful to avoid overlap with areas already treated [16, 21, 22]. Three sequential procedures are performed with a minimum interval of 3 weeks between each procedure. This allows for adequate healing of the airways between treatments and minimizes the likelihood of an asthma exacerbation [17]. Each treatment addresses a separate lobe, with the exception of the right middle lobe (RML). The RML remains untreated due to its narrow opening and the theoretical concern that inflammation related to the procedure may result in the development of right middle lobe syndrome [23]. The right lower lobe is treated first, followed by the left lower lobe. Finally, both the right and left upper lobes are addressed in a single treatment. Each treatment takes approximately 45 min to 1 h to perform [16].

Pre-procedure Preparation

In order to facilitate successful bronchial thermoplasty, adequate pre-procedure preparation is essential. Pre-procedure preparations include (1) reassessing asthma stability and status on the day of each procedure; (2) administration of oral steroids before, on the day of, and after each procedure; and (3) administration of inhaled bronchodilators, antisialogogues, anxiolytics, sedatives, and topical anesthetics to facilitate an uneventful procedure.

Clinical assessment of the patient on the day of the procedure is the first step in performing a bronchial thermoplasty. The patient should have no contraindications to routine bronchoscopy. It is imperative to rule out current respiratory tract infections and ensure that the patient has not had a severe asthma exacerbation within 2 weeks of performing the procedure. Finally, the patient should be at baseline with respect to their asthma symptoms and pulmonary function testing performed on the day of the procedure by confirming that the patient's FEV_1 is within 10% of their baseline value [18, 24]. If any of the recommended criteria are not met, bronchoscopy should be postponed.

To reduce inflammation resulting from the application of thermal energy, patients are prescribed oral corticosteroids (equivalent to 50 mg/day of prednisone) starting 3 days prior to the procedure, on the day of the procedure, and for one day following the procedure [17]. Antisialogogues are administered on the day of the procedure to reduce salivary and tracheobronchial secretions. At our institution, the antimuscarinic agent glycopyrrolate (0.2–0.4 mg IV/IM) is administered a minimum of 30 min prior to initiation of the procedure. Lastly, bronchodilators are administered prior to the procedure to help ameliorate bronchospasm. We make use of nebulized albuterol (2.5–5.0 mg), but albuterol may also be dispensed through a metered-dose inhaler (4–8 puffs) [25].

Maintaining adequate analgesia and proper sedation during bronchial thermoplasty is necessary because each procedure lasts for up to 1 h. BT is performed under moderate sedation. At our institution, this is accomplished with the combination of a short-acting benzodiazepine and a short-acting narcotic, specifically midazolam (Versed) and fentanyl (Sublimaze). Midazolam (1–2 mg IV initial bolus followed by repeated 0.5–1 mg IV doses) and fentanyl (50–100 mcg IV initial bolus followed by repeated 25–50 mcg IV doses) are administered alternately throughout the procedure. Sedation level is frequently reassessed during the procedure, and additional sedation is administered as needed. Benefits of this specific drug combination include familiarity with the drugs, rapid onset of action of both agents, and their additive effects, convenient dose titration, and the ability to rapidly reverse either agent if needed [18]. Other agents including propofol have been utilized for sedation. Some centers have utilized general anesthesia administered with anesthesiologist assistance. Ultimately, the final decision on sedation is dependent on the physician performing the procedure and institution-specific guidelines.

In order to suppress the cough reflex during bronchoscopy, topical anesthetics are administered prior to and during the procedure. At our institution, anesthetization of the upper airway is achieved using 4 ml of 2% lidocaine nebulized through a mask prior to the procedure. Next, the posterior pharynx and laryngeal area are anesthetized with 5 ml of 1% lidocaine using a syringe directed over the back of the tongue. The bronchoscopy is initiated, and the bronchoscope is advanced to the level of the vocal cords, which are directly anesthetized with two to three 2 ml aliquots of 1% lidocaine delivered through the working channel of the bronchoscope. Finally the trachea, carina, and each of the main stem bronchi are anesthetized with 2 ml aliquots of 1% lidocaine until the patient appears comfortable and exhibits minimal coughing. When the bronchoscope is advanced into the airway segments targeted for treatment, additional 2 ml aliquots of 1% lidocaine can be administered. During the procedure, it may be necessary to administer additional targeted doses of lidocaine utilizing the intervals when the catheter is removed from the bronchoscope for suctioning. In our experience, use of 1% lidocaine limits the potential for toxicity. While elevated levels of lidocaine have occurred, toxicity is rare. Lidocaine doses in the range of 400–600 mg appear to be safe in asthmatic patients undergoing bronchoscopy as long as patients are monitored continuously for evidence of toxicity [26, 27]. Signs and symptoms of toxicity include lightheadedness, dizziness, headache, visual disturbances, metallic taste, muscular twitching, tremors, perioral tingling, auditory disturbances, seizures, or loss of consciousness [28].

Due to the length of the procedure and the level of sedation required, use of an airway device may become necessary. An endotracheal tube (ET) can be used to maintain a patent airway and minimize the number of desaturations but runs the risk of irritating the asthmatic airways, potentially triggering bronchospasm. At our institution, a laryngeal mask airway (LMA) is used when performing bronchial thermoplasty. It does not enter the trachea, protects the upper airway, and provides comparable benefits to an ET tube. Ultimately the discretion of the bronchoscopist and their level of comfort with the various airway devices will determine which device is optimal.

Intra-procedural Technique

Pathway planning is performed at the beginning of each bronchial thermoplasty procedure. This is essential and guarantees that no targeted bronchopulmonary segments are missed during each procedure. It also ensures that each targeted segment is treated once, and only once, and that no overlapping ablations are performed. Pathway planning is accomplished by inspecting, identifying, and mapping out the segments targeted for treatment. A systematic, methodical, and consistent approach is key, working from distal airways to proximal and from airway to airway across the lobe being treated to ensure that all accessible airways are identified and treated only once [17, 18]. Within each segment, subsegmental airways should also be identified and treated. We recommend moving from superior airways to those that are more inferior, or from airways to the right of the field of view toward those on the left. Diagrams of the tracheobronchial tree can assist in both planning bronchial thermoplasty and documenting treated airway segments (Fig. 29.3).

Once planning is complete, RF ablation may be initiated. The bronchoscope is directed into the desired segment or subsegment of the lobe under visualization. The Alair Catheter is deployed through the working channel of the bronchoscope into the targeted area under direct bronchoscopic visualization until the desired location is reached. The diameter of the nonexpanded catheter is 1.5 mm and is used to determine the diameter of the targeted airways. Once the catheter tip is at the desired location, the actuator is gripped allowing the arms of the catheter array to expand into contact with the airway wall. The degree of pressure applied to the actuator is determined by visualization of the expanding array in more proximal airways, while resistance guides the bronchoscopist in more distal segments where visualization is not possible. Once all four electrode wires are firmly in contact with the airway wall (Fig. 29.4), the footswitch is depressed (activated) and released, and RF energy is delivered automatically for approximately 10 s [17, 24]. The actuator is then released, partially collapsing the electrode array, and the catheter is retracted 5 mm proximally. This distance corresponds to a set of black markings present on the distal end of the catheter just proximal to the electrode array. These markings guide withdrawal of the catheter during the thermoplasty ensuring that the electrode array is positioned adjacent to, but does not overlap, the previous activation site (Fig. 29.5). If contact with the airway walls is not adequate during an attempted activation, a different audible signal will be emitted from the RF controller notifying the bronchoscopist. In these instances, the array will need to be collapsed, and the catheter will need to be repositioned prior to treating that particular area. The airways are always treated from the smaller more distal subsegments all the way to the most proximal main lobar bronchi. The usual number of activations per treatment session varies, and the usual range for successful activations is between 50 and 100 per lobe.

In our experience, and based on the manufacturers recommendations, the following may assist with performing bronchial thermoplasty: (1) Be careful to ensure that the catheter does not kink or bend during insertion into the working channel of the bronchoscope as this can damage the catheter; (2) avoid flexing the distal end of the bronchoscope when the catheter tip is in the working channel for the same reason; (3) avoid deploying the catheter outside the view of the bronchoscope to ensure patient safety; (4) since most subsegments do not require full expansion

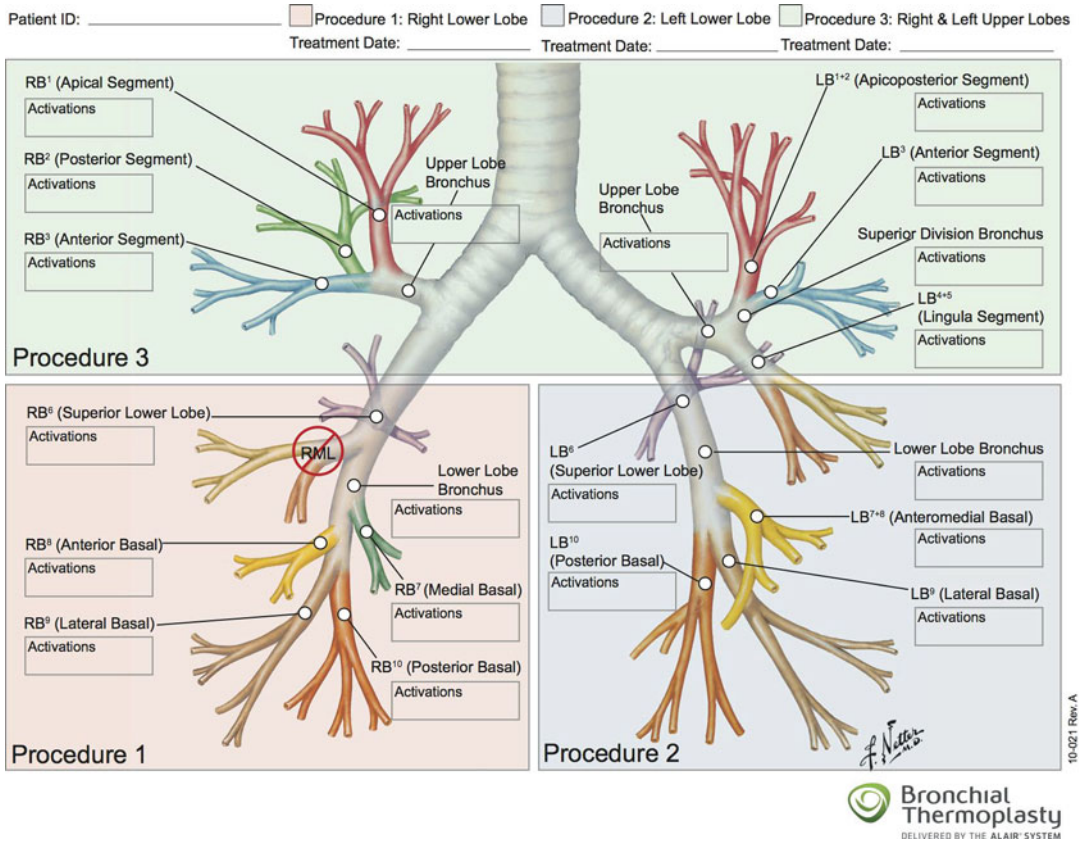

Fig. 29.3 Diagram of the tracheobronchial tree. The diagram can be used for mapping of the airways and thermoplasty planning prior to starting treatment. Activations performed during the procedure can be noted and recorded

of the catheter array for contact with the airway walls, avoid overexpanding the electrodes as this may cause inward deflection of the individual arms and loss of contact with the airway wall; (5) accumulation of mucus or secretions in the airways or on the electrode array may require periodic catheter removal from the working channel for catheter cleaning and patient suctioning—at these times additional topical lidocaine can be administered to provide continued patient comfort; and (6) the RF controller will automatically stop the RF signal if an abnormality is detected—if this happens repeatedly, the entire system should be checked for problems starting at the patient end and working backward to the controller [Alair package insert].

The technique for the second and third treatments is identical to the first with one important addition. Prior to initiating the second and third treatments, the lobe treated at the previous session must be inspected before starting pathway planning to evaluate for airway secretions or inflammation that may require suctioning or postponement of the current treatment.

Post-procedure Care

After the thermoplasty is completed, normal post-bronchoscopy monitoring is performed, often in conjunction with institution-specific practice guidelines. Because of the increased doses of sedation required for the prolonged bronchoscopy, patients should be monitored for the presence of an intact gag reflex and tolerance for oral liquids on recovery from sedation.

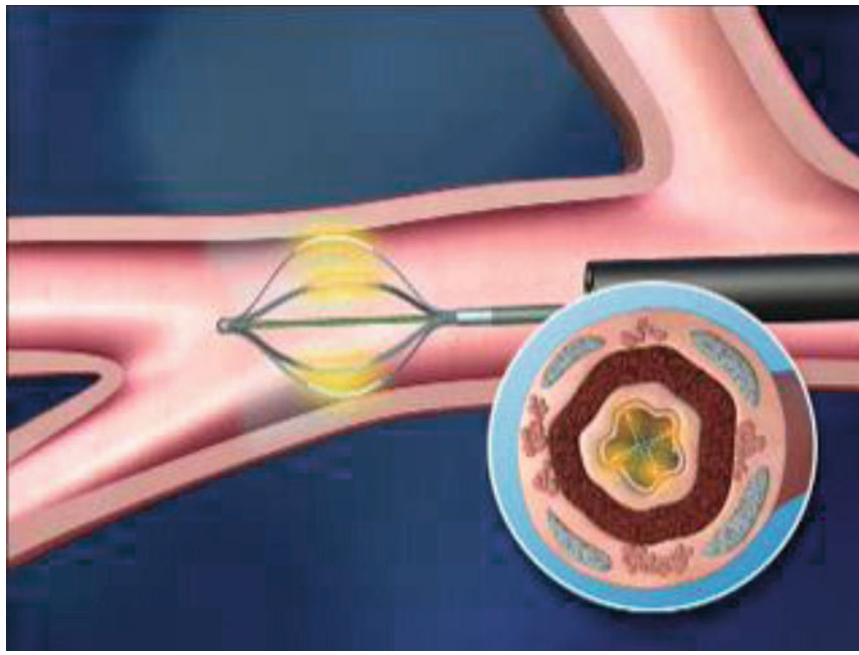

Fig. 29.4 Longitudinal and cross-sectional representation of an expanded Alair Catheter making contact with the bronchial wall during activation

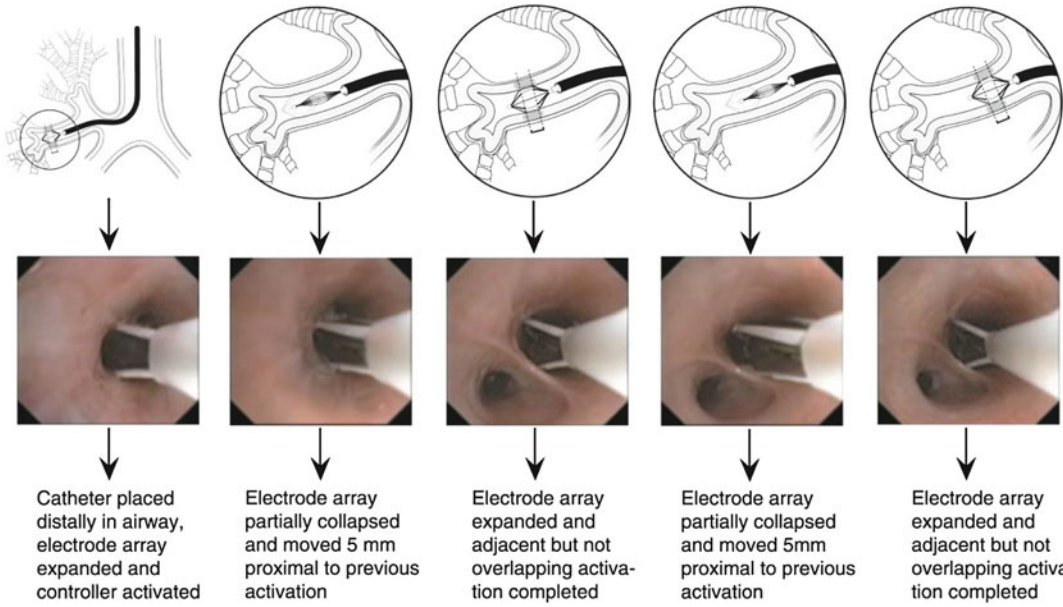

Fig. 29.5 Schematic and bronchoscopic views of the Alair Catheter during sequential activations

In addition, patients undergoing thermoplasty must have serial post-procedure FEV_1 tests performed after bronchodilator administration. In order to be discharged home, the post-procedure FEV_1 should be ≥80% of the pre-procedure *post-bronchodilator* value. Upon discharge, patients need to be advised of potential adverse events and reminded to take their remaining prophylactic steroid doses. Since patients undergoing bronchial thermoplasty have severe asthma, worsening of respiratory-related symptoms, including wheezing, dyspnea, chest discomfort, and cough, is not uncommon following the procedure [22, 29]. These typically occur within 1–2 days of treatment and resolve over 1 week with standard treatment with bronchodilators and systemic steroids. As a result, patients should be contacted at 24 h, 48 h, and 1 week post-procedure to assess their respiratory status. Lastly, the patient should be assessed at a clinic visit 2–3 weeks after the procedure to determine whether they are stable for the next thermoplasty treatment [24].

Possible Therapeutic Mechanisms of Bronchial Thermoplasty

The potential mechanisms of bronchial thermoplasty have been studied in a bovine tracheal smooth muscle model. Smooth muscle responsiveness is substantially reduced a few seconds after application of 60°C heat and is eliminated by 5 min posttreatment [30]. The intervention appears to be dose dependent, and the desired effect does not progress. The immediate loss of airway smooth muscle cell function in this model suggests that the high temperature disrupts actin–myosin interactions, possibly through denaturation of muscle motor proteins [30]. The loss of muscle function is less likely to be heat shock protein mediated or the result of apoptosis, autophagy, or necrosis due to both the rapid abolition of muscle response and the lack of progressive changes. Identification of this airway smooth muscle target also introduces the possibility of other therapeutic interventions focusing on abolition of the smooth muscle spasm cascade [16, 30].

Preclinical and Non-asthmatic Evidence for Bronchial Thermoplasty

Animal studies in non-asthmatic dogs demonstrated that the application of thermal energy to airway walls attenuated methacholine responsiveness for up to 3 years posttreatment [21]. Degeneration or lack of bronchial wall smooth muscle was seen as early as 1 week following treatment, and the extent of the smooth muscle changes was inversely proportional to bronchial responsiveness. No evidence of smooth muscle regeneration was noted over the 3 years of study. Adverse effects in these animals included cough, airway edema, increased mucus production, and blanching of airway walls at the sites of catheter contact.

The first human study of BT was a feasibility study in individuals undergoing targeted lung resection for lung cancers [31]. Eight individuals underwent thermoplasty treatments to visible airways within the areas of lung selected for resection. BT was performed at 3–9 treatment sites per patient, 5–20 days prior to scheduled lung resection. There were no significant adverse events, and at the time of resection, bronchoscopy was generally unremarkable. Only airway narrowing, excess mucus, or linear blanching was noted. The treated lung tissue showed airway smooth muscle changes at approximately 50% of the treated areas [31].

Clinical Evidence for Bronchial Thermoplasty in Asthmatic Patients

Since 2005, numerous human studies of BT in mild to moderate asthmatics, and later moderate to severe refractory asthmatics, have been performed to identify appropriate candidates, adverse events, and expected outcomes with BT [25, 29, 31, 32].

The first study of BT in mild to moderate asthma patients was a prospective observational study of 16 patients at 2 centers in Canada. It was a single-arm study designed to evaluate the safety of BT [22]. Patients were pretreated with

prednisone, either 30 or 50 mg, on the day before and the day of the procedure, and the three BT treatments were spaced 3 weeks apart. The right middle lobe remained untreated. There were no hospitalizations following the procedures. The most common post-procedure side effects were cough, bronchospasm, wheeze, or dyspnea. Symptoms commonly started 2 days after the procedure and resolved within 5 days of treatment [22]. Over 2 years of follow-up, the majority of adverse events were mild, and no severe events were felt to be procedure related. Improvement in peak flow rates at 3 months posttreatment demonstrated the early effectiveness of the procedure when compared to baseline, but there was no significant change in peak flows at 2 years of follow-up. Symptom-free days also increased significantly 3 months post-procedure. A significant decrease in airway hyperresponsiveness (measured by methacholine challenge) was maintained at 3 months, 1 year, and 2 years following the procedure. BT in this study was associated with a high level of patient satisfaction 14–36 months after treatment [33]. In addition, annual CT of the chest demonstrated no parenchymal or airway changes related to the procedure. However, the small number of subjects and their relatively stable asthma status limited the findings of this study [13].

The Asthma Intervention Research (AIR) trial was a multicenter, prospective, randomized, controlled, and non-blinded study to evaluate the effectiveness and safety of BT in subjects with moderate to severe asthma [29]. All subjects (56 BT group and 56 control group) were on standard asthma care, requiring ICS (≥200 mcg beclomethasone equivalent) and LABA to maintain asthma control. All subjects demonstrated impairment with LABA withdrawal. Subjects were randomized to either BT plus ICS and LABA (BT group) or to ICS and LABA alone (controls). Treatments occurred in three sessions over 9 weeks and were followed by attempts to discontinue LABA at 3, 6, and 9 months post-procedure. Acute exacerbations on ICS alone were the primary study end point. Daily diaries documenting symptoms and rescue inhaler use, and Asthma Quality of Life Questionnaire (AQLQ) and the Asthma Control Questionnaire (ACQ) were administered. Compared to the control group, the BT group experienced an increased number of adverse events during treatment period (up to 6 weeks after the last bronchoscopy). The events occurred largely within 1 day of BT and resolved on average seven days after the onset. There were more hospitalizations in the BT group (4 subjects required 6 hospitalizations) than in the control group (2 hospitalizations) [29]. Reasons for hospitalization included asthma exacerbations, left lower lobe collapse, and pleurisy. Compared to control subjects, there was a significantly greater reduction in mild exacerbation rates at both 3 and 12 months in the BT-treated group (10 fewer mild asthma attacks per year). Severe exacerbations were lower in the BT-treated group compared to control subjects, but the difference did not achieve statistical significance. The BT group demonstrated significantly lower rescue medication use at 3 and 12 months (400 fewer rescue medication puffs). BT patients also had significant improvements in asthma control and quality of life (86 more asthma symptom-free days). Hospitalization rates for respiratory adverse events were low in the posttreatment period (between 6 and 52 weeks posttreatment) and did not differ between the 2 groups. The AIR study, however, was limited by its non-blinded design and the strong placebo effect in the control group and highlighted the need for a trial with a sham treatment arm [13].

The Research in Severe Asthma (RISA) trial was a multicenter, randomized, controlled clinical trial designed primarily to study the safety of BT in subjects with severe refractory asthma. Patients whose asthma was more severe than those in the AIR study were evaluated for procedure safety, changes in asthma symptoms, and daily medication use [25]. Subjects had to be symptomatic despite treatment with >750 mcg/day of fluticasone or equivalent and could also be taking oral corticosteroids (OCS) up to 30 mg prednisone/day. Thirty-two subjects were randomized to BT with ICS+LABA±OCS ($n=15$) or medical management with ICS+LABA±OCS alone ($n=17$). Following a 2-week run-in period,

3 BT treatments were performed 3 weeks apart. After treatment the study was divided into a 16-week corticosteroid-stable phase followed by a 14-week corticosteroid wean phase and finally a 16-week reduced corticosteroid extension phase. During the last 2 phases, attempts at decreasing oral steroid or ICS doses were made. During treatments there was a higher rate of hospitalization in the BT group (7 hospitalizations in 4 subjects) compared to controls (no hospitalizations). Reasons for hospitalization included asthma exacerbations and a partial left lower lobe collapse. However, during the 6-week posttreatment period, the BT group had a similar number of hospitalizations compared to controls and a lower number of hospitalizations when compared to baseline. During the corticosteroid-stable phase, the BT group demonstrated a significant reduction in rescue inhaler use (25 fewer puffs/week) and improvement in pre-bronchodilator FEV_1 (15.8% improvement). In addition, both AQLQ and ACQ scores improved. In the corticosteroid wean phase, all subjects in the BT group were able to initiate steroid weaning, while 3 subjects in the control group did not attempt steroid reduction at all. During the reduced corticosteroid extension phase, 4 of 8 BT subjects were weaned completely off OCS through 52 weeks, compared to only 1 of 7 control subjects. Although there was significant potential for placebo effect, BT-treated patients demonstrated significant improvement in clinical asthma outcomes compared to the control group [25]. The study also demonstrated that BT could be safely performed in severe refractory asthmatic populations.

The most recent trial evaluating BT in severe asthmatics was the AIR2 Trial [32]. AIR2 was a multinational, multicenter, randomized, double-blinded, and sham-controlled study. Sham procedures were identical to active procedures and used an RF controller that provided audio and visual cues that mimicked the active controller, but did not deliver RF energy through the catheter. Neither subjects nor assessing physicians were aware of individual treatment assignments. AIR2 used a 2:1 randomization scheme (2 BT to 1 control subject) to randomize a total of 297 subjects (196 BT, 101 sham) to three bronchoscopy procedures, separated by 3 weeks. All patients had severe asthma and were symptomatic despite management with ICS (>1,000 μg/day beclomethasone or equivalent) and LABA (≥100 μg/day salmeterol or equivalent). The primary outcome was the difference in the change in AQLQ score between study groups from baseline measurements at 6, 9, and 12 months after the final BT treatment. During the treatment period, there was a higher rate of hospitalization for respiratory symptoms in the BT group (19 hospitalizations in 6 subjects) compared to controls (2 hospitalizations). Reasons for hospitalization included low $FEV_{1,}$ worsening asthma, segmental atelectasis, lower respiratory tract infections, an aspirated prosthetic tooth, and an episode of hemoptysis requiring bronchial artery embolization. Ten of the 19 hospitalizations in the BT group occurred on the day of the procedure. However, in the 6-week posttreatment period, there was a significant 34% reduction in severe exacerbations in the BT group compared with the sham group. There was also a 66% reduction in days lost from work, school, or other daily activities due to asthma in the BT group.

The AIR2 BT group experienced improved quality of life compared to the sham group. This was demonstrated by a significant difference between the groups in average improvement in AQLQ score from baseline at 6, 9, and 12 months (posterior probability of superiority of 96.0%). To further determine the clinical significance of the data, the AQLQ data were categorized into the proportion of subjects in each group that achieved a significant and clinically meaningful improvement in AQLQ score of ≥0.5. While 64% of the sham group experienced improvements in AQLQ scores of ≥0.5, 79% of BT-treated subjects demonstrated the same. For the intention to treat population, the difference between the groups had a posterior probability of superiority of 99.6%, proving that the AQLQ score improvement in the BT group was superior to that in the sham group. However, the large percentage of sham subjects demonstrating improved AQLQ scores emphasizes the importance of the placebo effect in asthmatic populations.

During longer-term follow-up (>6 weeks after the last BT treatment), secondary end points also demonstrated clinically meaningful and statistically significant differences in favor of the BT group. These included reductions in asthma adverse events, emergency department visits for respiratory symptoms, and hospitalizations for respiratory symptoms. In addition, blinded evaluation of CT of the chest from 100 BT and 50 sham subjects did not reveal any parenchymal or airway changes related to the procedure. Overall, the AIR2 study demonstrated improved short- and long-term quality of life along with decreased healthcare utilization in severe refractory asthma treated with bronchial thermoplasty [32].

FDA Approval and Long-Term Follow-Up

In early 2010, the FDA approved the Alair Bronchial Thermoplasty System® for severe refractory asthma [Alair package insert, Asthmatx, Inc, Sunnyvale, CA]. As part of the conditions of approval, the FDA required a post-approval study based on long-term follow-up of the AIR2 Trial population. In addition, a second prospective, open-label, single-arm, multicenter post-approval study (PAS2) is currently underway to assess the treatment effects and the short- and long-term safety profiles of BT. At the time of writing, long-term follow-up data are available out to 5 years from the lung cancer feasibility study [34], the AIR Extension Study [35], and the RISA Extension Study and out to 4 years in the AIR2 Trial [Asthmatx, Inc. personal communication]. Two-year follow-up of participants receiving BT in the AIR2 study demonstrated a sustained improvement in health outcomes [36].

Summary

In patients without significant contraindications to bronchoscopy, BT is a well-validated, FDA-approved therapeutic modality for the treatment of severe refractory asthma not well controlled on combination high-dose ICS and LABA therapy. Clinical trials have demonstrated its efficacy and safety for improving quality of life, respiratory symptoms, and healthcare utilization in carefully selected patients with asthma. Patient selection is paramount and should be based on the study populations described in published trials. In addition, proper monitoring of patients both during and after the treatment period (up to 6 weeks after the last procedure) is mandatory. As experience with the procedure increases, we will further characterize the subsets of severe asthmatic patients obtaining maximal benefits from BT and, in doing so, improve outcomes while minimizing adverse events.

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Part VII

Interventional Bronchoscopy in Special Situations

Percutaneous Tracheostomy

30

Anthony W. Gray Jr

Introduction and Definition of Procedure

The terms "tracheostomy" and "tracheotomy" refer to the creation of an opening in the trachea for the insertion of a tube. The procedure itself is sometimes referred to as a tracheotomy and the opening, a tracheostomy, though often the two terms are used interchangeably. The addition of the descriptor, "percutaneous," differentiates this technique from the previously standard surgical or "open" tracheostomy. This technique has transformed what was once a procedure performed almost exclusively in the operating room by surgeons alone, to one that can now be safely performed at the bedside by surgeons and internists alike.

History and Historical Perspective

The history of modern-day percutaneous tracheostomy is a relatively short one. At present, it is a procedure popularized by Dr. Ciaglia, a self-described "general thoracic surgeon," and published in 1985 [1]. The procedure of tracheostomy, however, has its roots dating back centuries ago, with descriptions found on Egyptian tablets dating before 3000 BC [2].

The term "percutaneous tracheotomy" was first described by Sheldon and Pudenz in 1957 [3] and "percutaneous tracheostomy" by Toye and Weinstein in 1969 [4]; however, these earlier descriptions of the procedure, initially using a slotted needle and cutting trochar and subsequently a modified Seldinger technique using a recessed cutting blade, did not gain in popularity.

Inspired by Brantigan's description of cricothyroidotomy [5], Ciaglia drew inspiration for his newly described technique from the percutaneous nephrostomy Amplatz renal dilator set [1]. Ciaglia's serial dilation technique has undergone minor modifications over the past 27 years however remains the procedure after which the current technique is modeled.

Indications and Contraindications

The indications for percutaneous tracheostomy are similar to those for a conventional tracheostomy [6–8] and include:

(a) Bypassing unobstructed airway, whether secondary to trauma, foreign body, vocal cord paralysis, infection, or angioedema
(b) Removal of secretions from the distal tracheobronchial tree
(c) Prolonged application a mechanical ventilation or positive pressure ventilation (most common indication)

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(d) Therapy for obstructive sleep apnea
(e) As an adjunct in preparation for head and neck surgery for temporary management of the airway in the perioperative period

Contraindications to percutaneous tracheostomy have changed over the years as more experience with the procedure is gained and published. The presence of an unstable cervical spine, a previous tracheostomy procedure, and the performance as an emergency procedure were, in years past, considered to be contraindications though there are numerous published reports (as well as personal experience) that has proven percutaneous tracheostomy a safe and acceptable procedure in these circumstances.

Anatomic abnormalities, such as significant thyromegaly, anterior neck mass, or retrosternal location of appropriate tracheal rings, should be considered as present-day absolute contraindications.

While admittedly subjective, patients with "uncorrectable" coagulopathy, such as those with a prolonged prothrombin time/international normalized ratio, thrombocytopenia, or acquired defects of coagulation (patients with renal failure or those being treated with antiplatelet agents), should be considered as having a relative contraindication.

Similarly, one must proceed with great caution in patients receiving significant support to maintain adequate oxygenation and/or ventilation; perhaps waiting until survival from critical illness is more assured, and support somewhat reduced.

Description of the Equipment Needed

There are a number of different kits approved for placement of a percutaneous tracheostomy. Following Ciaglia's description of the multiple dilator technique in 1985 [1], several modifications have been proposed including a guidewire dilating forceps [9], a translaryngeal technique [10], a single-dilator technique [11], a rotational dilation technique [12], and finally a balloon dilation technique [13]. While there are no randomized, controlled trials comparing tracheostomies performed by the different techniques, a recent systematic, meta-analysis review of six different techniques was recently reviewed by Cabrini in 2012 [14]. The authors found that "overall, the different techniques and devices appeared largely equivalent" though there were minor differences favoring the single-dilator technique in comparison with the translaryngeal technique (fewer severe complications or need to convert to alternate technique) and also in comparison with the rotational dilation technique (fewer failures). Additionally, the single-dilator technique had fewer mild complications compared with the balloon dilation technique and was more expedient (1.5 vs. 4 min). Still, the meta-analysis lacks the strength of a randomized study making the choice of technique operator dependent.

With these limitations in mind, the technique outlined within this review (below) describes the most commonly used method, the single-dilator technique.

Application Technique

As is true for the "open" or surgical technique, modeled after Chevalier Jackson's description in 1909 [15], there is no single, standard technique for performing a percutaneous tracheostomy though, in general, there are many similarities among the various percutaneous techniques.

The procedure can be performed either at the bedside or in the operating room though most prefer to perform at the bedside. When performed at the bedside, the risks associated with transportation of patients outside of the ICU is minimized, specifically the risk of accidental extubation or removal of catheters among others. Additionally, there is also evidence that transport out of an ICU is associated with an increased risk of ventilator-associated pneumonia [16].

In the intensive care unit, however, the proceduralist may not have the benefit of an experienced anesthesiologist who is dedicated to the induction and maintenance of adequate analgesia and anesthesia. Therefore, the operator must ensure patient comfort personally or by enlisting the help of an assistant for this purpose.

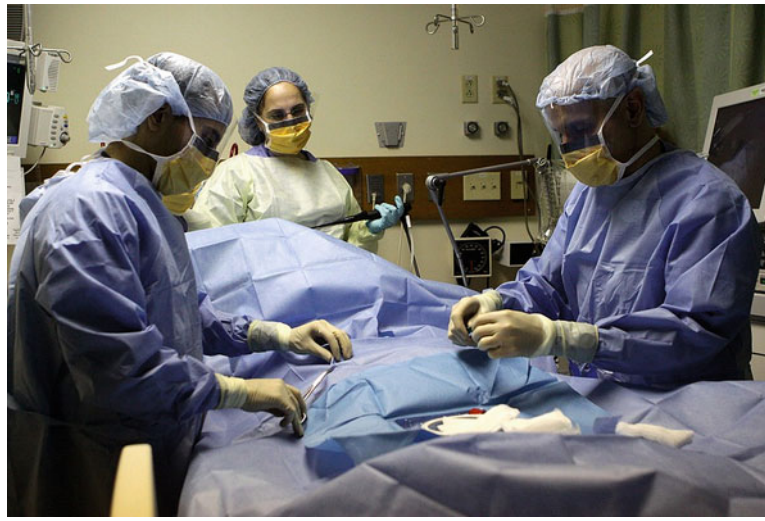

Fig. 30.1 Percutaneous tracheostomy team

Another variation in the performance of percutaneous tracheostomy is the use of the flexible bronchoscope by a skilled assistant. While not required for a successful procedure, and not outlined in Ciaglia's initial description of the procedure, it is nonetheless strongly recommended for a number of safety reasons. First and foremost, the correct placement of the newly placed tracheostomy tube can be assured under direct vision, rather than by indirect methods, for example, with the presence of bilateral breath sounds, absence of gastric air insufflation, or with monitoring of exhaled tidal volumes. Real-time avoidance of complications during the procedure, such as inadvertent placement above the first tracheal ring or below the third tracheal ring, or puncture through the posterior tracheal wall, for example, can be prevented.

Pre-procedure Checklist

1. The team (Fig. 30.1):
   (a) Physician/proceduralist
   (b) A surgical assistant (or trainee)
   (c) Bronchoscopist
   (d) Anesthetist (unless this role is delegated to the bronchoscopist or managed by the proceduralist)
   (e) Nurse
   (f) Respiratory therapist
2. Monitoring, to include pulse oximetry, electrocardiography, and blood pressure recording.
3. Emergency backup equipment to include laryngoscope, airway exchanger, endotracheal tube, tracheostomy tube (one size smaller), and resuscitation bag.
4. Flexible video bronchoscope, the purpose of which is to assist with endotracheal tube repositioning, surgical site verification, documentation of midline entry into the tracheal lumen, and confirmation of tracheostomy tube position. Additionally, specimens for culture can be performed at the time of the procedure (generally prior to performance of the percutaneous tracheostomy) and bronchial hygiene or removal of clot and debris post-procedure.
5. Appropriate procedural kit and components including appropriate-sized tracheostomy tube (and backup tube) (Fig. 30.2).

The Procedure in Detail

1. Pre-oxygenate with $FiO_2 = 1.0$.
2. Administer intravenous sedation and analgesia.
3. Positioning of patient: appropriate height, bed maximally inflated if appropriate, neck in neutral position or slightly hyperextended.
4. Identification of landmarks and surgical site (Fig. 30.3a).
5. Chlorhexidine skin prep, sterile drape (Fig. 30.3b, c).
6. Infiltration of the skin and subcutaneous tissues with local anesthesia (lidocaine 1% with epinephrine 1:100,000) (Fig. 30.4a).

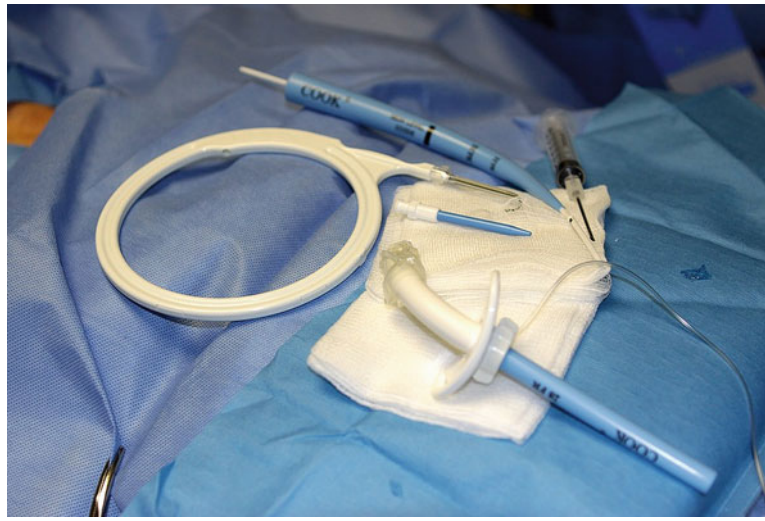

Fig. 30.2 Equipment

7. Skin incision (Fig. 30.4b, c). A 1.5–2.0 cm skin incision can be performed either in the vertical or horizontal plane. The benefit of performing a horizontal skin incision is primarily related to reduced scar formation post-decannulation as the incision follows the lines of Langerhans, once patient has improved and no longer is in need of a tracheostomy. The benefits of a vertical incision include avoidance of blood vessels, especially thyroidal vessels, as they approach the trachea laterally. Additionally, a vertical incision has the advantage of being extended either superiorly or inferiorly should either the initial incision location appear not to be above the first and second or second and third tracheal rings or, perhaps, should an enlarged thyroid or crossing vessel be encountered; a modification of the placement of the tracheostomy can easily be accommodated by extending the vertical incision. The major disadvantage of a vertical incision is primarily related to the possibility of a larger scar post-decannulation; however, since the incision is generally of a fairly small size, that is, less than 2 cm, a large surgical scar is generally not seen in either the horizontal or vertical approach. When performing a vertical incision, the superior aspect should start at the inferior aspect of the cricoid cartilage.
8. Following the skin incision, blunt dissection can be performed at the discretion of the proceduralist (Fig. 30.5a, b, c). Blunt dissection is often helpful in providing reassurance that appropriate tracheal landmarks are respected, that is, the cricoid cartilage and first and second tracheal rings. Blunt dissection is not necessary, however, in patients with thin necks or small distances between the skin surface and trachea. Dissection with electrocautery is to be discouraged given both the lack of adequate hemostasis that may be encountered when using deep electrocautery and the risk of fire given flammable skin prep and high oxygen concentrations used during the procedure.
9. Repositioning of the endotracheal tube. Following the skin incision, either with or without dissection, the bronchoscopist assists by advancing the flexible bronchoscope beyond the open end of the endotracheal tube as the proceduralist watches through the newly created incision for passage of the bright light of the bronchoscope, noted via transillumination. Once this is done, an estimate of the distance that the endotracheal tube must be withdrawn is performed. The bronchoscopy assistant then partially deflates the cuff of the endotracheal tube (which has been previously unsecured), and together with the bronchoscope which is held in position just above the distal

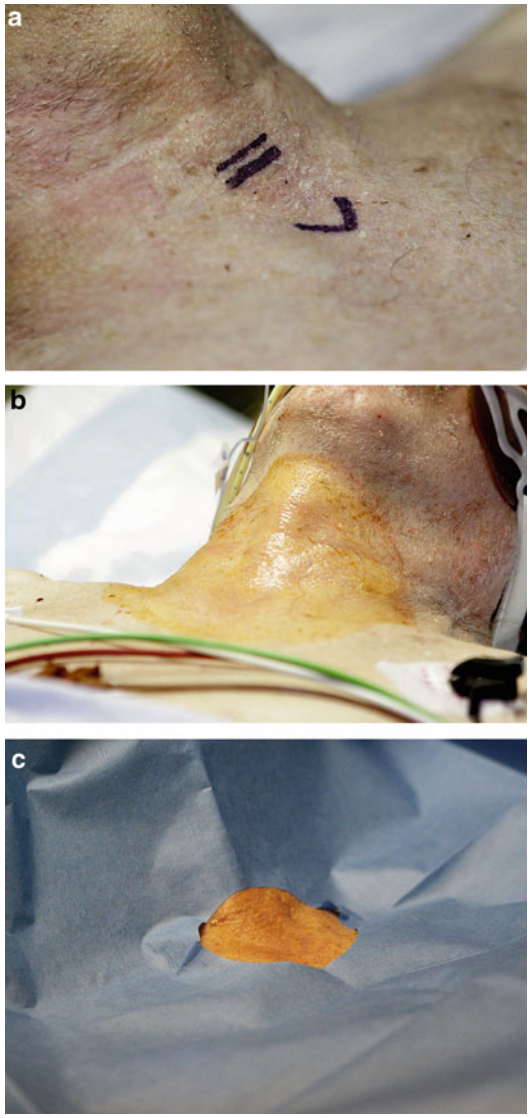

Fig. 30.3 (**a**, **b** and **c**) Position and landmarks: locate the cricoid cartilage and the sternal notch. Sterile preparation and drape

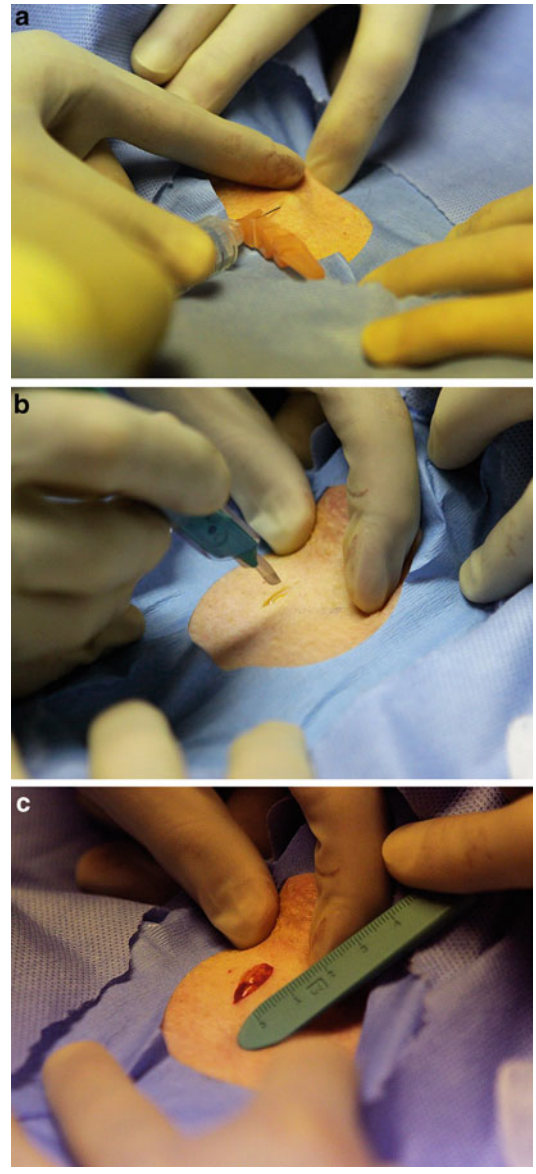

Fig. 30.4 (**a**, **b** and **c**) 1% Lidocaine injection and 1.5–2 cm long skin incision

end of the endotracheal tube, that is, within the endotracheal tube, the bronchoscope and endotracheal tube are withdrawn *en bloc* under direct vision of the proceduralist to a level just above the appropriate previously identified position of the first and second or second and third tracheal rings. The endotracheal tube cuff is then reinflated and held in position by the bronchoscopy assistant.

Note: Throughout the procedure, titration of sedation and analgesia is performed based on sedation guidelines [17]. At the discretion of the proceduralist, and in conjunction with the bronchoscopist and team caring for the patient, the administration of a neuromuscular blocking agent can be considered.

10. Using a 14-gauge finder (catheter) needle attached to a fluid-filled syringe, the anterior

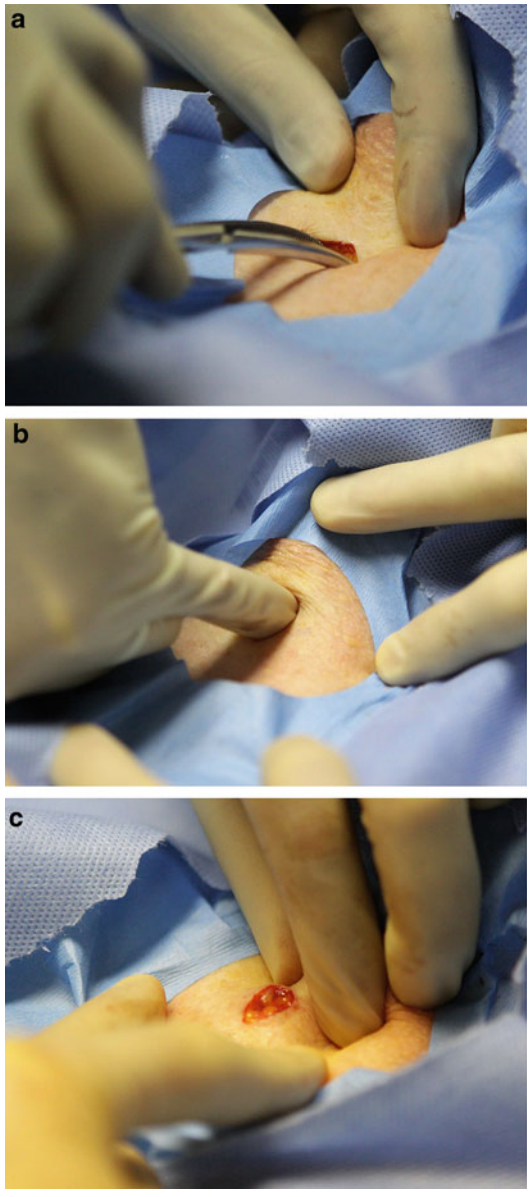

Fig. 30.5 (**a**, **b** and **c**) Optional blunt dilatation, manual palpation, and transfixing the trachea between index finger and thumb to prepare for a central access

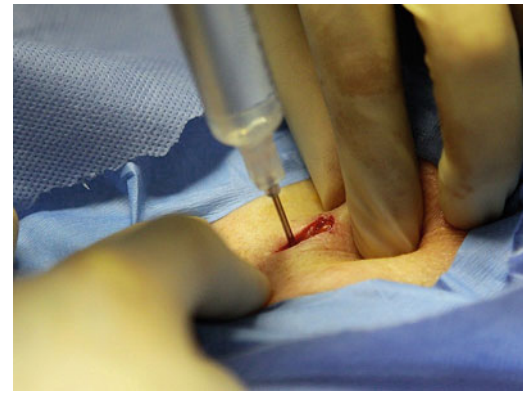

Fig. 30.6 Aspirate air with a fluid-filled syringe

trachea is punctured in the midline position between the first and second or second and third tracheal rings (Fig. 30.6). The presence of air bubbles entering the fluid-filled syringe provides reassurance that the trachea has likely been entered. This is one of the most important parts of the procedure as it determines the final location of the tracheostomy tube. To assist in finding the appropriate midline location of the puncture site, the proceduralist should transfix the trachea between the thumb and either second or third fingers of the nondominant hand, superior to the planned insertion site (Fig. 30.5c). The proceduralist should be standing on the same side where the patient has his/her dominant hand. That is, if the proceduralist is right-handed, he/she should be standing at the right side of the patient. The nondominant hand, then, is transfixing the trachea either just superior to the planned insertion site or higher at the level of the thyroid cartilage. By transfixing the trachea in this position, the proceduralist can enter the trachea midline between the 2 fingers that are being used to transfix the trachea, assuring a more likely occurrence that the finder needle will enter the trachea at the midline position. Confirmation of appropriate positioning is provided as the bronchoscopist describes the location based on the hands of a clock, for example, "the trachea has been entered at the 12 o' clock position." The proceduralist can also directly observe the video monitor if one is available. The optimal positioning of the puncture site is between the 11 and 1 o' clock positions; however, a more lateral approach may be necessary based on anatomic considerations.

11. The fluid-filled syringe is removed and a J-tipped guidewire is advanced either through the finder needle or, if a catheter over needle

approach is used, through the catheter after the needle has been withdrawn (Fig. 30.7a).

12. A lubricated punch dilator is then advanced over the guidewire and into the trachea in a slight twisting motion. This allows for passage of the stiffening catheter, as described in the next step (Fig. 30.7b).
13. The stiffening catheter is advanced over the guidewire to the skin surface.
14. The dilating catheter is then advanced over the stiffening catheter; its passage over or rather beyond the stiffening catheter is prevented by a small bulge near the distal end of the stiffening catheter. The stiffening catheter and dilating catheter can be preassembled and advanced over the guidewire as one unit to reduce the number of steps.
15. The dilating catheter, or catheters, is then held gently, similar to how one grasps a pen or pencil, and advanced over the guidewire into the airway (Fig. 30.7c). Excessive force should be avoided when advancing dilating catheter as this often represents placement of the initial puncture through a tracheal cartilage. If this occurs, it is the preference of this author to reposition the puncture site, that is, repeating step 10 to ensure placement of the dilating catheter between tracheal rings. In this way, fracture of a tracheal ring, while not contraindicated, can be avoided. The dilating catheter is advanced into the trachea gently and slowly up until the line of demarcation on the dilating catheter is at the same level of the skin surface (Fig. 30.8a, b). Less than full dilation may be preferable in patients in whom a smaller-sized tracheostomy tube is indicated and also in those patients in whom a coagulopathy is present or who are at a greater risk of post-procedural stomal bleeding.
16. Bronchoscopic confirmation is then performed both from above the newly placed tracheostomy tube, that is, from the view from within the endotracheal tube, and also via the newly placed tracheostomy tube (Figs. 30.9 and 30.10). Following inspection, bronchial hygiene may be performed to ensure the absence of airway bleeding or removal of blood from the airway if necessary.

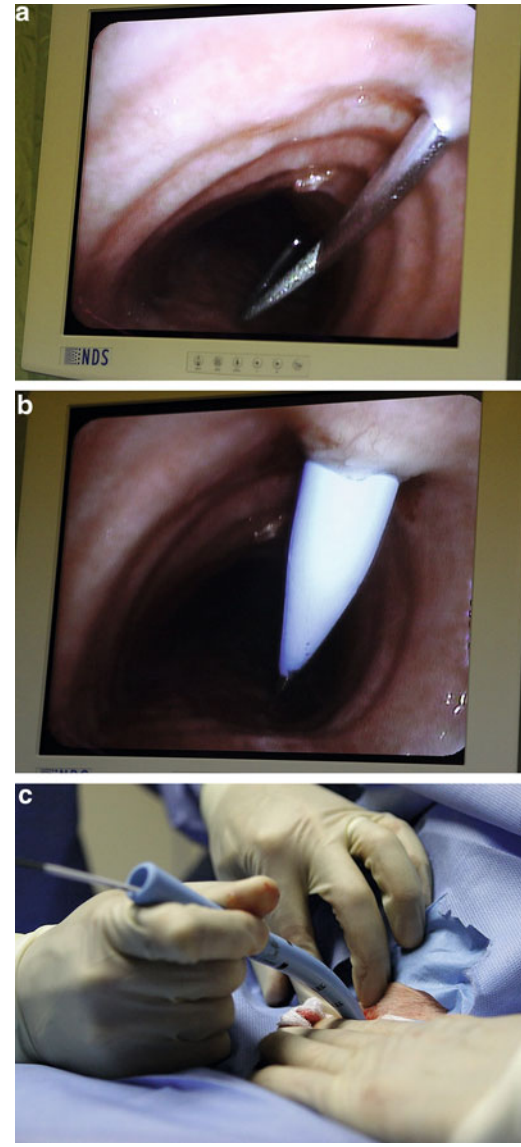

Fig. 30.7 (**a**) J-wire advancing through the finder needle, endoscopic view. (**b**) Advancing the punch dilator. (**c**) Advancing dilator catheter

Evidence-Based Review

Complications: Comparison with Surgical Tracheostomy

There are numerous studies that have attempted to compare the complications of the percutaneous technique compared to the open technique. These are best summarized by Higgins and Punthakee in a recent

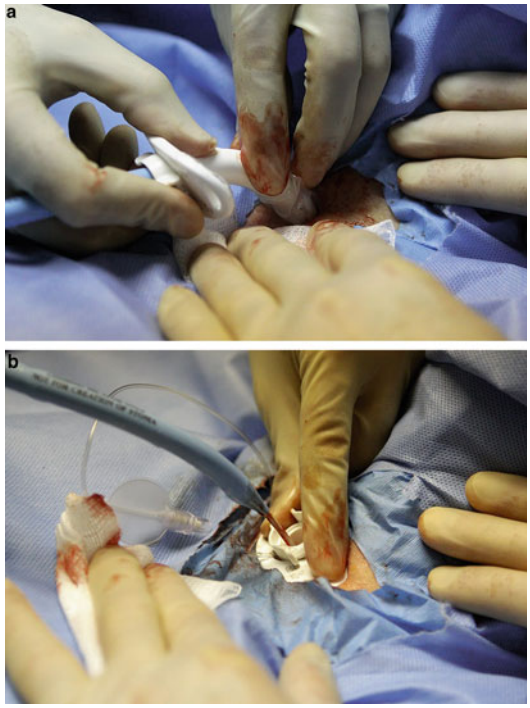

Fig. 30.8 (**a**) Advancing tracheostomy–obturator combination. (**b**) Removal of obturator

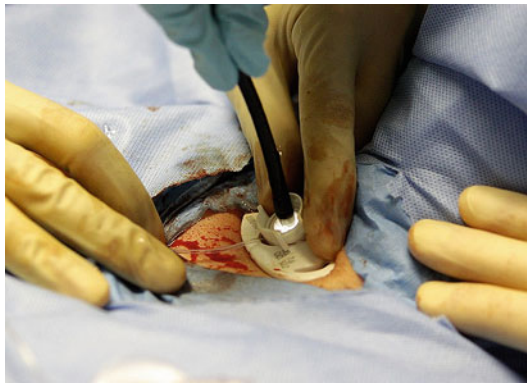

Fig. 30.9 Bronchoscopic confirmation through the tracheostomy

meta-analysis designed primarily to compare complication rates using randomized or quasi-randomized clinical trials only [18]. Fifteen studies met criteria for analysis with 973 the total number of patients included (490 in the percutaneous arm and 483 in open). Wound infection and unfavorable scarring favored the percutaneous route, while the risk of decannulation/obstruction favored the open route.

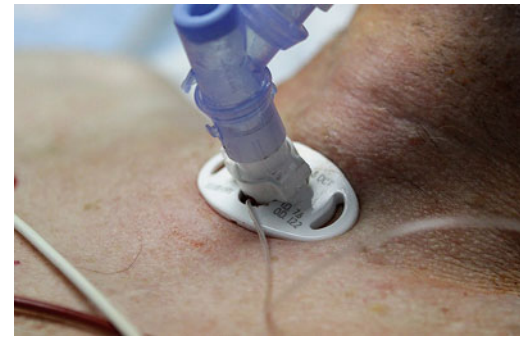

Fig. 30.10 Inflate cuff and attach ventilator system

There was no difference noted with respect to false passage, minor or major hemorrhage, subglottic stenosis, or death. Overall complication rate "trended" toward favoring the percutaneous route, mentioned here only because the *P* value *equaled* 0.05.

Competence

Procedural competence is institution specific and while there are no widely accepted guidelines for proof of competence, this author agrees with the American College of Chest Physicians recommendations which have been consistent over the past decade: a minimum of 20 procedures, performed in a well-supervised setting, is necessary to establish competency for trainees [19, 20]. Supporting this number is a well-conducted analysis of complication rates published by Massick [21] demonstrating a reduction in complication rate, and therefore an improved competency rate, after an initial cohort of 20 procedures.

Summary and Recommendations

The choice regarding which procedure to perform, that is, tracheostomy via the standard surgical route or by the percutaneous method, should not be guided by the desire to perform the least expensive or most expeditious or "newest" procedure, rather the skill and expertise of the operator and the right choice of the procedure for the individual patient—always respecting what is in the patient's best interest—should guide one's decision.

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Bronchoscopy Role in Interstitial Lung Disease

31

Maria Molina-Molina

Introduction

Interstitial lung disease (ILD) is a group of respiratory entities in which the main pathological alteration not only affects the interstitial alveolar structures but also can involve the small airways and the pulmonary vasculature [1]. Clinical presentation, radiological features and lung function tests can be similar in different types of ILDs, and do not allow a categoric diagnosis. Cytological evaluation and/or histological study are usually crucial to achieve a confident diagnosis and also to rule out other causes of interstitial lung pathology such as infections or cancer [1]. Surgical lung biopsy is usually too risky given the clinical, lung function or cardiovascular status and is only performed in 20–40% of cases [2]. Therefore, fiber-optic bronchoscopy with bronchoalveolar lavage (BAL) and transbronchial lung biopsy (TBLB) is often the initial procedure of choice [2–4]. Bronchoscopy with BAL and TBLB may provide sufficient evidence to diagnose sarcoidosis, amyloidosis, hypersensitivity pneumonitis, eosinophilic pneumonias, organizing pneumonia, pulmonary Langerhans cell disease (histiocytosis X), Goodpasture's syndrome, lymphocytic interstitial pneumonia, some pneumoconioses, pulmonary lymphangioleiomyomatosis, and pulmonary alveolar proteinosis, as well as infections and neoplastic processes presenting with interstitial lung infiltrates [3, 4]. When clinical information and HRCT findings are combined with BAL fluid analysis and/or transbronchial lung biopsy, a confident diagnosis may emerge that obviates the need for surgical lung biopsy [4]. However, some considerations should be made in order to take advantage from both procedures in ILD evaluation.

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Bronchoalveolar Lavage

BAL has gained wide acceptance as a safe method to obtain respiratory secretions for the examination of cellular and acellular components for both diagnostic and research purposes [5, 6]. Certainly, much data have been published over the past decades that demonstrate the utility of BAL to identify agents of respiratory infections and changes in the composition of the airspace environment associated with the presence of noninfectious parenchymal lung diseases. The introduction of high-resolution computed tomography (HRCT) at the end of the last century represented a revolutionary improvement in the diagnosis of specific forms of ILD and also a useful tool to decide the best place to obtain respiratory samples [6]. BAL is now routinely used as a tool to diagnose respiratory infections, study diffuse parenchymal lung diseases, and monitor the status of transplanted lung allografts [7]. Despite the widespread use of BAL, its cellular analysis, especially nucleated immune cell differential

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counts, may be underused in ILD diagnosis since its results differ from center to center and depend on multiple factors [8, 9]. BAL appearance and differential cell count should be interpreted appropriately and evaluated with an updated awareness of the potential diagnoses associated with each cellular pattern in order to provide useful diagnostic clues [7–9].

Technical Aspects of BAL Procedure

The usefulness of the BAL in ILD is only possible if (a) the bronchoscopist uses an appropriate technique to obtain the fluid, (b) the differential cell count is performed according to good clinical laboratory practice, by experienced personnel, and (c) cell count and evaluation is interpreted by an expert pathologist in ILD [6–8]. BAL technique through the fiber-optic bronchoscope is not difficult to perform but it could reach best results if certain advices are followed [10–12]. To retrieve alveolar cells or cells from distal airspaces, a sufficient amount of isotonic saline should be instilled [12]. Proximal large airway secretions contamination should be avoided by maintaining the distal end of the bronchoscope in a wedged position in a segmental or subsegmental bronchus throughout the period of time required for the instillation and retrieval of saline aliquots [12]. Furthermore, aliquots should be aspirated immediately once the entire aliquot volume has been instilled. Many different BAL protocols have been published and consist of multiple aliquots: five or six aliquots of 20 mL each, three of 50 mL, or four of 60 mL [12, 13]. The first aliquot frequently represents bronchial airway cells and secretions, so it is recommended to keep it separate and just use it for microbiological analysis. The other aliquots should be pooled and used for cellular analysis [12, 13].

The right middle lobe and lingula of the left upper lobe have traditionally been used for lavage since they are easily accessible areas and allow good return of BAL fluid [10]. Currently, patients with ILD are routinely evaluated with chest HRCT images that are used to target areas of the lung that may be more representative of the disease process (ground-glass attenuation, prominent nodularity, or fine reticulation) and that could increase the possibility to obtain relevant information (abnormal areas located proximal and peribronchial) [6].

If possible, the percentage of BAL fluid that is retrieved should be ≥30% of the instilled volume for a reliable cellular analysis [13]. An accurate cell count and evaluation of BAL requires examination of at least more than 300 nucleated cells [6]. The presence of squamous epithelial cells suggests that oropharyngeal secretions have contaminated the BAL fluid. More than 5% of squamous or bronchial epithelial cells mean that the BAL sample is unsuitable for cell analysis. It is of key importance that the technicians handling the samples and analyzing the BAL slide preparations and performing differential counts are adequately trained in proper identification of BAL cells [6]. Afterward, expert pulmonologists in ILD, familiar with BAL cell patterns, should interpret the BAL analysis results [8, 9].

BAL fluid obtained from healthy, never-smoking individuals contains a majority of alveolar macrophages (80–95%), some lymphocytes (5–12%), and very few neutrophils (<5%) or eosinophils (<1%) [4]. BAL cell count from smokers has a significantly increased total BAL cell amount, but the BAL differential cell count is similar than never smokers or ex-smokers, except for a lower percentage of lymphocytes [4, 14]. Age can modify the total and differential BAL cell account. It seems that elderly subjects present more lymphocytes and neutrophils in their differential cell count and that the volume of retrieved fluid declines with advanced age [15]. However, a volume of instilled saline that ranges from 100 to 250 mL appears to give similar cell differentials in individual patients with ILD [12]. When a bacterial infection is suspected during the study of diffuse lung infiltrates or coexists with noninfectious ILD, the first non-centrifuged aliquot of BAL should be examined for quantitative bacterial culture, including mycobacterial and fungal screening. If viral infection or intracellular bacteria (*Pneumocystis jiroveci*) are suspected, centrifuged BAL fluid enhances their detection through stains or viral nucleic acid probes [10].

Table 31.1 BAL findings are important for the diagnosis of different interstitial lung diseases

Diagnostic	Bronchoalveolar lavage finding
Milky BAL fluid, PAS+	Pulmonary alveolar proteinosis
Bloody fluid	Diffuse alveolar hemorrhage
Eosinophils ≥25	Eosinophilic pneumonia
Lymphocytes ≥70%	Lymphoid interstitial pneumonia, nodular lymphoid hyperplasia, lymphoma
CD1a+ cells >4%	Pulmonary Langerhans cell histiocytosis
CD4/CD8 T-cell ratio >3.5%	Sarcoidosis

ILD Cell Patterns and Diagnosis from BAL

A confident BAL cell evaluation, including differential cell count and other macro- or microscopic characteristics, the combination with clinical and imaging data, provides relevant information that contributes significantly to the diagnosis of specific ILD (Table 31.1) [1, 5, 16–18]. Furthermore, cytopathological examination may rule out other causes of parenchymal lung diseases with a similar radiological pattern such as malignancies (bronchoalveolar and lymphangitic carcinoma) or infection (*P. jiroveci*) [19]. In the appropriate clinical and radiological setting, certain gross and cellular findings in BAL may help in the differential diagnosis for a specific ILD. Recent data suggest that predictive value of BAL for ILD diagnosis is very useful for some entities such as sarcoidosis (common and with peribronchial affectation), in contrast to rare forms of ILD or common forms that predominantly affect subpleural space (such as idiopathic pulmonary fibrosis—IPF) [20].

BAL macroscopic appearance is very important. Retrieved BAL fluid that has milky or light brown appearance, with protein content that settles to the bottom of its container, clearly suggests pulmonary alveolar proteinosis (PAP) [21]. The diagnosis requires the confirmation through the positively staining with Schiff periodic acid (PAS+). In this case, whole-lung lavage is considered the treatment for PAP, although there is no scientific evidence that supports the best protocol to perform it. On the other hand, a grossly bloody lavage fluid is suggestive of diffuse alveolar hemorrhage (DAH) when it increases in the sequentially retrieved BAL fluid aliquots [20]. Furthermore, alveolar macrophages can stain positively for hemosiderin if the BAL is performed 24–48 h after the onset of hemorrhage.

BAL lymphocytosis can be found in cryptogenic organizing pneumonia (COP), cellular nonspecific interstitial pneumonia (NSIP), hypersensitivity pneumonitis (HP), sarcoidosis, drug toxicity, and lymphoid interstitial pneumonia (LIP) [20]. When mast cells or plasma cells are also increased, the diagnosis of HP is more probable, although mast cells can be observed in sarcoidosis, drug reactions, and ILD associated with collagen vascular disease or COP [20]. A percentage of eosinophils higher than 25% is usually associated with eosinophilic lung disease, mainly acute eosinophilic pneumonia [22]. Neutrophil predominance is usually due to infection or acute lung injury, although some IPF patients also present increased neutrophilic count, but to a lesser degree.

Some morphological changes in alveolar macrophages are also important: cytoplasmic inclusions are suggestive of viral infection, vacuolated cytoplasm with positive staining for fat can be observed in chronic aspiration pneumonitis, asbestos bodies in asbestos disease, dust particles in other pneumoconiosis, and phagocyted red blood cells in DAH [20].

BAL differential cell count utility in a patient with ILD that presents a usual interstitial pneumonia (UIP) pattern in the thoracic HRCT is limited. It mainly helps identifying other non-IPF entities that can also present the same radiological findings. An increased lymphocyte cell count in BAL would suggest the possibility of chronic HP, fibrotic NSIP, or other diagnoses associated with BAL lymphocytosis [2, 3, 23, 24]. Therefore, no fiber-optic bronchoscopy is required for IPF diagnosis. However, if clinical or epidemiological data suggest other UIP non-IPF, BAL could help in the differential diagnosis and it may help to identify some chronic HP [23, 24].

Flow cytometric analysis can improve the performance of BAL in some instances, mainly when the ILD differential diagnosis includes sarcoidosis, pulmonary Langerhans cells histiocytosis, and lymphoid malignancy [1, 20, 25]. However, due to the high cost of this procedure, flow cytometry is only used for the evaluation of CD4+/CD8+ cell ratio [20].

Alterations in BAL lymphocyte subsets have been widely examined, especially for sarcoidosis [1, 26]. Conventionally, a high CD4+/CD8+ T-lymphocyte ratio associated with BAL lymphocytosis is suggestive of sarcoidosis. However, elderly subjects can also present elevated CD4+/CD8+ ratio, so age is a variable to consider for appropriate interpretation [16]. Recent data have demonstrated that the presence of a CD4+/CD8+ ratio of ≥3.5 is relatively specific for sarcoidosis [20, 26]. However, the sensitivity of this ratio is low since many patients do not have an elevated ratio or may even have a low one [20]. On the other hand, a decreased CD4+/CD8+ ratio has been observed in HP, drug toxicity, COP, and eosinophilic diseases [4, 20]. Therefore, the efficacy of this ratio is low for other ILD different from sarcoidosis.

The diagnosis of pulmonary Langerhans cell histiocytosis can be supported by the presence of more than 4% CD1+ cells in BAL, which is more frequent in early stages of the disease [27]. These cells can be seen by means of immunohistochemistry or flow cytometry. Both techniques are also useful to identify monoclonal lymphocyte populations in the differential diagnosis of lymphoid diseases.

Finally, BAL cell analysis early in the study of an acute ILD such as acute interstitial pneumonia, eosinophilic pneumonia, DAH, acute HP, acute COP, drug toxicity, or acute exacerbation of an underlying ILD may help in their diagnosis [4, 20]. The study of BAL fluid can reveal infection or hemorrhage, large numbers of eosinophils (eosinophilic pneumonia), an increase of lymphocytes (acute HP and drug toxicity) or plasma cells (acute HP). Careful consideration on the respiratory and clinical status should be done before performing BAL, since worsening in those parameters is not unusual and has been reported after this procedure [3, 5].

Some centers use less amount of instillation while performing BAL in acute disease, with good results. A risk-benefit analysis is in order when dealing with this particular clinical situation [3].

Transbronchial Lung Biopsy

Some ILD are associated with typical histopathologic features that can be distinctive even in small lung biopsy specimens. Progressive ILD where the pathologic diagnosis is based on the recognition of different patterns and stages of the condition requires a surgical lung biopsy, whereas in most granulomatous pneumonias, transbronchial biopsies may be enough to achieve a confident diagnosis. For many other ILDs there is not enough evidence to make recommendations, but the possibility of bigger and better transbronchial samples using cryoprobes could open new possibilities.

The main utility of the TBLB in ILD is based on the possibility of making a specific diagnosis avoiding a surgical lung biopsy. Bronchoscopy can be done as an outpatient procedure, usually with minimal morbidity and mortality [28, 29].

TBLB is an appropriate first biopsy procedure in patients with bronchocentric interstitial lung disease, especially sarcoidosis, lymphangitis, infection, and the less frequent proteinosis, Wegener granulomatosis, Langerhans cell histiocytosis, and lymphangioleiomyomatosis (LAM) [30]. In other ILD, the combination of clinical, radiological, and BAL data can provide information for more specific diagnostic: cryptogenic organizing pneumonia, acute interstitial pneumonitis, eosinophilic pneumonia, hemosiderosis, and acute interstitial pneumonia [30–34].

We advise against performing TBLB in peripheric or subpleural lesions because the high risk of pneumothorax [4].

The efficacy of TBLB in the diagnosis of ILD depends in part on the differential diagnosis that is done after careful evaluation of clinical and radiological findings [30–34].

UIP cannot be accurately diagnosed by TBTB, since its histological pattern cannot be determined by this technique due to two main reasons: (a) the

"subpleural" space is quite impossible to be evaluated and (b) the size of the tissue sample obtained through TBLB is not enough to appreciate all the changes required to define this condition [30, 35]. A description of "interstitial pneumonitis and fibrosis" on a transbronchial lung biopsy is nonspecific and does not mean usual interstitial pneumonia [4].

In contrast, the flexible bronchoscope is the main source of diagnosis in sarcoidosis. A high degree of diagnostic accuracy is achieved if more than 4 samples are taken. The distribution of granulomas along pulmonary lymphatic routes is frequent, and also bronchial lesions can be sampled directly with the cupped forceps. It has been shown that TBLB samples can detect granulomas even when radiological findings fail to reveal lung parenchymal disease [36]. Some cystic interstitial lung diseases can also be diagnosed by TBLB. Langerhans cell histiocytosis is an airway-centered disease, and TBLB can identify the typical histological lesion. The performance of immunohistochemical stains for Langerhans cells (S100 protein and CD1a) is not required when histological findings are characteristic. On the other hand, in LAM, immunohistochemical staining may be useful even if definite lesions are not seen [32, 37]. Lymphangioleiomyomatosis lesions are eosinophilic on hematoxylin–eosin-stained sections, and HMB-45 immunohistochemical stains confirm the diagnosis.

Another determinant for the utility of TBLB in ILD is the technical procedure [30]. Biopsies from two different segments from the same lung can be obtained, but biopsy specimens from both lungs are contraindicated. After introducing the bronchoscope until a segmental bronchus, the forceps is distally introduced. The patient is asked to inhale and the forceps are opened. The patient is then asked to exhale and, at end-expiration, the forceps jaws are closed. If the patient experiences pain at this point, the forceps is opened and withdrawn because the only pain-sensitive structure in the area is the visceral pleura. Approximately four to six biopsies are the ideal number for pathologists, although this number of samples is not always possible due to many reasons. The main complication of TBLB is bleeding, which is the main limiting factor in obtaining more or larger biopsy samples; less frequent complications are pneumothorax, hypoxemia, or cardiac arrhythmias during the procedure. Although less common, pneumothorax may induce important deterioration in lung fibrosis. Fluoroscopic guidance is effectively used to reduce the rate of pneumothorax in TBLB.

TBLB is a safe procedure that does not require general anesthesia, with an overall mortality of 0.1% and can be performed as an outpatient procedure. Bleeding occurs to some degree in virtually all TBB procedures and in some cases can be substantial. Bleeding is a major concern because of the limited options available to manage excessive bleeding through the flexible bronchoscope. The suction channel is millimetric and the volume of blood that can be suctioned is limited and the blood can obscure the lens. Moreover, because the entire tracheobronchial tree is only about 150 mL in volume, a relatively small amount of blood can produce major problems with oxygenation [30]. TBLB is contraindicated in the presence of bleeding abnormalities. An international normalized ratio (INR) greater than 1.5 is an absolute contraindication. When oral anticoagulation therapy is taken, the treatment should be withheld for at least 4 days or until INR is <1.5 [30]. Fresh-frozen plasma can be administered to reverse oral anticoagulant therapy more quickly. TBLB is also contraindicated if the platelet count is less than 50,000/μL. The platelet count can improve quickly with platelet transfusions prior to the procedure. There are insufficient data on antiplatelet agents such as clopidogrel, but some bronchoscopists require withholding the treatment at least 1 week before the procedure. Finally, arterial pulmonary hypertension, which is quite usual in advanced stages of some ILD, may increase the risk of fatal bleeding.

Functional respiratory test and oxygen saturation should be evaluated prior a TBLB, since it is not recommended in severe hypoxemia, DLCO <30% or FVC <50% [3]. There are some contraindications inherent to fiber-optic endoscopic procedure such as uncontrolled cardiac arrhythmias, unstable angina, or high intracranial pressure. There is few data about TBLB performed in patients on mechanical ventilation, but it is known that there is a higher risk for pneumothorax [30].

Future Directions

The pathogenesis of different ILDs has been better understood thanks to continuous research on BAL samples [38–43]. Recently, it has been known that gene and protein expression patterns could identify key molecules involved in different ILDs [38–43]. These specific protein findings could provide relevant information for clinical diagnosis of ILDs and also target for effective therapies. Protein synthesis is determined by genetic and metabolic factors that may be the clue to some ILD development. Different technologies such as DNA and protein microarrays are useful to identify gene and protein expression patterns. The improvement in the world of genomic–proteomic approach may increase the utility of BAL for ILD diagnosis, management, monitoring disease activity, and assessing the effects of therapeutic interventions [44]. Recent investigations based on protein profile examination in BAL have demonstrated differences between IPF and other fibrotic lung diseases such as HP or fibrosis associated to connective tissue disease or other ILDs such as sarcoidosis [42].

Technical advances may also improve the utility of TBLB. The main limitation of TBLB using regular forceps is the small sample size. Recently, a new system for obtaining samples through fiber optic bronchoscopy has been developed: the cryoprobe (Figs. 31.1, 31.2, and 31.3). It is a device with a distal fast frozen probe that removes tissue samples. This new technique was initially used for the diagnosis and treatment of lung cancer, but during the last years, it has been found to be a safe method to study ILD [45–48]. Bleeding, usually mild, and pneumothorax represent the most important potential complications [45, 46]. It allows the evaluation of larger-sized samples, less artifacts, and better-preserved architecture than the samples taken by forceps, increasing the diagnostic yield [45–47] (Fig. 31.4). Clinical studies are ongoing to validate the usefulness of this new tool for ILD diagnosis. Many case reports have shown that it could be a valuable and safe method in some ILD cases with respiratory failure.

Fig. 31.1 ErbeKrio (ERBE Elektromedizin, Tübingen, Germany) equipment for cryotherapy

Summary and Recommendations

The number of recognizable cyto-histopathologic reaction patterns in ILDs is limited, and their morphological specificity in the diagnosis of ILDs is variable.

BAL should be considered in all patients with suspected infection, malignancy, and some ILDs in which it may be diagnostic. The utility of BAL in ILD diagnosis depends on different factors: expertise in obtaining, analyzing, and interpreting the results are the main ones. When diagnosis is uncertain after clinical assessment and HRCT scanning, typical BAL cellular profiles may provide important clues in some ILD such as sarcoidosis or HP. However, BAL is not a diagnostic tool in patients with clinical features and HRCT pattern typical of IPF. In this situation, BAL mainly helps to support other entities with similar presentation, such as HP or NSIP.

Some biopsy specimens may provide specific clues that are diagnostic of the underlying disease, whereas others reveal only nonspecific abnormalities. The transbronchial biopsy is a powerful tool for diagnosis of

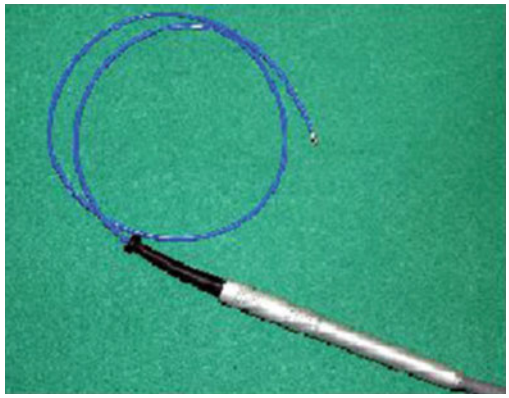

Fig. 31.2 Cryoprobe

Fig. 31.3 Defrozen and frozen cryoprobe

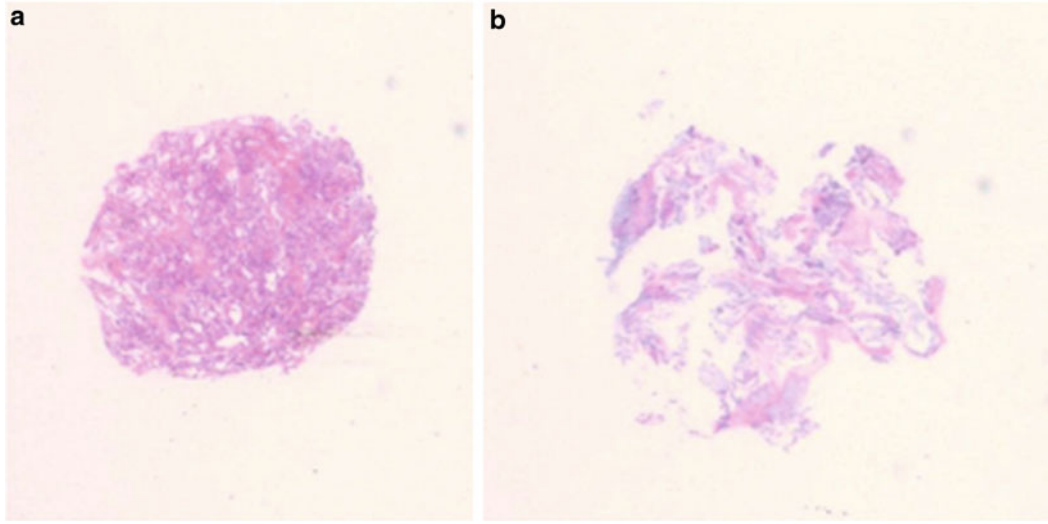

Fig. 31.4 Transbronchial lung biopsy using a cryoprobe allows the histological evaluation of bigger samples, with less artifacts, and better-preserved architecture (**a**) than samples taken by conventional forceps (**b**)

specific ILD when matched with appropriate expectations on the part of clinicians, radiologist, and pathologists.

HCTR images are essential for choosing the best place to biopsy and to help in the final diagnosis. TBLB is the initial procedure of choice in those patients in which small samples may be diagnostic, particularly if the disease has a tendency for bronchocentric involvement, and, when possible, BAL and TBLB should be performed before the initiation of any treatment. Conventional TBLB is not recommended in IPF or other ILD with UIP radiological pattern.

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Endoscopic Foreign Body Removal 32

Karen L. Swanson

Introduction and Definition of the Procedure

Aspiration of a tracheobronchial foreign body (TFB) is a fairly common emergency occurring more frequently in children than adults. In 2001, an estimated 17,537 children aged ≤14 years were treated in emergency departments for choking-related episodes [1]. One hundred sixty of these children died due to airway obstruction. A missed or delayed diagnosis of a TFB can cause additional respiratory problems including chronic wheezing that may mimic asthma, chronic cough, and recurrent pneumonia. A delay in diagnosis can also result in airway edema and granulation tissue around the TFB creating difficulty in extraction.

Bronchoscopy is a safe procedure allowing full inspection of the airway and visualization of the degree of TFB obstruction. Traditionally, the rigid bronchoscope has been the equipment of choice in the extraction of TFB due to a wide variety of instruments and control of the airway. More recent experience and advances in flexible bronchoscopy instruments, however, have shown that TFB can be safely and successfully removed with flexible bronchoscopy. A team approach to the extraction with anticipation of potential problems and solutions is essential for success. Surgical removal is rarely necessary.

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Historical Perspective

The first reported TFB extraction was by Killian in 1897 [2]. A farmer from the Black Forest in Germany was referred to Dr. Killian after swallowing a pork bone with symptoms of severe cough, dyspnea, and hemoptysis. Using a Kirstein laryngoscope, Killian was able to identify a solid object in the right main stem bronchus. His initial reaction was to perform a tracheostomy; however, not being a surgeon, he was not permitted to do the operation. After consultation with a laryngologist, Killian removed the foreign body (pork bone) using a Mikulicz–Rosenheim esophagoscope under local cocaine anesthesia.

In 1898, Coolidge performed the first successful bronchoscopy in the United States by extracting a piece of a tracheal cannula. In 1902, a light carrier was introduced into the esophagoscope by Max Tinhorn [3]. Prior to this, all illumination was provided externally. In the early 1900s, Chevalier Jackson further modified the instrumentation and techniques used to remove TFB [4, 5]. His landmark chapter in the book "Peroral Endoscopy and Laryngeal Surgery" detailed a surgeon's perspective on upper airway endoscopy describing different patient positions depending on the procedural indication in order to facilitate the procedure [6]. He pioneered the basic diagnostic

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and therapeutic principles used to evaluate and treat patients with TFB aspiration.

Edwin Broyles introduced magnification systems in the 1940s and developed further optical improvements with the application of fiber-optic illuminators in the 1960s [7]. By the 1970s, the first flexible fiber bronchoscope was introduced by Shigeta Ikeda leading to a new generation of instruments available in the evaluation and management of aspirated TFB.

Evidence-Based Review

Clinical Presentation and Evaluation

TFB aspiration is more common in children than adults likely related to developing dentition and hand-to-mouth curiosity. Symptoms vary depending on the size and location of the obstruction. If the TFB partially obstructs the larynx, for example, there will be evidence of significant respiratory distress and stridor. If a smaller TFB partially obstructs the distal bronchus intermedius, there may only be cough.

In adults presentation is variable and TFB aspiration may mimic other lung diseases including chronic obstructive pulmonary disease, asthma, or obstructive pneumonia. Baharloo and colleagues reported a 20-year experience comparing the presentation and management of TFB aspiration in both children and adults (84 children, 28 adults) [8]. They defined children as being up to 8 years of age and found the distribution of symptoms to be similar between the two age groups. Specifically, the most frequent symptom was sudden onset of choking and intractable cough with or without vomiting (49%) described as the "penetration syndrome." Other presenting symptoms included cough, fever, breathlessness, and wheezing. Only two patients, both of whom were in the adult group, were asymptomatic.

In a series of over 500 children (≤16 years), Oguzkaya et al. reported cough (83%) to be the most frequent presenting symptom [9]. Cyanosis was seen in 25%, dyspnea in 25%, unresolved pulmonary infection in 16%, wheezing in 11%, and stridor in 4%. Findings on physical examination included decreased breath sounds in 61%, tachypnea in 53%, and intercostal and/or subcostal retractions in 20%. Fifteen percent of their patients had a normal physical examination.

In the adult population, Limper and Prakash reported 60 patients with TFB aspiration [10]. Cough again was the most frequent presenting symptom in 45 of 48 adults followed by fever, hemoptysis, dyspnea, and chest pain. Only one patient was asymptomatic. There was a median of 10 days before bronchoscopy (ranged from 1 h to 13 years) following the onset of symptoms.

When witnessed, the diagnosis of TFB aspiration is usually made promptly regardless of whether the event occurs in an adult or a child. In a retrospective review of 155 children with bronchoscopy-proven TFB aspiration, Burton et al. found that 81% of cases were diagnosed within the first 7 days, 65% within the first 3 days [11]. Metrangolo and colleagues reported that the presence of a choking crisis is one of the most accurate indicators of TFB aspiration with a sensitivity of 96% and specificity of 76% [12].

Standard chest roentgenogram is often performed in patients with suspected TFB aspiration. Radiopaque foreign bodies can be seen on a plain film although most TFBs are radiolucent (Figs. 32.1 and 32.2). A complete obstruction can cause atelectasis, recurrent pneumonia, or bronchiectasis. An incomplete obstruction can function like a ball valve and cause hyperexpansion of the lung during expiration resulting in unilateral hyperinflation (Fig. 32.3). Limper and Prakash reported the chest X-ray to be useful in 72% of adult cases [10]. Abnormalities described included localization of metallic or radiopaque TFB, volume loss or atelectasis, and air trapping with mediastinal shift on post-expiratory films. In the large series by Oguzkaya, radiographic findings included atelectasis in 35%, hyperinflation in 27%, normal roentgenogram in 14%, and pulmonary infiltrates in 11% [9]. A radiopaque foreign body was seen in 13% of patients.

Silva et al. studied the utility of conventional roentgenograms in the diagnosis and management of children with suspected TFB [13]. Their hypothesis was that radiographic images should not alter the decision for intervention in patients

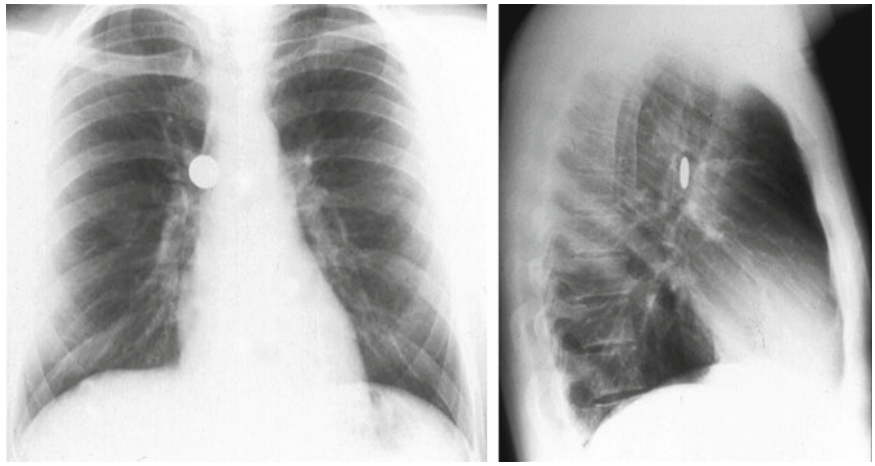

Fig. 32.1 Radiopaque foreign body (*coin*) seen on a posteroanterior chest roentgenogram

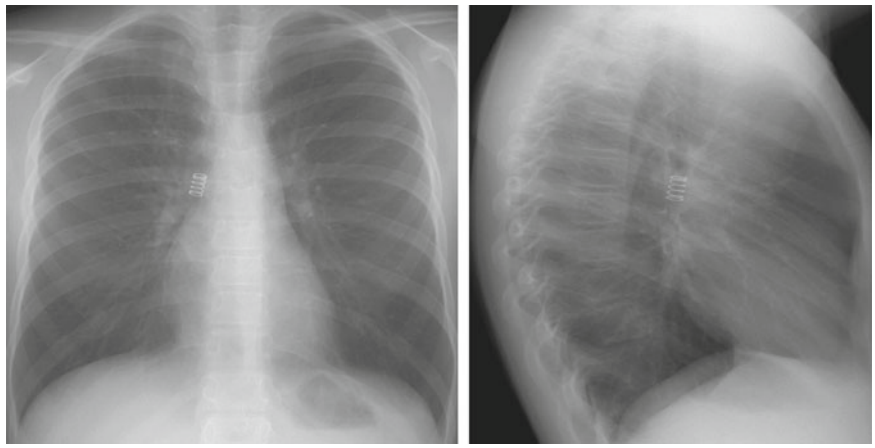

Fig. 32.2 Radiopaque foreign body (*spring*) seen on a posteroanterior chest roentgenogram

with a suspicious history and appropriate findings on physical examination. They reviewed 93 cases of suspected TFB aspiration with radiographic imaging prior to operative intervention. A total of 146 radiographic studies were performed in the 93 patients including chest radiographs in 88, inspiratory and expiratory chest radiographs in 15, lateral chest decubitus films in 7, fluoroscopic chest imaging in 22, and cervical airway films in 14. The sensitivity and specificity of the imaging studies in identifying the presence of a TFB were 73% and 45%, respectively. They concluded that radiography can be helpful in cases without a suspicious history and physical examination. If the clinical suspicion for TFB aspiration is high, however, the routine use of radiography may not be efficient or cost-effective.

Virtual tracheobronchoscopy is now available with the use of chest computed tomography with 3D reconstruction which may be helpful in cases where TFB aspiration is not certain, potentially avoiding the anesthesia risks of bronchoscopy [14]. Advantages of chest CT scanning include the lack of anesthesia, the rapid, noninvasive nature of the test, and its high sensitivity [14–16].

Hughes et al. retrospectively reviewed records of 234 cases of TFB removal in children at Johns

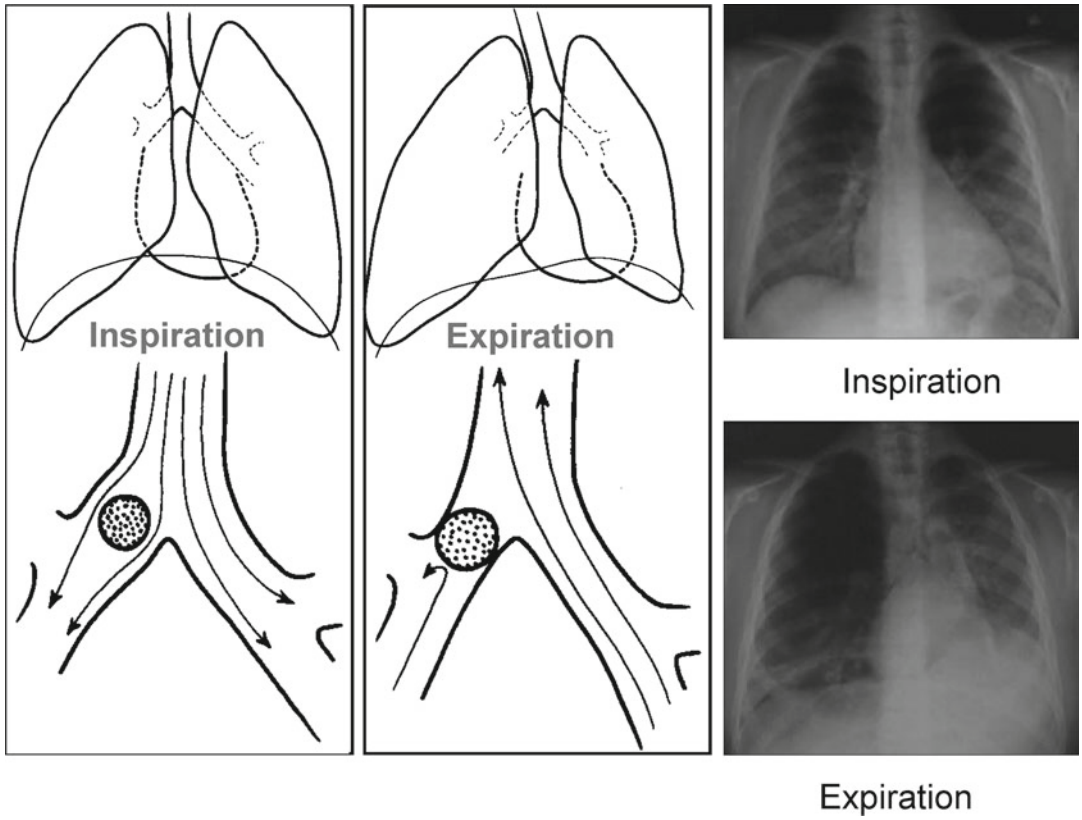

Fig. 32.3 "Check valve" mechanism whereby airflow passes by the foreign body on inspiration but then is completely obstructed on expiration leading to hyperinflation of the obstructed side on chest X-ray

Hopkins between 1939 and 1991 [17]. Seventy-eight percent of TFB occurred in children less than 3 years of age. The male-to-female ratio was 1.7:1. Peanuts were removed in 39% and vegetable material accounted for 60% of all TFBs. Fifty percent of TFBs were located on the right and 32% were on the left.

The diagnosis of TFB aspiration in adults requires a high index of clinical suspicion. In contrast to pediatric patients, the possibility of TFB is usually not suspected in adults unless the patient volunteers the information. Approximately half of the episodes are either not witnessed or mentioned by patients. Not infrequently, diagnostic bronchoscopy is performed for evaluation of recurrent or non-resolving respiratory symptoms or an abnormal chest radiograph. In such instances, TFB is not a consideration until it is visualized at bronchoscopy.

Indications and Contraindications

One major indication for bronchoscopic inspection of the airways includes suspicion for TFB aspiration. This is true for both children and adults and especially in the setting of a witnessed choking event. Other potential indications for bronchoscopy include recurrent pneumonia, refractory asthma, abnormal imaging, and chronic cough. There are relatively few contraindications to bronchoscopy especially in the setting of TFB aspiration. These would include lack of appropriate personnel to safely perform the procedure, inadequate airway experience, and the lack of necessary backup equipment or personnel in the event of complications.

The most common TFBs aspirated by children are nuts or other organic materials [9, 12, 17]. Peanuts are the most common in children seen in

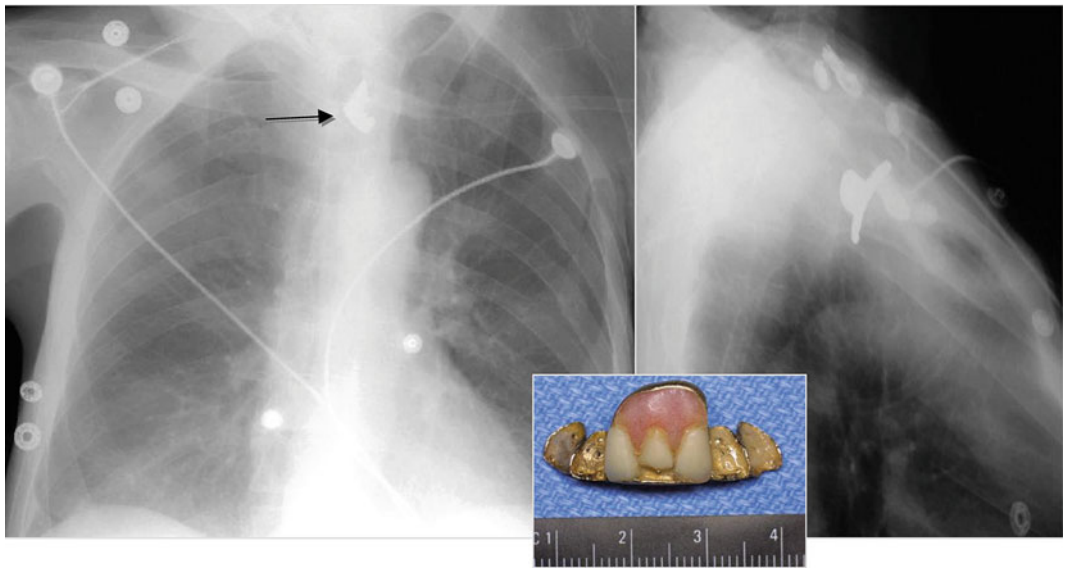

Fig. 32.4 Dental appliance that had been aspirated partially obstructing the trachea removed with rigid bronchoscopy under general anesthesia

38% in one series and 34% in another [11, 18]. Organic objects such as nuts or dry vegetable material have the potential to cause significant mucosal reaction and may swell by absorbing water. These objects should be removed promptly. Aspirated pills including iron tablets can cause long-term damage to the airway, and rapid inspection is extremely important. Similar caustic objects like batteries require immediate inspection as well. Once TFB aspiration is suspected, experienced clinicians with the skills necessary to manage the airway safely should be consulted.

In adults, dental and medical appliances tend to occur as TFB more frequently than food particles [10, 19]. Factors that predispose adults to TFB aspiration include dental and medical procedures under conscious sedation, primary neurologic disorders, traumatic loss of consciousness, and intoxication from drug or alcohol abuse.

Necessary Equipment

An array of both flexible and rigid bronchoscopic equipment is necessary when approaching bronchoscopy for potential TFB extraction. In general, a standard adult flexible bronchoscope should be used to inspect the entire tracheobronchial tree as 3–6% of patients may have bilateral TFB [20], and reduces the potential trauma to the larynx that may occur with the rigid tracheoscope or bronchoscope. The adult flexible bronchoscope can be used in children if the airway is secured with the use of a laryngeal mask airway rather than an endotracheal tube. A general rule of thumb is that the inner diameter of the endotracheal tube should equal the outer diameter of the bronchoscope +0.5. Even with these measurements, it can be difficult to ventilate the patient given the resistance generated. The flexible bronchoscope is also an important tool used in the extraction of TFB. A pediatric or ultrathin bronchoscope might also be needed to visualize subsegmental bronchi.

The rigid bronchoscope has been the primary tool for removal of TFB since Chevalier Jackson pioneered its use and developed many of the necessary tools used in the extraction of specific aspirated objects. Examples of these accessory tools include the peanut forceps used to remove peanuts and the straight pin remover used to remove hairpins. Young women would use these pins to hold their hair and, while fixing their hair, hold the pins in their mouth resulting in aspiration of the pins. Figure 32.4 illustrates a dental

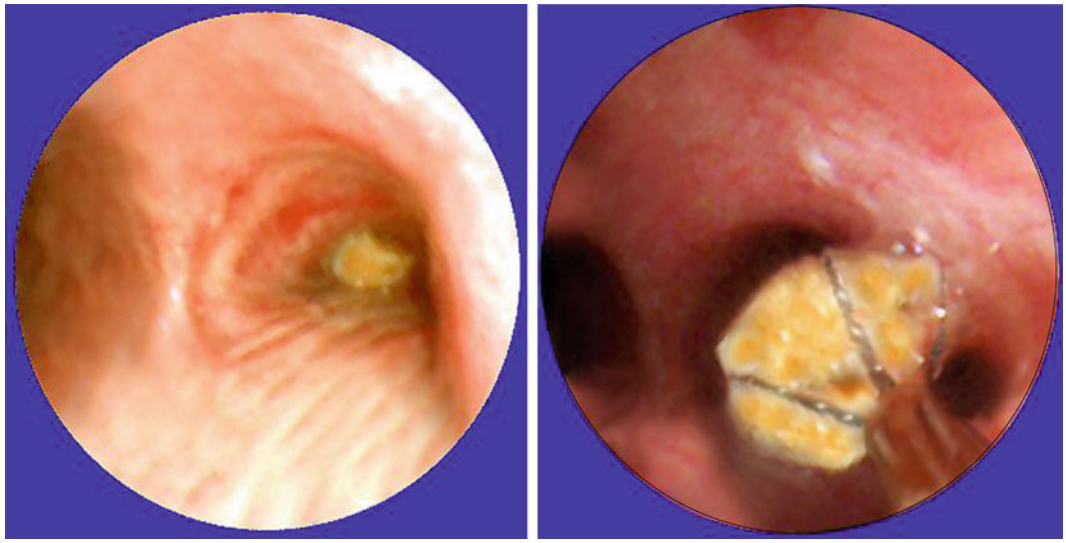

Fig. 32.5 Use of a ureteral stone extractor basket through a flexible bronchoscope to extract a piece of vegetable matter

appliance that was aspirated by a patient resulting in partial occlusion of the trachea. Given the location and the large size of the object, this was removed using rigid bronchoscopy under general anesthesia.

Ancillary instruments used for TFB extraction include the ureteral stone extractor basket, alligator forceps, biopsy forceps, Fogarty balloon catheter, rigid biopsy alligator and cupped forceps, YAG laser contact tip, cryotherapy probe, and suction. Figure 32.5 illustrates the use of a ureteral stone extractor basket through a flexible bronchoscope to extract a piece of vegetable matter.

Martinot and colleagues reported a prospective study to determine the complications of flexible and rigid bronchoscopy [21]. They also investigated the value of using an algorithm combining both flexible and rigid bronchoscopies. Patients with clear evidence of TFB aspiration from history and radiographic findings were immediately managed with rigid bronchoscopy. If the evidence was not convincing, they examined with a flexible bronchoscope first. Eighty-four children were evaluated for suspected TFB aspiration during the study. One presented in cardiopulmonary arrest due to airway occlusion from grapes and was excluded from their analysis. Twenty-eight children went directly to rigid bronchoscopy. Twenty-three had a TFB (negative first rigid bronchoscope 18%). Fifty-five children had flexible bronchoscopy performed as a first step. Seventeen of these had a TFB that was removed then by rigid bronchoscopy. These authors concluded that the flexible bronchoscope was useful as a diagnostic aid in patients without symptoms or radiographic signs of a retained TFB.

Procedural Description

The approach taken by the endoscopist depends to some degree on the suspected object that has been aspirated and the age of the patient. Reports show that the rigid bronchoscope remains the primary instrument for removal of TFB. This is particularly true for the series that report experiences of TFB removal in children. Oguzkaya et al. reported their 10-year experience in 548 patients [9]. The average age was 5.5 years (2 months to 16 years). The TFB localized to the right bronchial tree in 312 (57%), the left bronchial tree in 126 (23%), and in the trachea in 62 (11%). There were 48 cases in which no TFB was found. Twenty-five cases presented with acute respiratory distress and were treated immediately. All patients were managed with rigid bronchoscopy

under general anesthesia. Vegetable matter was the most common aspirated TFB. There was a high incidence of TFB aspiration in children over twelve with "beaded needles" being the most common. These needles are held between the lips while positioning a head cover and are easy to aspirate with simple inspiratory maneuvers or with speaking. Six cases required mechanical ventilation and 4 died.

Black and colleagues reported their experience in 548 children with suspected TFB aspiration [18]. TFB was identified and removed in 440 (80%). The age range was 4 months to 18 years (mean 32.4 months). TFBs were found in the right bronchial tree in 49%, the left bronchial tree in 44%, and the trachea in 6%. All patients were managed with a rigid pediatric bronchoscope system with optical telescopes and grasping forceps. Postoperative complications occurred in 30 patients (5%), but there were no deaths. The complications included atelectasis, pneumonia, retained fragments that were coughed up, stridor, bronchospasm, laryngospasm, pneumomediastinum, and hemoptysis. One patient who had aspirated a straight pin required thoracotomy for removal, and another patient had a retained TFB that was unable to be extracted and was left in place without sequelae.

Zaytoun et al. evaluated 504 patients with TFB aspiration who all underwent extraction with rigid bronchoscopy under general anesthesia [22]. A history of choking followed by paroxysmal cough was elicited in 447 patients (89%). Complications occurred in 42 patients (8%). The authors divided the complications into three groups: intraoperative (7 patients), postoperative (26), and failure to retrieve the TFB by bronchoscopy (9). The intraoperative complications included rapid desaturation causing cardiac arrest in 4 patients, transient apnea, bradycardia, and pneumothorax. There were no deaths. The postoperative complications included pneumonia, laryngeal edema, stridor, and pneumothorax. Of the patients in whom endoscopy was unsuccessful, 5 underwent a tracheostomy, 2 a thoracotomy, and 5 a bronchotomy. The location of the TFB had no significant effect on the complication rate, nor did the length of time the TFB was in the airway.

In contrast to the standard flexible bronchoscope used in adults, the pediatric flexible bronchoscope (external diameter 3.6 mm) inserted through an endotracheal tube with a smaller diameter (required in children) may interfere with ventilation. The standard pediatric bronchoscope requires an endotracheal tube with a minimal internal diameter of 4.5 mm. Even with this combination, it becomes necessary to momentarily halt ventilation during instrumentation. Ventilation by hand with the use of an anesthesia bag may adequately overcome the added airway resistance caused by the bronchoscope in the endotracheal tube. To avoid the complication of ventilatory difficulty, an ultrathin bronchoscope (outer diameter of 2.2 mm) may be used. However, since the ultrathin bronchoscope does not have a suction or working channel, the basket or forceps should be passed alongside the bronchoscope to extract the TFB.

Jet ventilation may be helpful in these instances. Li et al. in a study on ventilator techniques in pediatric TFB found that patients with spontaneous breathing during the procedure had lower success rates for bronchoscope insertions, higher incidences of hypoxemia and perioperative adverse events, and longer operation times [23]. They speculated that this may be due to an inadequate depth of anesthesia making the airway more sensitive and reactive.

The flexible bronchoscope can also be used as the primary means of TFB extraction. Castro et al. reported six cases of pediatric patients with TFB that were successfully removed using a small-caliber flexible bronchoscope and an ultrathin flexible bronchoscope [24]. TFBs were extracted using ureteral forceps and baskets usually used in the removal of ureteral stones. The accessory tools were either passed through the working channel or alongside the bronchoscope through the endotracheal tube. The TFB was then grasped and pulled up to the endotracheal tube at which time the endotracheal tube, bronchoscope, and grasping instrument with foreign body were all removed en masse. They reported no complications. It is imperative to have rigid bronchoscopy equipment immediately available and to be skilled in its use if attempting to remove a TFB

with the flexible bronchoscope. The major, serious complication during extraction of a TFB with the flexible bronchoscope is the potential to lose the object in the subglottic area and cause life-threatening asphyxia. If this were to happen, the object should be pushed distally into one of the main stem bronchi to allow ventilation prior to attempting its removal.

Between 1994 and 2002, the Mayo Clinic bronchoscopy group's experience in pediatric TFB removal (patients less than 15 years of age) has shown that either the flexible bronchoscope with the use of an LMA or the ultrathin bronchoscope has been effective in the removal of TFB [25]. Thirty-seven TFBs were removed, 24 of which were with flexible bronchoscopy at the time of the publication. All attempts at extraction of TFB utilizing the flexible bronchoscope had been successful. Complications have included laryngeal edema and stridor requiring post-bronchoscopy treatment with steroids. None of these patients required intubation or mechanical ventilation. Rigid endoscopy equipment was readily available during these attempts, and all patients were examined under general anesthesia.

Swanson et al. evaluated Mayo Clinic's experience with TFB extraction in adults [26]. The flexible bronchoscope was the instrument initially used in 61 of the 65 patients (94%). TFBs were successfully removed in 54 of these 61 patients (89%). Flexible bronchoscopy was unsuccessful in 7 patients. In six of these, rigid bronchoscopy with general anesthesia successfully removed the TFBs. One patient required a thoracotomy for the removal of a nail embedded in the right lower lobe. Rigid bronchoscopy was the initial procedure performed in 4 patients and was successful in two. In the two patients where the rigid bronchoscope failed, the TFB was successfully removed by passing the flexible bronchoscope through the rigid bronchoscope. The second patient in whom the rigid bronchoscope failed had a sewing needle in the left lower lobe that was unable to be removed with either bronchoscopic procedure. Complications from bronchoscopy were minimal and included minor bleeding in three patients. Complications of TFB impaction consisted of granulation tissue in 18 (28%). The TFB was dropped in the trachea during extraction with the flexible bronchoscope in one patient requiring conversion and removal with the rigid bronchoscope. There were no episodes of airway compromise in any patient.

The flexible bronchoscope has several advantages over the rigid bronchoscope for extracting a TFB. First, the flexible bronchoscope is a relatively easy and safe procedure in experienced hands. Second is that the procedure can be performed with local anesthetic and conscious sedation avoiding the added cost, risk, and morbidity of general anesthesia and rigid bronchoscopy. Finally, the flexible bronchoscope is superior to the rigid bronchoscope in cases of distal TFBs, mechanically ventilated patients, or in the patient with a difficult airway such as retrognathia and cervical spine problems. It cannot be overemphasized that there is a role for both flexible and rigid bronchoscopy techniques in the extraction of TFB. Rodrigues et al. found that in TFB aspiration cases, 19% required a combination of techniques including rigid and flexible bronchoscopes, fluoroscopy, and suspension laryngoscopy [27].

The importance of a successful procedure relies on the team approach when caring for the patient. Lando and colleagues described a 7-year-old male with severe developmental delay who had aspirated a tooth [28]. Their initial approach in extraction using rigid bronchoscopy failed due to the distal nature of the TFB and using flexible bronchoscopy failed due to granulation tissue securing the tooth in a subsegmental right upper lobe bronchus. With a multidisciplinary approach, they decided to treat the patient with steroids and reattempt extraction 48 h later where they were successful. This case emphasizes the team collaboration comprised of pulmonologists, otorhinolaryngologists, anesthesiologists, and surgical technicians in the approach to TFB extraction.

The procedure should be initiated with a preprocedural pause and briefing with all members of the team present and participating. Decisions about the types of sedation (conscious sedation, general anesthesia) and control of the airway and ventilation (endotracheal tube, laryngeal mask airway, rigid tracheoscope) need to be discussed before the patient is sedated. All neces-

sary equipments should be readily available including flexible and rigid bronchoscopy instruments and anticipated ancillary tools like the ureteral stone basket or Fogarty balloon catheter. A multidisciplinary team approach involving pulmonologists, anesthetists, nurses, surgical technicians, and possibly laryngologists and thoracic surgeons is critical to the success of the procedure.

During the bronchoscopy, it is also essential to avoid pushing the TFB further distally into the airway. Once a TFB is wedged into a lower lobe bronchus from a larger airway, it can be quite challenging to retrieve. The Fogarty balloon catheter can be helpful when passed by the TFB, inflated distally, and then pulled more proximally. The ureteral stone basket is most effective when used in larger airways to allow full expansion of the basket. It is passed by the TFB in the closed position and then opened distally. The basket is then pulled up proximally in the open position and agitated to get the TFB into the basket. The assistant then closes the basket tightly, and the TFB is pulled up to the endotracheal tube where everything is then removed together. The patient should then be reexamined to ensure there are no other issues with the airway. A short course of corticosteroids may be given if there is significant mucosal edema; however, there is little published data on its efficacy.

Summary and Recommendations

Aspiration of TFB occurs more commonly in children; however, it also occurs in adults. The most common symptoms are choking followed by a protracted cough. Physical examination findings include fever, stridor, retractions, and decreased breath sounds but may be normal. Radiographic imaging can be helpful if the object aspirated is radiopaque or if there are signs of hyperexpansion on expiration. Negative imaging studies however do not exclude the presence of a TFB in the airway. The longer a foreign body resides in the airway, the more likely it is to migrate distally. When this occurs, symptoms of chronic cough and wheezing may mimic an asthma-like condition. Bronchoscopy is indicated in this situation to thoroughly evaluate the airway. If a TFB is present, extraction can be performed with either flexible or rigid bronchoscopy. If flexible bronchoscopy is attempted, it is imperative that the bronchoscopist be familiar with rigid bronchoscopy and to have the equipment immediately available should airway compromise occur. The procedure is generally safe and well-tolerated usually under general anesthesia. Surgery should be performed only as a last resort.

In summary, airway foreign bodies in children can be safely removed by flexible bronchoscopy with minimal complications. If an attempt at flexible bronchoscopic extraction of a TFB is to be made, it is crucial that personnel and equipment be available to immediately proceed with rigid bronchoscopic extraction of the TFB, should the flexible bronchoscopic effort fail. The cooperation and coordination of the entire team consisting of anesthetists, technicians, nurses, and bronchoscopists is important for both the safety of the patient and the success of the procedure. Facilities should be immediately available if the emergent need for tracheotomy or surgery arises. Following the extraction, a complete examination of the tracheobronchial tree should be performed to exclude other foreign bodies and/or abnormalities.

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Interventional Pulmonology in the Intensive Care Unit

33

Hector A. Defranchi and Sebastian Defranchi

Abbreviations

BF	Bronchofiberscope
BPF	Bronchopleural fistula
CAO	Central airway obstruction
DAC	Dynamic airway collapse
ECA	Expiratory collapse of airway
EDAC	Excessive dynamic airway collapse
ETT	Endotracheal tube
ICU	Intensive care unit
MV	Mechanical ventilation
PAL	Prolonged airway leak
RB	Rigid bronchoscope
RMB	Right mainstem bronchi
TBM	Tracheobronchomalacia
TM	Tracheomalacia
TT	Tracheostomy tube

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Introduction

It is already well known that the pulmonologist plays a very important role in the intensive care unit (ICU). More recently, the interventional pulmonologist has become very important in this area as well, where he/she is frequently requested to solve different situations, particularly those related to the airway and/or the pleura. Patients in the ICU are critically ill, and many of these procedures have to be performed at the bedside, to avoid the additional risks involved in transferring patients to the operating room.

The bronchoscopist usually is required to perform bronchoalveolar lavage (BAL) samples to help diagnosing a pulmonary infection or for transbronchial lung biopsy in a patient on mechanical ventilation (MV). Less frequently, a transbronchial needle aspiration is needed, or a patient with hemoptysis is evaluated. These procedures are almost exclusively diagnostic.

The most classic therapeutic intervention requested in the intensive care setting is the evaluation and treatment of persistent atelectasis. However, in the last few years, the role of the interventional pulmonologist in the ICU has broadened, and the number of procedures that the interventionists can perform has evolved. In this chapter, we will review different situations that can require assistance from the interventional pulmonology team. We will limit our discussion to airway-related problems.

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Central Airway Obstruction

Respiratory failure due to central airway obstruction (CAO) is more frequently recognized than in the past. Various disorders can cause CAO, and different degrees of airway obstruction can be seen. First of all, this entity needs to be suspected; second, it needs to be confirmed; and third, a therapeutic measure must be offered. We will limit our discussion to the adult population, since airway obstruction in children is very different, both in etiology and clinical presentation [1].

Causes of CAO

CAO can be located at any of the three different segments of the major airway (Table 33.1).

CAO can develop gradually (i.e., progressively growing malignant tumors) or acutely (i.e., respiratory infections, where secretions totally occlude an already compromised tracheal lumen) and can be caused by benign or malignant conditions located inside or outside the airway lumen (Table 33.2).

The severity of symptoms depends on the pressure drop along the stenosis, which is directly proportional to the flow speed and inversely proportional to the radius of the stenosis [26, 27]. Symptoms at rest appear when the stenosis occludes more than 70% of the airway lumen. Since flow speed is inversely proportional to the length of the stricture, the same degree of stenosis is more symptomatic when the length of the obstruction is shorter.

Table 33.1 Obstruction in the airway—location

Location	Types
Larynx	Supraglottic
	Glottic: anterior or posterior
	Subglottic
Trachea	From carina to vocal cords
Bronchi	Only important if affects both mainstem bronchi

Acute Central Airway Obstruction

Clinical Presentation

The usual clinical presentation is a patient admitted to the ICU in acute respiratory failure. Frequently patients have a history of progressive dyspnea, with or without a prior known condition (e.g., tracheal carcinoma), that suddenly worsen due to disease progression or to a new respiratory infection. The infection generates swelling of the already compromised mucosa triggering acute respiratory distress.

The main priority is to secure the airway through endotracheal intubation. Once the endotracheal tube (ETT) is in place and ventilation is assured, any required endoscopic intervention can be performed safely either in the ICU or the operating room.

We, as most of the authors, prefer the rigid bronchoscope (RB) to explore the airway in a patient with CAO. However, the flexible bronchoscope should also be available to help throughout the procedure.

In the event that the ETT cannot be progressed through the stenotic airway or if the patient cannot be intubated, RB should be immediately performed by a skilled bronchoscopist. In these severe situations, to obtain a secure airway is critical, and it should be done to save the patient's life.

RB serves two purposes:

1. Diagnostic: RB is the best method to identify the cause of obstruction.
2. Therapeutic: RB can be used to dilate or to resect an intrinsic airway mass and place an airway prosthesis to support the airway if necessary.

In some situations (stenosis located right below the subglottic segment), a tracheotomy is the preferable procedure to secure the airway.

Therapeutic Options to Relieve CAO

In order to decide which procedure is best to solve the acute CAO, the bronchoscopist has to

Table 33.2 Acute causes of CAO and their location in the airway

Location	Cause
Larynx	
Laryngeal edema	Anaphylactic reactions [2]
	Angiotensin-converting-enzyme inhibitors [3]
	Burns [4]
	Post-extubation [5]
	Epiglottitis [6]
Bilateral vocal cord palsy	Laryngeal dystonia
	Parkinson's disease [7]
	Shy-Drager [8]
	Laryngeal dyskinesia [9]
	Myasthenia gravis [10]
	Relapsing polychondritis [11]
	Rheumatoid arthritis [12]
	Foreign bodies [13]
	Recurrent nerve damage after thyroidectomy [14]
Trachea	
Extrinsic compression	Thyroid disease [15] • Benign intrathoracic or substernal goiter • Malignant tracheal ingrowth of thyroid carcinoma [14] • Tracheomalacia secondary to direct sustained compression produced by thyroid enlargement [16]
	Mediastinal bronchogenic cysts [17]
	Esophageal foreign body [18]
	Thymic cysts [19]
	Vascular causes • Arterial puncture [20] • Descendent aortic dissection [21] • Rupture of the aorta [22]
Intrinsic obstruction	Primary tumors • Squamous cell carcinoma [23] • Adenoid cyst (cylindroma) [24]
	Metastatic tumors [25]: breast, renal, colon
	Benign tracheal stenosis (including subglottic stenosis) • Post-tracheostomy • Post-endotracheal intubation • Idiopathic (rarely of acute presentation)

consider three important factors: bronchoscopic findings (location, extension, and degree of airway damage), equipment availability, and preference of the operator.

Bronchoscopic findings are assessed during inspection of the airway with the flexible or rigid bronchoscope. If pure extrinsic compression without damage of the airway mucosa is found, dilatation with the RB followed by stent placement is a good therapeutic option.

When the obstruction is caused by a mass compromising the airway lumen, bronchoscopic dilation is also an option, but removal either mechanical or with the aid of a coagulation instrument such as Nd-YAG laser, argon plasma coagulation, or electrocautery is preferred. After opening the airway, the need for a stent to help keeping it open has to be evaluated, and it is not always necessary.

In mixed lesions, where there is some intrinsic and extrinsic component, therapeutic options can be combined to open the airway.

Treatment modalities vary from center to center, and airway lesions can be very different from

patient to patient, so the choice of the best method for a given situation has to be taken case by case and according, as we said, to equipment availability and the experience of the endoscopist with each one of the techniques.

All interventional procedures involve a dedicated bronchoscopist and his/her trained team that includes an ICU nurse or scrub nurse and one assistant. Also, they are performed under general anesthesia, and an experienced anesthesiologist has to monitor the patient closely. When this procedure is done emergently in the ICU, an intensivist and a respiratory therapist are needed. All supporting personnel should be well trained and familiar with the procedure taking place.

Equipment Needed

All the following items are required to the procedure:

1. Equipment to perform rigid and flexible bronchoscopy (rigid tracheoscope, and different sizes of rigid tubes for trachea and bronchus, rigid lenses, and accessories such as alligator forceps). A large bore suction catheter is necessary to clear the field of secretions and blood. Hemorrhage, dense secretions, bulky tumors, difficult anatomy, and inflammation [28] can all be factors that complicate the intubation with the RB.
2. When electrocautery is to be applied, a high-frequency electric generator and insulated probes will be necessary. Usually, the monopolar mode is suitable for endoscopic application, and a grounded plate must be attached to the patient.
3. When laser is available, laser-specific equipment will be necessary (specific laser fibers with matching protective glasses and gloves).
4. More than one type of stent should be available, with their different deployment devices and accessories.
5. The procedure is usually performed under total intravenous anesthesia. Jet ventilation is used as ventilatory support and connected through a side port of the rigid bronchoscope.

Endoscopic Techniques

Endoscopic Dilatation

Mechanical dilatation is usually the best approach to offer as a first therapeutic measure. Dilatation is achieved with the rigid bronchoscope. In the patient with ventilatory failure and without a secure airway, sometimes a forceful dilatation is needed in order to solve the acute situation. However, it has to be avoided if not strictly necessary, and it should be performed by an experienced operator. Mucosal trauma has to be minimized since it is followed by disorganized healing and scarring. This leads to proliferation of fibrous tissue, and restenosis usually takes place [29].

In emergent situations, when the lesion is visualized, the scope is advanced through the stenosis, and the beveled end is pushed through the lesion rotating the rigid tube at the same time. Compression of the lesion with the rigid tube usually is sufficient to avoid bleeding. The bronchofiberscope (BF) is then passed through the rigid instrument, and a quick toilette and inspection are performed.

When the patient is stabilized and oxygenation is appropriate, the scope is withdrawn and an ETT is placed. The diameter of the ETT must be the biggest that can be passed through the stenosis. We have to bear in mind that if a flexible scope needs to be passed through the ETT, it has to have a minimum of 8 mm of internal diameter. To calculate the external diameter of the ET tube, 2–4 mm are added to its internal diameter.

Balloon dilatation is not a good option in emergent situations and is preferable in benign stenosis that involves the mainstem or the lobar bronchi [30]. It is usually performed with a mitral valve valvuloplasty balloon [31], esophageal balloons, or a Fogarty catheter.

Mechanical Removal

When endoscopic dilatation cannot be done or if it was not enough to open the airway, mechanical removal of the obstructing tissue may be attempted. It is recommended to flush some millimeters of diluted adrenalin before starting

mechanical debridement with forceps, to lower the risk of hemorrhage after removal. After that, the surface can be coagulated with laser, electrocautery, or argon plasma coagulation in order to prevent bleeding or to complete the resection (see advantages and disadvantages of each one in Table 33.3) [32].

Table 33.3 Advantages and disadvantages of the different methods of reopening airway [32]

Type of treatment	Results	Complications
Mechanical removal	Immediate but short duration of effects	Bleeding
Electrocautery	Immediate and superficial	Perforation, bleeding, fire, and electric shock
Laser	Immediate and in-depth action	Perforation, bleeding, and fire

Electrocautery–Laser Nd YAG–Argon Plasma Coagulation

A more detailed description for these procedures is presented in a dedicated chapter of this book.

Since electrocautery is available in our center, it is our instrument of choice. The probe is directly applied to the tissue that needs to be removed, always in coagulation mode.

The observed damage produced by cautery to the tissue has a very good correlation with the histological damage. This is very important and represents one of the main differences with laser therapy, where the immediate visualization does not correlate with histological damage, since laser acts much deeper (6 mm depth) than electrocautery whose action is superficial.

A ground plate has to be attached to the patient's back to avoid electric injury to both the patient and the endoscopist. If the plate is not used, electric current can travel directly to the operator if the RB is not insulated. The best way to avoid this event is to utilize bipolar probes through insulated BF [33].

Tips for Using Electrocautery

The electric current dissipates within the tissue, moving through it and generating heat that vaporizes the targeted lesion. When resistance is high, difficult in the passage of electricity is met. This situation occurs in dry tissues and in the presence of detritus and blood.

The generated heat reaching different targets is proportional to the square of the intensity. If the electric current is duplicated, the heat obtained will increase four times. Before augmenting the electric power of the cautery, other causes of failure to dissolve tissues must be ruled out [34]. Always have in mind that the presence of blood and detritus dissipate the electric current, and the desired effect will not be achieved in those circumstances unless removal of debris cleans the field.

There is a significant risk of catching fire when cautery is applied with high fraction of inspired oxygen (FiO_2 over 0.4). Therefore we recommend to keep FiO_2 at 21% (room air) while electrocautery is in use. A power setting of 50 W is sufficient for coagulation, achieving the desired effects and avoiding adverse events.

Stents (Prosthesis)

When obstruction is caused by pure extrinsic compression [12, 13, 15, 17–20], stent placement after dilation is literally the unique option.

The rigid bronchoscope is the best instrument to place an airway prosthesis. Selecting the best stent size can be very difficult in emergency situations [35]. Before placing the prosthesis, an appropriate lumen must be achieved, usually applying a quick dilatation maneuver with the rigid scope. When intrinsic obstruction is present, electrocautery or laser may be used to help resection. Stent diameter can be calculated based on the diameter of the scope that can overcome the stenosis. A tight fit is advisable to avoid migration. If the maneuver is successful, a second elec-

tive procedure can be performed after careful planning, for a most definite solution.

Stent type will depend on the preference of the operator and availability, but we recommend to use silicone stents [36–38]. Their main advantage in these situations is that they can be easily removed. However, in the presence of a malignant obstruction, a metallic prosthesis is also acceptable.

Having proper aspiration is of utmost importance during interventional procedures. Rigid plastic catheters, passed through the lateral ports of specially designed bronchoscopes, provide insufficient aspiration in these critical cases. We prefer the rigid metallic aspiration canula or the use of the BF through the rigid instrument. A faster and more efficient procedure can be favored by having the BF connected to its own vacuum port and a different power light source than the one utilized for the RB, ready for use at all times during the treatment.

Once a good lumen is obtained, an ETT tube is placed and the patient is connected to mechanical ventilation.

Murgu et al. [39] published their experience with bronchoscopic resection in patients admitted to the ICU in acute respiratory failure that required mechanical ventilation due to CAO for inoperable non-small cell lung cancer. After the bronchoscopic resection, 9 of 12 patients (75%) were immediately extubated. An additional patient was extubated 8 days after the procedure. The authors conclude that if these findings are confirmed in prospective and multicentric studies, the model of admission of these patients to the ICU must be reviewed.

Post-intubation or Post-tracheostomy Stenosis

Acute respiratory failure developing from tracheal stenosis requires a different approach than when the failure is progressive. It usually presents in the setting of an elective extubation during weaning from mechanical ventilation.

The permanence of the ETT in the larynx may produce ulcers in the posterior aspect of the vocal cords, followed by edema, granulation tissue, and scar formation [40]. Similarly, its permanence inside the trachea produces, in the early phase, mucosal lesion and ulceration followed by cartilage destruction, granulation tissue, and scar formation, leading to the formation of a stenotic area. In severe cases, tracheal rings are exposed, infection takes place, and they soften, fragment, and disintegrate, leading to a variety of tracheal lesions. Later, they may be reabsorbed, and the tracheal mechanical support is lost, resulting in collapse of the compromised segment [41] and, as we will discuss later, ultimately ending up in tracheomalacia.

To minimize the injury produced by the endotracheal tube cuff, high-volume–low-pressure cuffs have been replaced by low-pressure–high-volume ones. These low-pressure cuffs have a large residual volume prior to inflation. When the cuff is inflated and the operator feels a resistance, an important overexpansion of it may already exist [42]. High inflation pressures interfere with the submucosal vascularization of the trachea, causing ischemia and necrosis. Infected secretions above the cuff contribute to tracheal damage (that is why it is so important a careful subglottic aspiration). When pressure generated by the ETT cuff exceeds the mucosal capillary perfusion pressure, usually 20–30 mm Hg, tracheal injury occurs. It is very important to maintain a low pressure on the tracheal mucosa, so when a cuff pressure of 25 mm Hg is reached and air leak persists, it is advisable to intubate the trachea with a bigger tube instead of inflating the cuff over that pressure [43].

The usual clinical scenario is a patient weaned from MV that develops acute respiratory distress with stridor and other signs of upper airway obstruction and must be re intubated. After the emergency has been solved, the following inspection is advisable: the bronchoscopist, with the aid of an anesthesiologist if possible, introduces the BF through the ETT until reaching its distal end. Once in place, an assistant proceeds to slowly remove the ETT while the endoscopist is inspecting the airway as they go. Areas of malacia and other lesions may be observed. Careful must be taken not to overpass the vocal cords level with the BF, since it may be necessary to intubate again and that can be easily performed over the bronchoscope. It is also very important to make an inspection of

the airway proximal to the vocal cords. Once inspection through the ETT is completed, the BF can be introduced again via nasal route, while the patient is connected to mechanical ventilation. Most of the times no injury is found in the airway, and extubation fails for important edema of the supraglottic area. A plan to proceed can be outlined after finishing this evaluation.

When a stenotic area is found, dilatation, electrocautery, or laser may be necessary, alone or in combination. When the only finding is edema, a trial of steroids is advisable. More complex lesions require a planned procedure, taking into account the type and extension of the affected area.

One very common cause of tracheal stenosis is granuloma formation. They develop from persistent inflammation, and they do not compromise the tracheal wall. Weblike stenosis, in turn, represents a different form of stenosis developed from fibrous tissue that produces a subtotal stenosis, also sparing the tracheal wall. Bottleneck stenosis consists of a localized collapse of the tracheal wall less than 5 cm in length. Weblike and bottleneck are referred as simple stenosis.

Complex stenosis are large, affecting more than 5 cm in length or six tracheal rings or localized in more than one segment of the tracheobronchial tree. Usually, only the bottleneck and the complex type are responsible for severe obstructions. A detailed classification and therapeutic strategies of stenosis may be found in Dumon and Diaz Jimenez [44], and tracheal stenosis is also discussed elsewhere in this book.

If the stenosis is limited exclusively to the subglottic area, dilation is the procedure of choice since subglottic stents, in our experience, are not useful. Sometimes the obstruction is produced by pure tracheo or tracheobronchial malacia and in these cases a stent may be deployed. We will discuss this entity in the next section.

Tracheobronchomalacia

Tracheobronchomalacia (TBM) can be a cause of CAO in the ICU. The most usual clinical setting is a patient that is already extubated and develops signs and symptoms of acute upper airway obstruction and requires reintubation, and during endoscopic inspection, TBM is found.

TBM is a confusing term, of unclear meaning for healthcare professionals, where a variety of different pathologies have been included [45]. Briefly, we will refer to the correct utilization of these different terms.

TBM is an expiratory collapse of the central airway due to softening of the airway cartilage. The airway lumen at bronchoscopic examination acquires a saber sheath shape or the crescent-type shape. The first is produced by a collapse of the lateral walls of the trachea and the second one by the collapse of the anterior wall [46]. Tracheal cartilages are always compromised. When the anterior and lateral walls are involved, it is called circumferential type.

Expiratory collapse of the airway (ECA) refers to the collapse of some part of the tracheal wall. It is generally produced by the anterior bulging of the posterior membranous tracheal wall during expiration that decreases tracheal lumen. This is entirely due to the laxity of the tracheal posterior membranous wall, and cartilages are not damaged. In this specific case, the ECA is called dynamic collapse of the airway (DAC). It may be normal when the reduction of the lumen is less than 50% at forced expiration. TBM is also an ECA, but in this case the expiratory collapse is not produced by the laxity of the membranous wall of the trachea, but due to the softening of the tracheal cartilages [45, 46].

By consensus, when expiratory collapse is less than 50% of the tracheal lumen, it is considered normal. If it is 50% or higher, it is considered abnormal.

DAC is frequently found in COPD and asthma patients. Some authors refer to this normal expiratory collapse as DAC and apply the term excessive dynamic collapse of the airway (EDAC) only when the expiratory obstruction exceeds 50% of the airway lumen. We resume these terms in Table 33.4.

Upon bronchoscopic examination, the pathologic findings may be of pure TBM, pure EDAC, or both. Stent placement can be indicated, with or without previous dilatation. A tracheobronchial or a tracheal stent may be deployed depending on the location of the lesion. These entities are usually diagnosed after patients are

Table 33.4 Accurate meaning of the different terms for expiratory collapse of the airway

Term	Meaning	Normal or abnormal
Expiratory collapse of the airway (ECA)	Collapse of one or more tracheal wall during expiration	May be normal or not
Dynamic airway collapse (DAC)	Expiratory collapse of the posterior wall of the trachea due to laxity of the membranous wall	Abnormal if more than 50% (EECA) Normal if equal or LESS than 50%
Tracheobronchomalacia (TBM)	Expiratory collapse of the anterior or/and lateral walls of trachea and bronchi due to softening of cartilages	Abnormal
Tracheomalacia (TM)	Similar to TBM but compromises only trachea	Abnormal
Excessive expiratory collapse\(EECA) (is the abnormal DAC)	Expiratory collapse that exceeds 50% of the lumen	Abnormal

extubated since the ETT functions like a stent, precluding airway collapse.

If the patient has a tracheotomy in place, we prefer to use TRACOE tracheotomy tubes, which are available in different sizes and lengths. They have the advantage of producing a good sealing of the trachea, and migration is uncommon.

In cases of pure tracheal compromise, referred as tracheomalacia (TM) or EDAC limited to trachea, the distal tip of the tracheotomy tube needs to lie above the carina, in order to stent all the tracheal length. Appropriate placement can be assessed by BF.

In summary:

- TM, EDAC, or TBM in the ICU are generally caused by cartilage damage produced by ETT and tracheotomy tubes.
- Pure EDAC is seen especially in patients with comorbidities, such as COPD or asthma, whom might have some prior degrees of EAC.
- Bi-level or continuous positive airway pressure (noninvasive ventilation) may temporarily help in these situations acting as pneumatic stents [47].
- Metallic stents are not indicated since they cannot be removed.
- A definitive solution has to be planned by a multidisciplinary team, in a case-by-case basis. Surgery may be useful in well-selected cases [48].

In addition to bronchoscopy, there are other diagnostic procedures that can help to evaluate these patients, but they are difficult to apply in the ICU (e.g., paired inspiratory–expiratory dynamic computed tomography or cine magnetic resonance imaging) [49, 50].

Tracheostomy Bleeding

Another frequent consultation from the ICU is the evaluation of bleeding through a tracheostomy. Most of the times, bleeding is scant and represents mucosal injury produced by the tip of the tracheotomy tube, forceful aspirations, or tracheobronchitis and has no consequences.

It is very important to consider the timing of bleeding. When it takes place the first days after a tracheostomy, usually a surgical complication is responsible: poor hemostasis, injury to a small vessel, or misplacement of the tracheostomy tube.

When it occurs after the first week, the usual findings are ulcers resulting from tracheostomy tube movement, forceful aspirations, or tracheobronchitis secondary to infection.

However, when a sudden massive hemorrhage occurs, a tracheo-arterial fistula must be suspected [51].

This dangerous complication has a mortality rate near 90% and can present as an early or late complication (after more than 4 weeks). There is no role for the bronchoscopist here, because during this particular massive bleeding, no endoscopic procedure is useful.

Two different situations might lead to a fistula between the trachea and the innominate artery: the first one occurs when the surgical tracheostomy incision is performed in the lower trachea. That might occur in young people with good neck extension, when the sternal manubrium is used as the landmark and the tracheostomy is placed below the

4th tracheal ring. The recommendation is to choose the cricoid cartilage as the landmark in order to avoid this complication, since it is easier to count down the rings appropriately. The tracheotomy must be placed in the 2nd or 3rd; in rare cases, the 4th ring is needed. Placement below the 4th tracheal ring increases the risk of eroding the innominate artery, and this location should then be avoided.

When massive bleeding occurs and this complication is suspected, one should exert direct finger pressure through the ostomy, pointing downwards and against the back of the sternum as much as possible. The patient must be taken to the operating room and the injury repair through a partial sternotomy and suture.

The second situation occurs when an hyperinflated tracheostomy tube cuff erodes through the tracheal wall into the innominate artery. Since this point cannot be accessed through the neck, no finger compression will be possible at all. The bleeding might be controlled by hyperinflating the cuff to tamponade the bleeding site, while the patient is taken to the OR for repair [52]. This complication is avoided by limiting the cuff pressure to 20 mm Hg. As in the first case, there is no role for the bronchoscopist in this setting.

Massive Hemoptysis or Life-Threatening Hemoptysis

Although there are several definitions of massive hemoptysis that consider the amount of blood expectorated in 24 h (ranging from 100 to 1,000 mL), only the careful clinical evaluation at the bedside allows to judge how severe is the hemoptysis. More frequent etiologies are:

- Bronchiectasis.
- Active or residual tuberculosis.
- Bronchogenic carcinoma.
- Carcinoid tumor.
- Endobronchial metastatic tumor: metastatic renal cell carcinoma is a particularly bleeding tumor.
- Pulmonary aspergilloma.
- Idiopathic hemoptysis: no evident cause is found.

Signs of severe hemoptysis are fast bleeding, presence of comorbidities (COPD, ischemic heart disease, renal failure) [53], the presence of bright red blood (indicating arterial bleeding), hemoptysis that does not slow down, and impending airway compromise.

In a chest X-ray, an obvious cause of hemoptysis can be observed such as a cavitated tumor. In this case the patient must be placed in the lateral decubitus with the side of the lesion down, feet elevated, and headboard lowered. CT scan is even more useful to find pulmonary causes of hemoptysis.

It is of utmost importance to maintain a patent airway. If the patient is in respiratory distress, he/she will have to be sedated and intubated. Another option is to proceed directly, under general anesthesia, to a rigid bronchoscopy. We prefer the RB to assess the airway in these cases, because the BF can have a weak suction (compared to the rigid) and the visibility can be very poor because of clots and bubbles. Almost all the times, a careful inspection with the rigid bronchoscope identifies the origin of bleeding.

Once the site of bleeding has been identified, a cold saline solution (at 4°C) lavage [54] is initiated in the affected bronchus or segment. This can be done with the flexible bronchoscope introduced through the rigid one. We utilize aliquots of 30 mL, aspirating at intervals of 10–20 s. Sometimes large volumes are necessary to control the bleeding. If cold lavages are not successful and the affected bronchus has been identified, a bronchial blockage can be attempted.

The simplest way to perform a bronchial tamponade is by placing a Fogarty arterial embolectomy catheter (Fig. 33.1). They are available in different sizes. We prefer the 4 French, 80 cm in length. The balloon that is close to the tip has a diameter of 9 mm when inflated. Inflation can be performed with a tuberculin syringe, pushing 1.7 mL of gas or 0.75 mL of saline solution. Right placement can be assessed by direct visualization of the occluded bronchus. A modification was described by Gotlieb and Hillberg [55], inserting a 14 F rubber T drain between the FB and the hub of the Fogarty, introducing it through the T rubber, so lavage can be done at the same time while the balloon is inflated.

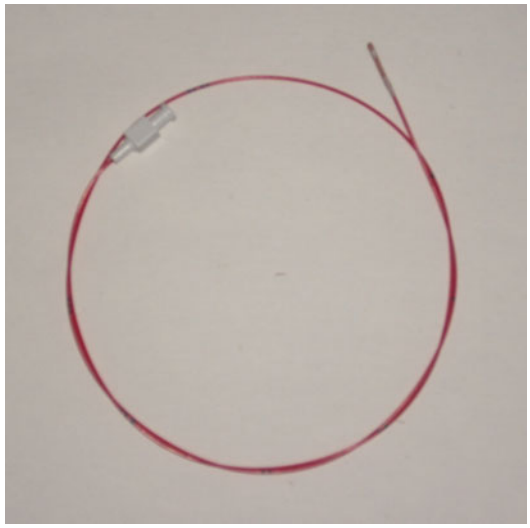

Fig. 33.1 Fogarty catheter used in massive bleeding to produce bronchial blockage in an attempt to stop bleeding. In its proximal end a hub is present, and in the distal end a balloon is inflated

Once the catheter is in place, and the hemorrhage has apparently ceased, the balloon is deflated three times a day during a brief period of time to verify that bleeding has really stopped. If bleeding continues, the catheter is left in place, and the patient can be transferred for a definitive treatment to surgery for resection or to hemodynamics to perform an arterial embolization.

The main problem placing these catheters arises when the flexible bronchoscope is withdrawn with the balloon occluding a bronchus, since the hub of the Fogarty has to be cut, resulting in balloon deflation (Fig. 33.2). To inflate the balloon again can be troublesome and time consuming, and the blockade can be accidentally lost. To avoid this inconveniences, Freitag and cols [56] introduced in 1993 a new double lumen, 2-mm outer diameter catheter with a proximal valve that can be detached and easily reconnected. The flexible bronchoscope can be thus retired, detaching the valve and reapplying it once the bronchoscope has been taken out. Also, as the catheter has two lumens, it allows instilling saline through the second lumen while the balloon is inflated.

Some other reports describe other methods to treat massive hemoptysis. If saline lavage and adrenaline fail, a solution of fibrinogen–thrombin instilled through the working channel of the flexible bronchoscope can be utilized [57].

At our institution, we prefer the use of fibrin glue-type products (Tissucol Duo Quick®). Two different solutions (fibrin solution and fibrinogen solution along with factor XII and plasminogen) are simultaneously injected through a double lumen catheter. At the distal end, both solutions mix in at the selected bronchus and achieve a hemostatic effect (Fig. 33.3).

Valipour et al. [58] described good results with the use of oxidized regenerated cellulose, available in knitted fabric strip that they trim in 4–10 fragments sized 30×40 mm (Surgicel®). These mesh layers are grasped with a biopsy forceps and pulled back into the operating channel of the BF, leaving only a small piece in the visual field of the BF. When the bleeding site is identified, the flexible bronchoscope is moved out while pushing the forceps as far as possible deep in the bronchial tree.

In summary:

- Massive hemoptysis is an entity with a high mortality rate (up to 80%), and a rapid intervention is required.
- First, airway patency must be secured; second, the bleeding source has to be identified; and third, a therapeutic procedure has to be offered.
- The rigid bronchoscope is the instrument of choice in this setting, and again, the flexible instrument should be ready to inserted through the RB in case of need.
- Electrocautery or laser equipment for coagulation must be available.
- Many procedures can be useful in massive hemoptysis, as described, but we have found that bronchial blockage by insertion of a Fogarty catheter occluding the bleeding bronchus is the most effective.

The Fogarty catheter should not be kept in place for more than 3 days. If bleeding continues, a definitive treatment (i.e., bronchial arterial embolization or pulmonary resection) has to be performed or another kind of treatment can be attempted as described above (fibrin glue instillation or the use of oxidized regenerated cellulose).

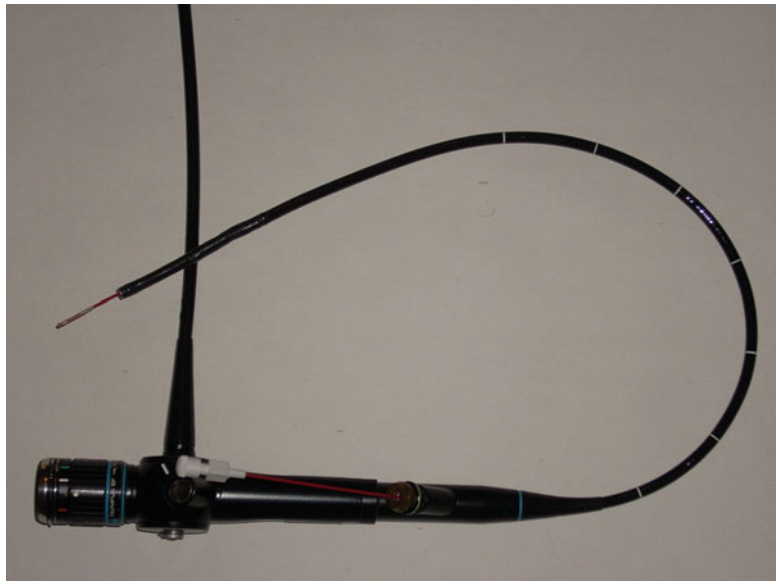

Fig. 33.2 Fogarty catheter passed through the working channel of the bronchofiberscope. When it is retired, the hub at the proximal end has to be cut off, producing deflation of the balloon

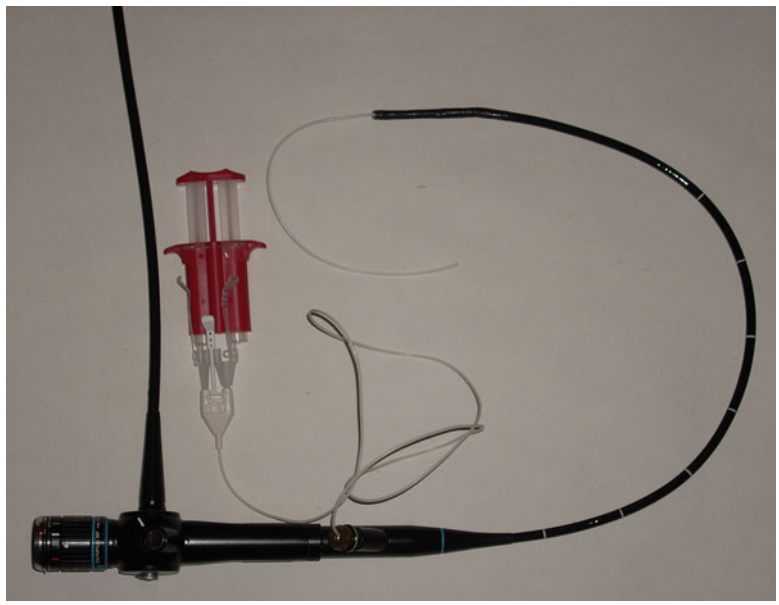

Fig. 33.3 Thrombin and fibrinogen solutions are injected simultaneously through this double lumen catheter. They mix at the distal end to produce a hemostatic effect. It can be used to treat hemoptysis and bronchopleural fistulas

Tracheoesophageal Fistula

This is an infrequent but fearsome complication of prolonged airway intubation. The presence of an ETT may produce erosion of the membranous wall of the trachea, resulting in a tracheoesophageal fistula (TEF). High cuff pressures and endotracheal tube or tracheostomy tube movements are factors commonly involved in this complication. The presence of a nasogastric tube within the esophagus may also contribute to its development.

The most frequent predisposing factors are:

1. High cuff pressures
2. High airway pressures that result from a non-compliant lung, requiring high tidal volumes and high cuff pressure to avoid air leaks
3. Excessive motion of endotracheal or tracheostomy tubes

Others predisposing factors are [59]:

1. Prolonged intubation
2. Respiratory infections
3. Steroids
4. Hypotension
5. Insulin-dependent diabetes
6. Advanced age

The single most important measure to avoid this complication is to regularly check the ETT cuff pressure and maintain it between 20 and 25 mm Hg. Other preventive actions are:

1. Fixing properly the endotracheal tube and if a prolonged intubation is anticipated, consider nasotracheal intubation that assure less movement of the tube or proceed directly to tracheostomy.
2. Maintain the head of the patient in a neutral position, as hyperextension produces close contact between the cuff and the tube with the posterior wall of the trachea, while flexion can injury the anterior wall.
3. Prompt and appropriate treatment of infections.
4. Maintain a stable hemodynamic status.

TEF is suspected on a ventilated patient that requires higher tidal volumes to maintain adequate ventilation, combined with higher pressure in the ETT cuff to avoid leaks. The amount of airway secretions increase markedly, as saliva empties in the airway. Accordingly to the size of the defect, pCO_2 increases, since part of the delivered tidal volume is lost through the tracheal defect and hypoventilation takes place.

To confirm TEF in a ventilated patient is troublesome, due to the fact that a barium esophagogram cannot be performed. The instillation of methylene blue diluted in saline into the esophagus will appear in the tracheal secretions or around the tracheostomy. An interesting approach is to analyze the inspired fraction of oxygen set in the ventilator and the oxygen fraction in the gastric air (it can be obtained aspirating air by the nasogastric or the gastrotomy tube). If there is a relative coincidence between both measurements, the diagnosis is almost confirmed. To rule out swallowed air, it is useful to take a sample of room air close to the patient's mouth.

The definitive diagnosis requires flexible bronchoscopy with or without an esophagoscopy. Bronchoscopy can be done through the ETT or the tracheostomy tube as well. It allows visualization of the fistula at the membranous portion of the trachea.

Outcomes of various treatments are discouraging in patients on mechanical ventilation, and mortality is very high. Deflation of the cuff may be attempted to alleviate esophagus trauma; combined with high-frequency jet ventilation, a decrease in the mean airway pressure and volume lost can be achieved. If the fistula is identified, placement of an endotracheal tube with the cuff inflated below the lesion may be attempted. Success is not always possible and depends on fistula location.

If the patient can be appropriately ventilated and oxygenation can be maintained without air leakage through the fistula, a definitive therapeutic approach can be offered. Surgery is considered the best treatment, but is not always possible. It involves separating the trachea from the esophagus and closing the esophageal defect. Many times a segmental tracheal resection is needed to fix the tracheal orifice, and a muscle flap should be placed in between the trachea and the esophagus [60]. This approach requires the patient to be extubated as soon as possible after surgery, as there is a significant increase in the rate of failure if positive pressure ventilation continues after surgical repair.

Frequently, the poor medical condition of these patients precludes surgery. In these cases, an endoscopic approach may be attempted.

There are several reports of different methods applied, but the majority are anecdotic.

A single stent (tracheal or esophageal) or even better a double stenting (trachea and esophagus) may be tried. We prefer the use of a Dumon stent for the trachea. One problem that appears when placing only an esophageal prosthesis is that

positive pressure ventilation often times will cause displacement of the esophageal stent since the tracheal wall defect has not been solved. Freitag et al. [61] recommend the tracheobronchial dynamic stent, since it is slightly concave and the flexible posterior silicon portion adapts better to the convexity of the already placed esophageal prosthesis. As we referred previously, stenting a patient on mechanical ventilation is not easy, and sometimes results are discouraging. These maneuvers must be performed fast and only by a skilled bronchoscopist. If the procedure was tolerated and successful, next problem is the coexistence of a tracheobronchial stent and the ETT or tracheotomy tube. Before the procedure, careful attention must be paid to the selection of proper-sized tubes and stents since they have to adapt perfectly to the inner diameter of the prosthesis. In our experience, this is a very difficult matter to resolve.

The instillation of fibrin glue in the fistulous orifice is another possibility [62]. This might work only in patients with very small defects.

Another option is to apply silver nitrate on the mucosa surrounding the fistula, with a bronchial brush. Dehydrated alcohol injected circumferentially around the orifice (2.5–5 mL) may be added [63]. It is assumed that the inflammatory and profibrotic response produced around the fistula might lead to its closure. Like the fibrin glue, it only might be applied in very small fistulas, less than 5 mm in diameter.

Bronchopleural Fistula and Prolonged Air Leak

Bronchopleural fistula (BPF) is a communication between the trachea or bronchi and the pleural space. BPF can complicate major pulmonary resections such as pneumonectomy, lobectomy, or segmentectomy, due to healing failure of the bronchial stump. It is more common after a right pneumonectomy than any other lung resection. Risk factors for the development of BPF are residual tumor in the bronchial closure, a large bronchial stump, preoperative radiotherapy, an active infection in the resected lung, and the need of mechanical ventilation in the postoperative period. BPF is always associated with empyema as the secretions of the major airways contaminate the pleural space. For this reason, a drainage procedure of the pleural space is the most important part in BPF treatment.

Although unusual, BPF is a severe complication with high morbidity and mortality, and most of the times requires surgery with some kind of muscle flap to be repaired. To develop this condition, a patient has to have undergone at least a segmentectomy, but it generally represents a complication of a major lung surgery or chest trauma.

BPF needs to be differentiated from prolonged air leaks (PALs). PALs are one of the most common complications of lung resection surgery and involve a communication between lung parenchyma (alveoli) and the pleural space. PALs are defined as an air leak lasting more than 7 days. PALs are much less morbid than BPFs, they do not contaminate the pleural space, and most of the times the treatment is drainage of the pleural space, time, and patience. Although more benign, PALs are a common cause of prolonged hospitalization.

When the bronchoscopist is called from the ICU to evaluate a patient with an air leak, the most important information to request is whether or not the patient had a lung resection surgery. If that is the case, PAL will be the most likely cause. However, if the patient has been on the ventilator for a prolonged period of time and especially if the ventilator volume needed was high, BPF should be then suspected. Clinical clues that point at BPF are increasing amount of air leaking from the chest tube, purulent drainage from the tube, or a new pneumothorax.

If the patient did not have lung surgery and is on mechanical ventilation, barotrauma will be the most likely cause. The physiopathology of barotrauma is similar to that of postoperative PAL: overdistention of the alveoli caused by high tidal volumes, which damages somewhere the surface of the lung and an air leak is produced. Barotrauma is treated as PALs: placement of chest tube for pleural drainage. According to location, barotrauma can present as pneumothorax, pneumomediastinum,

pneumopericardium, pulmonary interstitial emphysema, subcutaneous emphysema, or BPF (only in patients with prior lung surgery, for the reasons discussed earlier). Recently, clinicians refer to volutrauma to make reference to the pernicious action caused by overdistention of the alveoli produced by high tidal volumes. The evidence is not clear in differentiating which factor is responsible for the alveolar rupture: peak inspiratory pressure, mean airway pressure, or peak alveolar distending volume. Animal models, in fact, favor the volume overdistention theory.

There are several potential causes of barotrauma in patients on MV [64].

When pneumothorax appears few hours after the initiation of MV, the most likely cause is previous trauma from overinflation produced by manual, mouth-to-mouth ventilation or some other resuscitation maneuvers. Pierson calls this "pseudobarotrauma" that is external trauma to the lung produced by a central line placement, a laceration during intubation, or injury from a bronchoscopic procedure.

However, much more often, extraalveolar air is a consequence of overdistension, resulting in a pressure gradient between the alveoli and the surrounding tissues (bronchovascular sheets), leading to alveolar rupture. This rupture is rare in the presence of normal lungs, but it can occur in patients with lung disease such as COPD or ARDS.

Diagnosis

When BPF is suspected in the mechanically ventilated patient, inspection bronchoscopy is indicated to visualize the bronchial stump. Bronchoscopic findings can range from a very tiny bubbling observed over the bronchial closure when it is flushed with saline through the bronchoscope to a bigger opening and necrotic tissue at the stump area. When the orifice is small, less than 6 mm, or only bubbling is seen at the stump area with no recognizable orifice, a bronchoscopic procedure can be attempted in order to seal the BPF.

If no orifice or bubbling is seen at the bronchial stump, the diagnosis is prolonged air leak from the alveoli, the most common cause of air leak after lung resection.

Most of the times, PALs from alveolar leaks seal off by themselves. A chest tube should be placed for pleural drainage. However, when sealing is delayed, more often in the postoperative patient that has required mechanical ventilation for a prolonged period, there are some bronchoscopic maneuvers that can be of help. A selective occlusion maneuver can be used to identify the lung segment causing the alveolar leak. Fogarty balloon catheters of 5, 4, or 3F are used to occlude the airway from the more proximal to the more distal segment until the air leak stops. The air leak might not stop when there is significant collateral ventilation, and in these cases the procedure will not be useful to detect the site leaking. If a lung segment is identified as the source of the air leak, a bronchoscopic approach might be tried.

Treatment

There are some general measures that can be taken to reduce the air leak from a BPF or from an alveolar leak:

- Reduce the tidal volume in the ventilator: in a patient with high risk for developing volutrauma, the effective tidal volume should not be more than 6 mL/kg.
- Minimize inspiratory phase by:
  - Decreasing the inspiratory/expiratory ratio, setting a high inspiratory flow rate, about 70–100 L/min.
  - Maintaining an inspiratory/expiratory ratio to about 0.3.
- Chest tubes under water seal (no active suction or minimal suction to maintain lung expansion).
- Pressure support ventilation and synchronized intermittent mandatory ventilation are the preferred ventilation modes. High-frequency ventilation may be useful in patients with large air leaks.
- Extubate the patient as soon as possible.
- Treat aggressively bronchial obstruction.

The first measure is to have drained the pleural space, by placing a chest tube. It is recommended

to apply the least possible suction to maintain the lung expanded. Antibiotics are started as well as enteral or parenteral feedings.

Surgery is the best option for the treatment of BPF. However, it involves transferring the patient to the operating room, reopening the chest, empyema drainage, lung decortication, BPF closure, and placement of a muscle flap to repair the bronchial stump. A serratus muscle flap can be used as it serves not only to provide vascularization to the bronchial stump but also to fill in the pleural space. Intercostal muscle flaps can also be used, but they do not provide as much vascularization to the stump and are not that useful in filling in the pleural space. In high-risk patients with small orifices, bronchoscopic treatment can be an option when spontaneous closure seems unlikely.

Several sealants have been used through BF to close a BPF. Regardless of the one applied, there are several considerations. If the orifice is visualized, the area to be treated must be washed and cleaned from secretions. Once the segmental bronchi leading to the air leak is identified by using a Fogarty balloon, a catheter should be advanced distally under direct vision after deflating the Fogarty balloon, and then the sealant can be administered through the catheter.

Available sealants are: (Table 33.5)

- Fibrinogen–fibrin glue (Tissucol®): a double lumen catheter needs to be used to apply this glue. Two milliliters of each compound are injected simultaneously through each one of the ports of the double lumen catheter. They mix at the tip of the catheter forming the glue that blocks the leak. Once it is administered, apnea is necessary for 1–2 min to avoid disruption of the sealant [65] (Fig. 33.3).
- Tetracycline and blood clot: Martin et al. [66] described the successful BPF closure by instillation or tetracycline (0.5 g diluted in 25 mL of normal saline) through an inflated Fogarty catheter, followed by 10 mL of fresh non-heparinized autologous blood taken from the radial artery. The inflated Fogarty balloon is held in position during 10 min to allow clotting.
- Oxidized regenerated cellulose (Surgicell®): the technique was described in the massive hemoptysis section [58, 67].
- Cerebral angiographic occlusion coils can be tried as well, deploying them as it is done for neurosurgery. Following coil placement, fibrinogen–fibrin glue may be also applied. The instillation of 1 mL of cyanoacrylate after the coils are deployed has been also described [68].
- Silver nitrate: as described in the tracheoesophageal fistula section, silver nitrate can be of help treating BPF.
- Cyanoacrylate glue is an agent that polymerizes in solid material when in contact with body fluids. After injection, it acts as a plug then induces an inflammatory response, followed by fibrosis and mucosal proliferation with closure of the fistula.
- Ethanol can be applied alone or in combination with another sealant. Before injection, it is convenient to use a cytology brush to scratch the mucosa of the fistulous orifice. Then, the absolute alcohol is applied as a submucosal injection, in aliquots of 0.1 mL via transbronchial needle, until the edematous surrounding tissue closes the fistula. More than one application might be needed. Ethanol treatment should be applied only if the FBP can be seen and may be effective in fistulas smaller than 3 mm [69].
- Spigots: Watanabe Y [70] developed radiopaque silicone spigots for the treatment of BPF and PAL. The spigot is placed through the rigid bronchoscope with grasping forceps, advancing until it occludes the BPF area. This method is preferred by many endoscopists (Fig. 33.4).
- Stents: based on the same rationale as the spigots, airway prosthesis sometimes are useful to occlude a fistulous orifice when it is visible at bronchoscopic examination. Our experience in the treatment of BPF utilizing Dumon stents is not conclusive. Usually the air leaks diminish, but does not cease com-

Table 33.5 Brand names and manufacturing companies mentioned

Tissucol Duo Quick	Baxter Immuno
Surgicel and Surgicel Fibrillar	Johnson and Johnson's Ethicon
Arndt Endobronchial Blocker Set	Cook Company

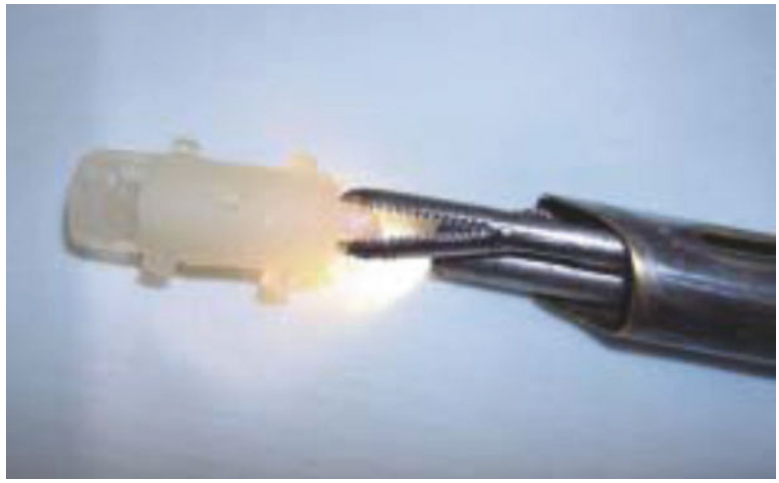

Fig. 33.4 Forceps grasping a spigot used through the rigid bronchoscope to seal a bronchopleural fistula or to block an air leak

pletely. We have used a specially manufactured Y-stent (Stening Company®) occlusive on the right arm, to treat a BPF after a right pneumonectomy. The result was not optimal, because the stent did not adapt properly to the stump surface.

- Emphasys valves: these valves are used for bronchoscopic treatment of emphysema. They work through a mechanism that closes during inspiration and opens during expiration, allowing deflation of the lung and mobilizing distal secretions. Their application for BPF can be of help in selected patients [71, 72].
- Neodymium Yag laser may be used to produce mucosal erosion of the bronchial orifice when it is visualized, causing inflammation and ultimately resulting in healing.

Some authors report good results applying laser to treat these lesions, but we do not recommend it, based on the potential damage that laser can exert, which may result in increasing the fistulous orifice.

- Amplatzer device: this device was originally designed for transcatheter closure of interauricular communication. It is a double nitinol disk that can be deployed bronchoscopically over a guide wire through the fistulous orifice. After right placement, the device acts as a cuff link, occluding the fistula. It may be useful only in visible BPFs [73].

Surgery is the best therapeutic approach to patients with BPFs, but in high-risk patients, an endoscopic approach can be offered first, since it is generally well tolerated and it does not exclude a subsequent surgical approach if the bronchoscopic treatment fails. Selection of the appropriate endoscopic procedure to treat BPFs should be decided case by case in a multidisciplinary fashion, depending on personal experience and availability.

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Part VIII

Conclusions

34 Bronchoscopy and Interventional Pulmonology: Reflections on the Past, the Present, and the Future

Udaya B.S. Prakash

Introduction

The clinical application of bronchoscopy has been available for over a century [1]. In its infancy at the tail end of the nineteenth century, the technique was used on an infrequent basis. As it has matured over the years, bronchoscopy is now frequently utilized to diagnose and treat a vast range of pulmonary disorders. Significant advances in the instrumentation, techniques, and ever-increasing indications over the past century have established bronchoscopy as an essential tool not only in the practice of pulmonary medicine but also in critical care medicine, thoracic surgery, rhinolaryngology, and pediatric pulmonology. Currently, bronchoscopy is perhaps the most commonly employed minimally invasive diagnostic procedure in pulmonary diseases.

The ever-expanding indications and the specialized tools required to manage certain clinical conditions now require advanced training and practice before the clinical application can begin. Several of these techniques are inherently time consuming and call for well-developed skills beyond that required in standard or "routine" bronchoscopy procedures. To denote these aspects of bronchoscopy practice, the term "interventional pulmonology" is being used more frequently. This area encompasses not only bronchoscopy but also minimally invasive procedures to diagnose and treat the disorders of the pleural space and percutaneous tracheostomy. Some experts believe that esophageal ultrasound-guided needle aspiration of lymph nodes in lung cancer staging be considered under the term interventional pulmonology. In this chapter, the term bronchoscopy–interventional pulmonology (B-IP) will apply to procedures performed by the pulmonary specialists.

As the vast field of medicine and medical research continues to expand at a rapid pace, it is natural to wonder and contemplate what the distant future holds in the B-IP field. Before one embarks on this speculative endeavor, it is essential to trace back the origins of this field and acknowledge the remarkable contributions made by our predecessors and the trials and tribulations they encountered.

The Past

Interest in the Airways

The references to the study of the human airways and their diseases have been attributed from Hippocrates (460–370 BC) to subsequent generations of scientists through the successive centuries. Concerted efforts to study the human tracheobronchial tree based on scientific principles began in

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the early part of the nineteenth century. The inquisitiveness of medical practitioners to examine the internal cavities led to development of early instruments which were basically made of metallic tubular instruments. Subsequently, polished mirror plates were used to take advantage of the external sunlight for inspection.

In 1807, the German army surgeon Philipp Bozzini developed the *lichtleiter* or "light conductor," precursor of the endoscope for examination of bodily orifices [2]. Neither Bozzini's paper nor his inventions, the lichtleiter described as "the magic lantern in the human body," were taken seriously by his peers. During Bozzini's short life, others continued their work to visualize the larynx with the help of various lighting devices. Benjamin Guy Babington, a British physician, is credited by some for the invention, in 1828, of the "glottiscope," the precursor of the laryngoscope [3]. Manuel Garcia, a Spanish music teacher, singer, and vocal pedagogue, is also credited for being the first to perform laryngoscopy [4, 5]. The next subsequent developments in endoscopy did not appear for at least two decades following Bozzini's death in 1809 at the age of 36 years from typhus.

Advent of the Endoscope

In 1828, Horace Green demonstrated that the larynx could tolerate the presence of a foreign object without endangering the life of the patient [6]. Green became quite adept at catheterizing the larynx and trachea. He subsequently inserted a gum-elastic catheter through the larynx and into the lower bronchi. When Green presented his technique and results of his work at the Surgical Society of New York in 1847, the technique was condemned as "an anatomical impossibility and an unwarranted innovation in practical medicine." As a result, Green was subsequently expelled from the society [7]. Several decades later, Green's technique and clinical usefulness were universally approved. In 1867, Johnson used a laryngoscope to extract a penny coin impacted in the throat of a child [8].

Kirstein, Killian, and Jackson and Protégés

Alfred Kirstein of Germany is credited for the first direct visualization of the vocal cords in 1895, using a modified esophagoscope which he named the *autoscope* [9]. In 1897, Gustav Killian (1860–1921) of Freiburg used the Kirstein laryngoscope to examine the trachea and main stem bronchi of a hospital janitor [10]. In the same year, Killian used an esophagoscope to extract a bone from the right main stem bronchus of a 63-year-old farmer [11]. One year later, Killian extracted tracheobronchial foreign bodies in three patients and coined the word "directe bronkoscopie" to describe the procedure [12]. In 1898, Algernon Coolidge of Harvard Medical School used an open urethroscope, a head mirror, and reflected sunlight to remove a hard-rubber canula from the right main bronchus [1]. Subsequently, several clinicians took up the procedure and almost all procedures involved removal of aspirated foreign bodies [13–15]. As Gustav Killian was instrumental in introducing the technique, he is generally considered the father of bronchoscopy.

In the 1920s, Chevalier Jackson, a laryngologist from Philadelphia, made several modifications to the rigid bronchoscope. Because of his many innovations and contributions to the field of bronchoesophagology, he came to be known as the father of American bronchoesophagology. Jackson and his protégés popularized bronchoscopy and modified the rigid bronchoscope [1]. One of Jackson's students, the British laryngologist Victor Negus, modified one of Jackson's endoscopes, subsequently known as the "Negus bronchoscope." Chevalier Jackson and his son Chevalier Lawrence Jackson, also a laryngologist and better known as C. L. Jackson, wrote several books on bronchoscopy and esophagoscopy [16]. C. L. Jackson further popularized bronchoesophagology by founding the Pan American Association of Otolaryngology and the International Bronchoesophagological Society.

For the next five decades, the rigid bronchoscope and the esophagoscope and their many modifications reigned supreme in the exploration

of the airways and the esophagus. Over the years, several newer developments were incorporated into the rigid bronchoscope. In 1904, Chevalier Jackson had introduced a bronchoscope with a small light at the distal end. Edwin Boyles, another Jackson protégé, developed the optical telescope with forward and angle viewing which permitted inspections of the upper as well as lower lobes of the lung. Paul H. Holinger introduced bronchoscopic photography to document the visual findings [17]. Other developments included instruments for pediatric patients, better lighting and illumination techniques, photographic documentation, and improved anesthetic drugs. The rigid bronchoscopy practice quickly spread to other countries including Japan.

Among the main indications for bronchoscopy, airway foreign body topped the list [16]. The bronchoscope was primarily used as a therapeutic instrument to remove airway foreign bodies, treat atelectasis, drain post-tonsillectomy pulmonary suppuration, and treat bronchitis, asthma, and pneumonia. The Mayo Clinic records indicate that in 1943, of the 436 rigid bronchoscopes performed, the main indication was the foreign body [18]. In 1965, Howard Andersen of the Mayo Clinic employed the rigid bronchoscope and a biopsy forceps to obtain lung parenchymal samples in patients with diffuse lung disease [19]. Andersen termed this technique "transbronchoscopic lung biopsy." A report of 450 cases in 1972 documented the safety of transbronchoscopic lung biopsy using the rigid bronchoscope [20]. However, these advancements in technology could not address the rigid bronchoscope's difficulty in the visualization of the upper lobe bronchi.

Fiberoptics and Shigeto Ikeda

The ability to convert the light rays from their natural predisposition to travel in straight lines to bend them with the fiberoptic technology had its origins in the early 1800s. The physical properties of glass fibers were first described by John Tyndall in 1872. The rod and lens fiberoptic lighting technique was adopted as cold light source for the rigid bronchoscopes in 1963 [21, 22]. Further refinements by countless investigators eventually culminated in the development of a clinically useable fiberoptic system. In 1957, Basil Hirschowitz at the University of Michigan presented the first gastrofiberscope at the Gastroscopic Society of America [23, 24].

Shigeto Ikeda of Tokyo, Japan, was responsible for developing and introducing the flexible fiberoptic bronchoscope into clinical practice in 1968 [25, 26]. In 1970, the first Olympus model became commercially available. Ikeda traveled widely and disseminated the technique and popularized it. As a result, the flexible fiberoptic bronchoscope moved rapidly into clinical practice and revolutionized the practice of pulmonology. The ability to reach and visualize the distal bronchial tree in all segments of all lobes permitted the diagnosis of endobronchial lesions and other abnormalities. Ancillary instruments that could be introduced into the working channel enabled the bronchoscopist to obtain brushings and biopsies of not only the endobronchial lesions but also the lung parenchyma. Simultaneous use of real-time fluoroscopy made it possible to more precisely direct the instruments to the lesion in question. Special cameras to capture both still and video images were developed to complement the system. Within a brief period after its introduction into clinical practice, the flexible bronchoscope became an important aspect of pulmonary practice.

Professor Ikeda continued his work to develop newer techniques and instruments. His work eventually led to the development of the flexible video bronchoscope in the late 1980s. The main difference between the fiberoptic bronchoscope and the video bronchoscope is the mode of capture and transmission of the bronchoscopic images. With fiberoptic system, the images are directly carried by the fiberoptic bundles through the bronchoscope to the objective lens and then viewed by the examiner. The video bronchoscope uses a charge-coupled device (CCD) to capture the digital images which are transmitted to a processor and then projected on to a larger video screen. This has resulted in our ability to capture still and video images with far greater resolution

for documentation and educational purposes. Smaller-diameter bronchoscopes are available to examine pediatric patients with respiratory disorder. Further refinements in the ancillary instruments have improved specimen collection from the respiratory tract. At present, over 95% of all bronchoscopies are performed with the flexible bronchoscope. Ikeda who introduced the flexible bronchoscope continued to work on improvements in and modifications to the flexible bronchoscope until his death on December 25, 2001 [27]. His legacy continues, carried on by a countless number of bronchoscopists from around the world who benefited from his invention in the management of thousands of patients with respiratory disorders.

Revival of the Rigid Bronchoscope and Dumon

The continued improvements in flexible bronchoscopy and associated equipment vastly increased the indications for bronchoscopy. As the popularity of the flexible bronchoscope grew, it became universally accepted as the instrument of choice for airway diagnostics. Nevertheless, thoracic surgeons and laryngologists continued to use the rigid bronchoscope for procedures involving the major airways and for the extraction of airway foreign bodies. Several pulmonologists continued to use the standard rigid bronchoscope for traditional indications such as extraction of airway foreign bodies and dilatation of major airway stenosis. Jean Francois Dumon of Marseilles foresaw the need for better rigid bronchoscopes and associated ancillary equipment for the treatment of airway lesions such as obstructing tumors and benign stenosis of trachea and main bronchi. Dumon developed and modified many aspects of the rigid bronchoscope and peripheral equipment. In 1981, Dumon and colleagues reported on the use of YAG laser to treat tracheal lesions [28, 29]. Over the next decade, Dumon developed a newer type of rigid bronchoscope and stent insertion instrument [30]. Many specialists in B-IP became interested in the rigid bronchoscopy technique and its application in clinical medicine. As a result, the rigid bronchoscope regained its importance in the treatment of major airway lesions. A variety of silicone and metal stents have been developed to relieve airway stenosis from benign as well as malignant processes.

The Present

As the past innovations and applications of bronchoscopic techniques have gradually and imperceptibly melded into the present, the current practice wisely utilizes all clinically available and applicable techniques from the past and present to manage a variety of respiratory disorders. This view is reflected by the leading specialists in their excellent rendition of the current status of B-IP in the preceding chapters of this volume. Therefore, this part of this chapter will not dwell on the technical and other details and the nuances of the current practice. However, a few brief summarizing paragraphs might be in order to summarize the current status.

Diagnostic Procedures

In the realm of diagnostic bronchoscopy, the standard indication, namely, the visualization of the airways for suspected and unexpected abnormalities, remains among the main indications for bronchoscopy. Collection of bronchial secretions, washings, and bronchoalveolar lavage for cytologic analysis and culture of pathogenic organisms continues to maintain its importance, especially in immunocompromised patients with pulmonary abnormalities. The standard procedures used are well described in the preceding pages. To summarize, these include visualization and documentation, collection of bronchial secretions, and bronchoalveolar lavage for cultures, cytology, quantitation of cells and cell types, quantitation of hemosiderin- or lipid-laden macrophages, and brushing and biopsy of endobronchial as well as pulmonary parenchymal lesions, bronchoscopic ultrasound-guided needle aspiration of thoracic lymph nodes and masses,

electromagnetic navigation to obtain tissue from nodular parenchymal lesions, and many other miscellaneous indications.

Therapeutic Bronchoscopy

Therapeutic bronchoscopy plays a major role in the critically ill patients with respiratory manifestations. The primary indication is the retention of airway secretions, mucous plugs, blood, or blood clots. The flexible bronchoscope is very capable of clearing airways of these obstructing materials. The bronchoscope is now an essential part of the equipment in the intensive and critical care units. Other well-known therapeutic indications for bronchoscopy include airway foreign bodies. The availability of small-diameter bronchoscopes has permitted flexible bronchoscopic extraction of foreign bodies from the pediatric airways. Uncommon indications include treatment of airway fistulae, drainage of lung abscess and cysts, etc.

Bronchoscopy in Lung Cancer

A major role for the bronchoscope is in the diagnosis and treatment of lung cancer. As described in the preceding chapters, fluorescence bronchoscopy is used from time to time in patients suspected of having cancer of the airway mucosa. This technique permits localization of the lesion to obtain biopsies and in the follow-up of patients with persistent cellular atypia or other suspicious cytologic abnormalities. Optical coherence tomography is another technique used for detailed analysis of epithelial surface abnormalities in the airways. Narrow band imaging is yet another method to analyze abnormal mucosal surface. More recent encouraging developments in the diagnosis and treatment of lung cancer are the techniques available to isolate the molecular genetic variations among different histologic types of lung cancers. This advance has led to the development of newer chemotherapeutic agents targeted to treat specific types of lung cancer.

Bronchoscopic ultrasound-guided sampling of abnormal mediastinal and hilar lymph nodes now allows proper staging of lung cancer. The ability to stage lung cancer with the help of the flexible bronchoscope has significantly obviated the need for mediastinoscopy and video-assisted thoracoscopic surgery for staging purposes. It is essential to note that the role of computed tomography and positron emission tomography is important in guiding the bronchoscopist to the abnormal or suspicious areas for biopsy.

Fluoroscopy-guided bronchoscopic brushing and biopsy of peripheral nodular lesions has been in use since the advent of the flexible bronchoscope. During the past decade, electromagnetic navigation technique to localize and biopsy peripheral lung lesions has been used in a limited number of medical centers. Another technique is the virtual bronchoscopic navigational bronchoscopy. This system uses the CT-developed virtual images of the airways to guide the biopsy forceps to the peripheral lesion.

Bronchoscopy techniques offer an important role in the treatment of patients with primary and metastatic malignancies. Many patients with an endobronchial component of the neoplasm present with hemoptysis, increasing dyspnea caused by luminal obstruction, post-obstructive atelectasis with pneumonia, and extrinsic compression of the airway lumen. Control of hemoptysis from a visible bleeding source in the airway lumen can be treated with simple aspiration of blood and repeated iced-saline irrigation. Other methods to stop the hemorrhage include bronchoscopic cauterization of the bleeding point, argon plasma coagulation (APC), cryotherapy, and laser coagulation [31]. Luminal obstruction is more likely to cause dyspnea and respiratory distress if the tumor involves the trachea or the main bronchi. In such situations, the techniques mentioned above can remove the obstruction and improve luminal air flow. Mechanical debridement is also an option.

Patients with respiratory symptoms caused by airway obstruction from the endobronchial component of the cancer can be relieved of the dyspnea with the bronchoscopic use of a variety of techniques. In the early 1980s, Jean Francois Dumon of

Marseille, France, showed that bronchoscopic laser ablation of airway lesions can successfully relieve dyspnea as well as significant endobronchial hemorrhage. Subsequently, Dumon developed silicone stents for insertion in the airways to maintain a patent lumen after laser resection of the lesion [30]. To facilitate the laser resection and placement of airway stents, Dumon modified the rigid bronchoscope and developed a series of rigid bronchoscopes and ancillary instruments.

In addition to the techniques mentioned above, other techniques used include mechanical debridement, balloon dilatation, brachytherapy, and photodynamic therapy [32–35]. An overwhelming majority of these procedures are used for palliative purposes in patients with advanced or inoperable airway malignancies. The success of these procedures depends on the expertise of the operator, equipment available, and their optimal use.

Interventional Pulmonology

What is "interventional pulmonology?" My *PubMed* review of the medical journals and periodicals published in English language revealed that the term was first used in 1997 by Witt and colleagues [36]. It is unclear if the term was used in books published at an earlier date. Initially, interventional pulmonology referred to all aspects of bronchoscopy, especially the more invasive procedures such as rigid bronchoscopy, laser resections, airway dilatational procedures, and stent insertion. Currently, all these and any pleural procedure performed by a nonsurgeon and percutaneous tracheostomy are included under the term interventional pulmonology.

Currently, involvement of the interventional pulmonologists has increased in the management of pleural disorders. Thoracentesis; pleural biopsy; placement of indwelling tunneled pleural catheters to treat recurrent benign and malignant pleural effusion, chylothorax, pneumothorax, and trapped lung; pleuroscopy; and pleurodesis are among the procedures being performed [37–39]. The term "medical thoracoscopy" has been used to describe thoracoscopy performed by nonsurgeons and without subjecting the patient to tracheal intubation and general anesthesia [40–42]. Another procedure included in the interventional pulmonology is the percutaneous tracheostomy in patients who are expected to require prolonged mechanical ventilation. The current trend indicates that an increasing number of interventional pulmonologists will be performing these procedures.

Bronchoscopic lung volume reduction to treat emphysema has undergone multiple trials and is currently being used in many European countries [43–45]. The current status of this technique is such that further work and innovations are required to convince the majority of pulmonologists to consider this in suitable patients. Several chapters in this volume describe the various techniques available and the details of the indications, technique, and the results of clinical studies.

Bronchoscopic thermoplasty is a technique developed to treat patients with refractory asthma [46–48]. While it is approved for clinical use in the USA, the technique has not been universally accepted by asthma specialists. Better definition of indications and long-term results will determine if this procedure will gain significant popularity.

The Future

While it is hazardous to guess and predict what the future holds for B-IP, it is safe to surmise that the prospect for B-IP is very promising. The medical science is advancing rapidly and the advances will determine the indications and for B-IP. As outlined above, the continued technical advances in B-IP have altered the indications and role for the procedures. Newer diseases or increasing prevalence of well-known diseases may bring about important and new indications for B-IP. Advances in technology are another reason for increased use of B-IP procedures. On the other hand, advances in nontechnical diagnostic methods can decrease or entirely eliminate the need for B-IP procedures. Newer therapeutics to treat nonpulmonary disorders can result in respiratory

complications which in turn would require B-IP procedures for the diagnosis and treatment of such complications.

Changing Role of Bronchoscopy and Interventional Pulmonology

A further reflection on the above brings to mind some examples from the past three decades. An excellent example is the discovery of acquired immunodeficiency syndrome (AIDS) in the early 1980s. As clinicians quickly recognized, the lung involvement was common in AIDS and the etiologies of these were unknown. Very soon, bronchoalveolar lavage became very important in the diagnosis of lung infiltrates in these patients. The procedure remains an important tool in the management of patients with AIDS. Another group of patients who benefit from B-IP procedures are those who are immunosuppressed because of chemotherapy or medications administered to prevent tissue rejection following organ transplantations. The number of such patients is likely to increase as more and more organ transplants are performed. Major airway stenosis in lung transplant recipients may require frequent bronchoscopic evaluations.

Newer Technology

The prevalence of asthma as well as the proportion of patients with asthma refractory to aggressive medical therapy has increased. This has been the impetus for the consideration and development of bronchial thermoplasty. Advanced emphysema is another condition that is associated with significant mortality and morbidity. Medical therapy has limited role in alleviating the severe dyspnea and hypoxia in the affected persons. As the surgical lung volume reduction has been associated with high mortality and morbidity, less invasive procedures such as bronchoscopic lung volume reduction have been introduced in clinical practice. As of this date, it is difficult to be certain whether these two procedures will be generally accepted and frequently used.

Lung cancer will continue to be a major condition encountered by pulmonary physicians. Better understanding of genetic mutations in cancer cells has led to targeted chemotherapy in certain histologic types of lung cancer. The general expectation is that improved understanding of the basic abnormalities in genetic mutations may lead to so-called individualized medicine. It is easy to infer that the role of B-IP procedures will increase in the management of patients with lung cancer.

Lessons from the Past and Present

The past history of B-IP shows that some techniques languished for considerable length of time before being accepted by the majority of specialists in B-IP. Bronchoscopic needle aspiration/biopsy is such an example. After the bronchoscopic ultrasound-guided needle aspiration technique and technology became reliable in securing optimal tissue samples from affected lymph nodes, the technique has assumed a very important and essential tool in the nonsurgical staging of lung cancer. Further improvements may increase the indication for the technique. On the other hand, several techniques have yet to gain universal acceptance and widespread use, with only a few medical centers and interested specialists in B-IP using them. These include electromagnetic navigation, virtual bronchoscopic navigation, confocal bronchoscopy, optical coherence tomography, and several miscellaneous techniques. It is important to recognize that many of these require expensive equipment and extensive training. These are major considerations in determining the extent of usage.

Several of the B-IP techniques have established their valuable role in clinical pulmonology. Because of the very nature of the technique, expense, and the limited indications and the limited number of patients who might benefit from their deployment, these techniques are limited to a smaller number of medical centers and B-IP specialists. Included among these are rigid bronchoscopy, airway debridement, laser bronchoscopy, airway stent insertion, medical thoracoscopy, indwelling tunneled pleural

catheters, management of complex conditions of major airways, and percutaneous tracheostomy.

The indications for B-IP have significantly decreased following the introduction of improved diagnostic methods in associated procedures in pulmonology. A classic example is the universal availability of high-resolution computed tomography. Based on clinical information and chest CT images, it is now possible to confidently diagnose several interstitial lung diseases and avoid bronchoalveolar lavage and bronchoscopic lung biopsy. Examples of such disorders include idiopathic pulmonary fibrosis/usual interstitial pneumonitis, nonspecific interstitial pneumonitis, lymphangioleiomyomatosis, Langerhans cell granuloma, pulmonary alveolar proteinosis, and certain cases of sarcoidosis. Advances in serologic testing and other tests have obviated the need for bronchoscopic lung biopsy. Previously, lung biopsies were considered essential for the histologic diagnosis of granulomatosis with polyangiitis (also known as Wegener's granulomatosis). Currently, however, biopsy has been replaced by the reliable antineutrophil antibody testing (ANCA). While the advent of video-assisted thoracoscopic surgery (VATS) decreased the number of bronchoscopic lung biopsies, the improvements in bronchoscopic ultrasound guidance have decreased the need for surgical mediastinoscopy. If and when newer and less invasive tests become available for clinical use, the need for B-IP procedures may diminish. These considerations imply that multitude of factors may increase or decrease the need for B-IP procedures. Simultaneously, it is essential to recognize that the competing tests and procedures can also assume complimentary roles.

Education

Proper initial training and ongoing training including didactic and hands-on practice is required to enable the specialist in B-IP to provide optimal care to the patients. The increase in the number of different procedures performed by the specialists in B-IP had led to the establishment of dedicated training programs in B-IP. Ongoing training programs and refresher courses have increased in numbers. All professional respiratory organizations have established hands-on workshops and training programs in B-IP. A major advance is the introduction of simulation centers where the novices as well as experts are trained and retrained in techniques using mannequins or animal models. In this volume, a chapter is dedicated to the discussion on the various modes of teaching and training. The World Association for Bronchology and Interventional Pulmonology as well as national associations dedicated to the dissemination of B-IP continue to provide guidance and training in B-IP procedures, and this activity will continue and expand.

Summary

It is likely that the importance of B-IP will increase in the future. The caveat that accompanies this statement is that a multitude of factors will increase or decrease the need for and the importance of B-IP procedures in the future. It is essential to concurrently recognize that the newer nonpulmonary tests and procedures do not compete with B-IP procedures but are complimentary. As the number of indications increase and newer instruments and techniques become available, more and more training becomes imperative. Even now, in some major medical centers with a large number of specialists in B-IP, not every procedure can be performed by each and every B-IP specialist. Subgroups of specialists have dedicated themselves to the practice of certain B-IP procedures.

Further reflections on the history of B-IP and current practice and trend provide ample evidence to state with confidence that the field of bronchoscopy and interventional pulmonology will remain dynamic.

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